DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING
OPEN SESSION

Tuesday, October 28, 2003

1:15 p.m.

Holiday Inn Gaithersburg
The Ballrooms
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

James E. Leggett, Jr., M.D., Chairman
Tara P. Turner, Pharm.D., Executive Secretary

MEMBERS:

John S. Bradley, M.D.
Alan S. Cross, M.D.
Celia J. Maxwell, M.D.
Jan E. Patterson, M.D.
Donald M. Poretz, M.D.
Ciro V. Sumaya, M.D.
Ellen R. Wald., M.D.

CONSULTANTS (Voting):

Janet D. Elashoff, Ph.D.
Joan F. Hilton, Sc.D., M.P.H. (Consultant-CBER)
L. Barth Reller, M.D.
Keith A. Rodvold, Pharm.D. (Acting Consumer Rep)

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Kenneth R. Brown, M.D.

CONSULTANTS (Non-Voting):

David G. Armstrong, DPM, M.Sc.
Allan R. Tunkel, M.D., Ph.D.

FDA:

Mark Goldberger, M.D., MPH
Edward Cox, M.D., MPH
John Powers, M.D.
Janice Soreth, M.D.
David Ross, M.D., Ph.D.
Regina Alivisatos, M.D.
Alfred Sorbello, D.O.

GUEST SPEAKERS (Non-voting):

Carl Norden, M.D.
Dr. Tony Bennett, BM, BCh, FRCP

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LEGGETT: Good afternoon. I hope we can get started on the topic of clinical trial design in diabetic foot infections. Members of the committee, you can sort of relax. There is no yes or no vote this afternoon, so we can all pontificate and there is nothing afterwards. Why don't we get started with introductions? Mark, do you want to start?

Introductions

DR. GOLDBERGER: Mark Goldberger, Director of the Office of Drug Evaluation IV.

DR. COX: Ed Cox, Deputy Director, Office of Drug Evaluation IV.

DR. POWERS: John Powers, Lead Medical Officer, Antimicrobial Drug Development and Resistance.

DR. SORETH: Good afternoon. I am Janice Soreth, the Director of the Anti-Infectives Division.

DR. ROSS: David Ross, Medical Team Leader, Anti-Infectives.

DR. ALIVISATOS: Regina Alivisatos, Medical Officer, Special Pathogens.

DR. SORBELLO: Fred Sorbello, Medical Officer, Division of Anti-Infective Drug Products.

DR. ELASHOFF: Janet Elashoff, Biostatistics, Cedars-Sinai and UCL.

DR. HILTON: Joan Hilton, Biostatistician, University of California San Francisco.

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

DR. RELLER: Barth Reller, Infectious Diseases and Clinical Microbiology, Duke University.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Oregon Health Sciences University.

DR. WALD: Ellen Wald, Pediatric Infectious Diseases, University of Pittsburgh.

DR. CROSS: Alan Cross, Infectious Diseases, University of Maryland.

DR. PATTERSON: Jan Patterson, Infectious Diseases, University of Texas Health Science Center San Antonio.

DR. SUMAYA: Ciro Sumaya, School of Rural Public Health, Texas A&M University.

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

DR. MAXWELL: Celia Maxwell, Infectious Diseases, Howard University.

DR. ARMSTRONG: David Armstrong, Podiatry, with the Diabetes Lower Extremity Research Group at the VA in Tucson.

DR. TUNKEL: Allan Tunkel, Infectious Diseases, Drexel University College of Medicine.

DR. BROWN: Ken Brown, retired from industry and University of Pennsylvania.

DR. LEGGETT: Thank you. Tara, could you please read us the conflict of interest statement?

Conflict of Interest Statement

DR. TURNER: Thank you. The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

The Food and Drug Administration has granted waivers to the following special government employees which permits them to participate in today's discussions, Drs. Jan Patterson, John Bradley, Keith Rodvold and David Armstrong.

A copy of the waiver statements may be

obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. The committee participants have been screened for their financial interests as they may apply to the general topic at hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each participant.

We would also like to note for the record that Dr. Kenneth Brown is participating in this meeting as an acting industry representative, acting on behalf of regulated industry.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, these potential conflicts are mitigated. In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest,

the participant's 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 firm whose products they may wish to comment upon. Thank you.

DR. LEGGETT: Thank you. There has been a slight change in the agenda, and Janice Soreth will give us some opening remarks on the guidance for diabetic foot infections.

Guidance for Diabetic Foot Infections

DR. SORETH: I have only one slide, so don't look for any copies in your folder.

We begin now the open portion of our two-day advisory meeting on anti-infective guidance development, specifically this afternoon diabetic foot. You might ask why more guidance. Well, very simply, despite our agency effort in the last decade to tackle anti-infective guidance development infection by infection, we have not yet for some infections put pen to paper or finger to keystroke.

I would like today publicly to renew our commitment to tackle some of the guidances that we

have left to the end, I think necessarily some of the more difficult ones. To name a few, I think we have left as yet unwritten anti-infective guidance development particular to sepsis products, topical anti-infectives, bone and joint infection and our topic for this afternoon, diabetic foot infections. While we have written guidance on complicated skin and skin structure infections, of which a part is diabetic foot, we have discussed everything but the diabetic foot aspects of that guidance, and not for some time.

As we look across applications that we have received from sponsors looking to get a claim for diabetic foot infections, we see pretty variable case definitions, a collection of data in a given drug development program that is sometimes inconsistent between investigators and certainly inconsistent between drug development programs and, lastly, endpoint assessment that is quite variable.

So, the main reason we are here today is to address definitions and point assessment, and to try to bring, I think, consistency, reproducibility, if not accuracy, to the trials that we design and then conduct. Why? So that we will know what treatments work best.

The stats that you will hear this afternoon in greater detail I think are staggering. Since the year 2000, in the U.S. we make a diagnosis of diabetes mellitus in over one million patients per year. There are over 100,000 hospital admissions for diabetic foot infections yearly and almost a similar number of lower extremity amputations.

[Slide]

For me, the personal statistics are equally staggering and my only slide is a family portrait of my grandfather who, unfortunately, became a type II diabetic as an adult and died, to me, at the very young age of 60 of complications of diabetic foot infection. He had twin daughters, my mother and her twin sister, my aunt. My aunt developed diabetes mellitus as an adult as well and she also succumbed to complications of diabetic foot infections. While my mother is not a diabetic, she has given birth to children who, unfortunately, are becoming diagnosed with type II diabetes.

My hope today is that our discussions will outline definitively and clearly how best to design trials to study diabetic foot infections,

modalities to treat them, including the use of antimicrobial agents, so that we might have a better outcome for my generation and for my children's generation. Thank you.

DR. LEGGETT: Thank you, Dr. Soreth. The next two speakers will have lots of areas of overlap so we are going to take questions after Dr. Norden's presentation. Our first presenter will be Dr. Tony Berendt, and he will talk about diabetic infections, an overview. I would like to ask all the speakers to try to stay on time and stop at that red light.

Diabetic Foot Infections: Overview

DR. BERENDT: Thank you very much. I am very conscious of the honor that has been done to me by inviting me to come and address the committee today, as a Brit speaking to something run by the federal government of America.

[Slide]

I think my only real claim to be here is my involvement in both the IDSA Clinical Practice Guidelines Committee on Diabetic Foot Infections and also a subgroup of the International Consensus on the Diabetic Foot which, this year, produced a supplement to the International Consensus,

specifically looking at the management of infection in the diabetic foot. I will talk more about that later.

[Slide]

The main messages that I would like to get across to the committee today are that despite considerable advance in these areas, there is still a great deal we don't know about diabetic foot infection and that, despite some progress in the production of expert consensus guidances, that really doesn't compensate for the dearth of optimally conducted studies which do leave us with many unanswered questions. So, I will be talking to you really with more questions than answers today but at least you will get some perspective of where we are. There certainly is a definite and I think urgent need for standardized definitions of infection in the diabetic foot both to allow the kind of multicenter studies that your draft guidance recommends and, indeed, to permit comparison between different studies conducted independently but, therefore, capable of more rigorous analysis and meta-analysis.

[Slide]

So, in the rest of my time I am going to

try and get through the following points really, the epidemiology and importance of infection; the clinical spectrum and whether that leads us onto a working definition of diabetic foot infection for the purposes of this group; how one goes about diagnosing a diabetic foot infection--slightly different to defining it perhaps; and then where expert opinion has got to in this area. This is necessarily brief and will miss some areas but they will be covered in more detail by others later today I think.

[Slide]

To put the numbers back onto that very personal view of diabetic foot infection that we have just heard, the worldwide projections are for there to be some 250 million diabetics by 2025, of whom all the evidence would suggest some two to five percent will develop foot ulceration annually, with a point prevalence of ulceration estimated at between four and ten percent depending on the study one looks at. Some 40-60 percent of all non-traumatic lower extremity amputations are in diabetics and the overwhelming majority are preceded by foot ulceration.

[Slide]

When we look at the socioeconomic importance of that, we see that foot problems account for the largest number of bed days used by diabetic persons; that their average length of stay is some 30-40 days, which is considerably longer than diabetic patients who do not have foot ulceration; and that over three-quarters of the over 75 year olds in the U.S.A. who have amputation for the foot ulceration do not return to independent living. Quite apart from the unpleasantness of that from a personal point of view, the costs to themselves or society are enormous.

[Slide]

It is not, therefore, surprising that a number of studies have suggested that it may well be cheaper to save a limb than to amputate it. Although it is at some distance, you can see the broad figures there--but they are on the handout--and the figures highlighted in yellow are from the U.S. Those are U.S. specific studies. But the general theme of this is the same around the world, some 7,000 to 10,000 U.S. dollars to heal an ulcer, and considerably more to deal with the consequences of removing the limb the ulcers

are formed on. That long-term cost analysis, carried out in Sweden by Apelqvist, shows you that the primary healing at a three-year endpoint is between $16,000 and $26,700 in patients, the difference depending upon the level of ischemia, whereas healing with amputation is between $43,000 and $63,000, the differences depending upon minor versus major amputation.

[Slide]

So, infection has a key role in this area. It is known to be a major event on the road, as it were, to amputation. It does that because it contributes to soft tissue loss, to delayed wound healing. It is a threat to foot biomechanics. If it compromises the issues and the bones enough, it is a cause of acute or chronic systemic effects. Any of those may ultimately end up being a good reason to remove a limb rather than to keep it on.

[Slide]

The clinical spectrum is broad and confusing. I have chosen to split it into those conditions with intact soft tissues and include a small number of primary muscular or skeletal infections and those that really complicate an obvious breach in the integument, either a

paronychia at the site of a nail or, more usually, an infected ulcer, cellulitis and then the formation of more complex forms of soft tissue infection and, of course, ultimately bone infection.

So, there are may different manifestations but I am going to suggest that perhaps the ones that we are really the most interested in that, if you like, constitute the diabetic foot syndrome and the infectious end of that, are those that complicate ulceration.

[Slide]

So, we then move to this difficult area of how we define a diabetic foot infection, and there are a number of possibilities here. In fact, I spoke with Ben Lipsky who, as many of you will know, has worked extensively on this subject in Seattle but who couldn't be here today.

Here are a couple of possible definitions that one can debate. The first would be the broadest possible view, which is that a diabetic foot infection is a foot infection in a diabetic. In other words, any infection as defined by the International Consensus or some other consensus process that involves the foot--and I think we have

to call that the structure below the malleoli--in a person with diabetes, for which there are formal definitions.

But there is a more specific version of that, if you like, where we would include the necessity for the infection to have originated in some injury to the skin that might be chronic or acute and that might be complicated by neuropathy or ischemia, or both.

[Slide]

That I think is an area that is clearly open to debate. One can justify that. It starts there by saying that neuropathy is undoubtedly the dominant cause of skin breaches in the feet of people with diabetes; that the clinical features of the majority of infections that we deal with in this context support a contiguous focus model. So, the ulcer is evidently the portal of entry of the infection and the infected structures are contiguous to the ulceration.

The presence of ischemia is known to have a major bearing on the outcome of infection, and it is absolutely clear that effective foot care services have a major impact on reducing amputation rates, at least in the initial stages where one is

able to catch large numbers of people who can be managed for their neuropathy correctly to prevent episodes of further ulceration, and who can be spared precipitate amputation when more conservative treatments can be effective. It does have to be conceded that there is no evidence comparing outcomes one way or another in the so-called non-neuropathic, non-ischemic patients but perhaps we might actually more accurately call pre-neuropathic and pre-ischemic diabetic persons compared to those without diabetes.

What am I saying there? The question really is if you don't have neuropathy and you don't have ischemia and you get a foot infection, are your outcomes worse than for someone who doesn't have a diagnosis of diabetes? And, I am not sure we know the answer to that.

[Slide]

This picture is really put up just to illustrate some of those problems in definition. Does this person have a diabetic foot infection? They have an area of ulceration above the malleoli and clearly have numerous soft tissue changes related to their diabetes. Although you can't see it very well here, they do in fact have an ulcer

that looks uninfected on the end of the hallux. But I think I would suggest that is not a diabetic foot infection in terms of what one would be wanting to study even if we thought the cellulitis there is originating from that ulcer.

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So, how do we diagnose diabetic foot infection? This is a big problem. Just a quick reminder for those not thinking constantly about this, infection describes the multiplication and invasion of tissues, usually associated with a host response, and this is distinct from the inevitable colonization of either normal skin or an ulcer with bacteria that may not be causing harm in a discernible way. That is also distinct from contamination, which is more of a problem for those trying to make a diagnosis from a sample that should normally have no organisms present.

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So, the diagnosis of infection really has remained a clinical one. I realize this is a problem potentially for the committee needing very specific definitions of infection. It has generally been made on the basis of systemic signs or symptoms of infection, local signs and symptoms

of infection and, clearly, there are some things that would alert one to that possibility such as gangrene or necrosis or very fetid odor.

Laboratory diagnosis of infection is, by definition, nonspecific unless it is a positive blood culture. The sensitivity in diabetic persons has been shown to be low in a number of studies.

The role of imaging I think is more in identifying the anatomic nature of infection rather than the presence or absence of it. So, it is more about identifying where there are structures that probably need surgery, rather than saying this is an infection.

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We are left with a number of controversies if we are using clinical diagnosis, particularly how to diagnose infection in the context of some of these confounders that diabetic patients also frequently develop--acute Charcot changes, gout, other common co-morbidities producing inflammation of the skin.

We are left also uncertain when ischemia can significantly confound the inflammatory response so that individuals might have infection but with false-negative signs of it. That, I

think, again is a debatable matter but one that people certainly worry about at times.

We are left with the question as to whether clinical criteria really allow us to reliably distinguish an infected from an uninfected ulcer.

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At the microbiological level, I have already explained that because of colonization of ulcers there is a real issue about how one makes a microbiological diagnosis of infection. It is really on that basis that I think many of us in the field would say we are not able to diagnose these infections by their microbiology. There are, of course, some exceptions to that statement. The culture of pus taken from an obvious abscess or a positive culture from what should be a sterile site taken in a reliable way, preferably through a non-infected field, is clearly going to be diagnostic. So, a bone biopsy that yields a Staph. aureus that has been taken through uninfected skin is going to be a truly diagnostic microbiology result.

But a much more common scenario is what we do with cultures taken from ulcers or from necrotic

tissue that is at the base of an ulcer but may have been ultimately contiguous with the outside world. Then, this intermediate difficult area is probably what we face most of the time with relatively expert practice. That is to say, someone has done a debridement of an open lesion and then taken some cultures of the material, the base of it, and that is what we would consider the most reliable but that still is potentially confounded by the flora of the more superficial parts of the ulcer.

[Slide]

The recommendations that have emerged through the International Consensus process and the IDSA Clinical Practice Committee take account of previous studies that have shown a poor relationship between superficial swabs and deep microbiology. This is from cases particularly with osteomyelitis but also other deep infection. Therefore, the recommendations are that the ulcer should be debrided in order to expose essentially viable but infected tissue at the base of the ulcer. If pus is present, it can be aspirated and preferably some form of tissue sample is taken from that ulcer with a curette or scraped with a scalpel blade and that tissue is processed rather than

using swabs.

Swab cultures are generally discouraged in the guidance, although that has been an area of some controversy and there are certainly some who would argue that swabs taken from the base of the debrided ulcer may be as close and as accurate as tissue samples that have been taken from slightly deeper.

There is a question that emerges from a number of the clinical trials and antibiotics already done as to whether all the microorganisms that have been isolated from these more reliable samples actually need to be treated. There is certainly a school of thought that suggests that maybe some of what we would definitely see as being important and pathogenic might actually be in some way fellow travelers with more virulent organisms like Staph. aureus. This doesn't get away from the fact that there are some cases where enterococci or coagulase negative staphylococci are the sole pathogen isolated, particularly from cases of osteomyelitis.

There is a question that is left also as to whether quantitative microbiological approaches can do any better than clinical judgment in

diagnosing actual or incipient infection.

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To understand the basis of this, I think it is worth a quick diversion into laboratory science and what we now understand about the pathogenesis of staphylococcal infections, given that Staph. aureus is one of the dominant pathogens in this condition.

If we look at the course of an infection over time from initial inoculum, we can see that organisms move out of lag phase and start to proliferate in logarithmic phase before they run out of nutrients and flatten off into this post-exponential phase. We know that Staph. aureus is an organism formidably armed with adhesive structures on the surface of its cell wall and with a number of toxins, and we know that initially organisms tend not to be expressing toxins but to be expressing adhesins. As they move into logarithmic growth, the phenomenon of quorum sensing kicks in, and this is a process by which organisms are releasing certain substances that are able to act as density-dependent triggers to gene expression. In the case of Staph. aureus, it is clear that this is a cyclic octapeptide and as the

amounts of this material build up the action of a gene NSHGR is triggered, and this results in the global expression of a number of different toxin genes.

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So, the organism moves from being in a sense non-toxigenic to one that is producing large numbers of toxins. We might see this as a mechanism for breaking down tissue and moving out into other areas where nutrients are no longer limiting. This phenomenon probably also operates in terms of the maturation of some of the adhesive forms of growth that are seen in the form of biofilms. That may be of more importance in osteomyelitis than in other contexts.

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That has led a number to suggest that in the context of the infected or uninfected ulcer the density of organisms present might be critical in triggering the moment when infection is about to happen or can be defined as just beginning. There is some evidence in acute wounds and burns that density of organisms greater than 105/g is a crucial transition point between infection and colonization. The evidence for that in chronic

wounds in the diabetic foot I think is less clear, and there is certainly alternative evidence one can cite, for example, clear evidence of inhibition between other species of staphylococci and Staph. aureus that this quorum sensing can be in some way down-modulated, that is to say one species of bacteria can affect the signals that another one is using to trigger its own behavior. That might mean that high loads of pathogens could, in fact, be tolerated in a mixed wound flora because some of the other bacteria are trying to effectively hold the staph. in check.

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So, there is a lot we don't know. Where has expert opinion got to in this area?

[Slide]

I am going to refer very briefly to clinical guidelines. I have already mentioned that there is now an International Consensus on diagnosing and treating the infected diabetic foot. This is in the public domain via CD ROM which is purchasable from a website but I think will shortly be published as well. There are also clinical practice guidelines coming out by the IDSA, which are probably being finalized this year and I guess

will be published either late this year or, more likely, early next year.

These have been both interdisciplinary and international expert panels, with clinical representation both from academia and government health services. They worked on a consensus basis, and what has been striking is that the recommendations are really not graded for their level of evidence because of problems in the overall quality of the studies and in the definitions that have been used. So, if you like, this is a group of experts but nobody pretends that the last word is here in terms of the quality of the evidence.

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The approach to infection that these panels have adopted is that in view of the varied clinical spectrum simplicity is what is required, and this needs to begin with assessments of the patient, the limb for ischemia, the foot for biomechanics and then the ulcer for its depth, its size and the presence of infection. Infection is assessed in relation to its severity, mainly in terms of impact on the host and the limb, and really put into three very broad categories, mild

infections, moderate infections that can be summarized as limb threatening, and severe infections that are immediately life threatening.

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You can see here the kinds of thinking that has gone into this. Mild infections are characterized by a small amount of erythema but clinical evidence of infection in an ulcer. They are usually monomicrobial, mainly with aerobic gram-positive cocci.

Moderate infections have more spreading erythema or evidence of involvement of deeper tissues including bone and joint. Moderate can be mono or polymicrobial.

Severe infections are really defined specifically by the presence of systemic symptoms. These are known to be relatively muted in diabetic patients and, therefore, the presence of them is considered to be evidence of potentially life-threatening conditions such as septicemia or fasciitis. The ulceration is often deeper and these are often polymicrobial infections.

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In terms of duration, there really is not good data on this but there have been a number of

clinical studies using those kinds of classifications already that suggest pretty clearly that you can treat mild infections for one to two weeks of oral therapy. You can probably treat them with topical therapies as well. I know that may not be an area of where the committee wants to go today.

Moderate infections can be treated for up to four weeks unless there is osteomyelitis present where it is generally considered wise to treat for longer.

Severe infections are usually going to require surgery, in fact, which is probably part of the reason it is still not necessary to treat them for more than about four weeks. It is just that they need more doing.

For osteomyelitis, the expert consensus view is that a lot depends on what you do. If you are taking all the bone away that is involved in the infection and you are doing that through normal soft tissue, then really there is nothing left to treat and a long duration of antibiotic treatment is not necessary.

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Bony ablation with no residual infected

soft tissue can be treated from the basis of a soft tissue infection. Whereas once you are leaving behind parts of the bone involved in infection, it is really necessary to decide where there is dead and infected bone left and that really helps set the duration of therapy needed.

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What about classifications--in my last remaining minute? The consensus process came up with a classification scheme called PEDIS, the Latin word for foot. This is intended to be a specific rather than sensitive scheme. It should allow what we want, that is to say, multicenter studies and categorization of case mix.

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To quickly take you through it, perfusion is given three grades, in line with the Trans-Atlantic Inter-Society Consensus. This is people who study peripheral vascular disease. Grade I is apparently normal. There is no nought because you can't be sure something is absent. Grade II is noon-critical ischemia; III is critical. These are rigorously defined in the guidance. E is extent of the ulcer in square centimeters, and suggested studies could report

ulcer size in quartiles to get an idea of the spread there. D is the depth which follows very closely the University of Texas system of making a transition between bone and joint and other subcutaneous tissues. Fir infection I will show you the grades very quickly in a minute. Sensation is either the presence or absence of protective sensation.

In fact, if the depth was given four grades so that grade I was no ulceration, one would have a catch-all for classifying all diabetic feet, but this was a research classification scheme for ulcers so it has to begin with ulceration.

[Slide]

What are they very quickly, and you will see some of the problems? There is a clinically uninfected ulcer but obviously one can see from looking at that the kinds of problems frequently arising. Infection involving the skin and subcutaneous tissue would be a grade II infection. This has, as before, the 0.5-2 cm cutoff for its erythema, at least two of these other features of infection, and no more probably cause of the inflammatory response.

[Slide]

Just to show you the kinds of problems on has with using this is that this would be a moderate infection. Sorry, I got myself in a muddle because I am rushing. That is the mild infection with a 2 cm radius of erythema.

[Slide]

The difficult one I think is the grade III because it encompasses such a wide range of infections, deep sort tissue, or bone, or joint, but is specified as having no systemic inflammatory response.

[Slide]

So, this case with a probe going into a joint and obvious infection of the whole of that toe would be moderate. So would the case on the left with penetration into the joint, but also the case on the right with very substantial Charcot infection in the mid-foot. Even in that case, with a lot of gangrene and obvious gross infection, if the patient remains systemically well, would be categorized as moderate with these scheme.

[Slide]

Finally a grade IV infection would be one that we would otherwise call severe, with a systemic inflammatory response, rigorously defined

here. So, what makes that a grade IV infection is not the appearance of the foot but the appearance of the whole patient.

[Slide]

Where are we left? We really do need to finalize and agree on how to use these more robust definitions and classification schemes. Almost any scheme that everyone uses will probably be better than having no scheme. The role of antimicrobials in uninfected ulcers and in wound healing after infection needs to be sorted out. Duration of treatment and the role of surgery in osteomyelitis and the cost effectiveness of limb salvage in these very much more complex cases that many of us are now seeing. So, really a lot does need to be done.

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In conclusion, while I think there has been some progress in general understanding and the existence of these consensuses is I think major progress. There are some difficulties that we have to solve.

I think that that PEDIS classification might actually help us considerably and, certainly, further consensus definitions, for example of osteomyelitis, would be helpful.

It is worth noting that some of these changes in practice, assuming that not all osteomyelitis needs many, many weeks of antibiotics, might be useful for allowing some cases, depending on their surgical management, to be included in cSSSI trials.

[Slide]

I would like to conclude by acknowledging Ben Lipsky from Seattle, Carl Norden whom you all know, and the drivers of the International Consensus process who have done a tremendous job, and my own clinical colleagues in Oxford. Thank you.

DR. LEGGETT: Thank you for that whirlwind tour. The next speaker is Dr. Norden.

Clinical Trials Consideration in DM Foot Infections

DR. NORDEN: Thanks very much, Jim. It is a pleasure to be here. It is an honor to have been invited by Dr. Soreth, and it is nice to be back at a committee where I spent four of the most challenging and I think stimulating years in terms of my academic career.

What I am going to try and do today is to talk about potential guidelines for clinical trials of diabetic foot infection. I think Tony has given

a very nice overview and background. My talk is going to be based primarily on my own experience, as well as a large clinical trial that we recently conducted with the help of Ben Lipsky from Seattle, whose name you have heard a couple of times already.

I am going to present ideas which are designed to elicit discussion and, obviously, not final ideas in any sense of the word, and to take some positions for the sake of argument so that the committee can debate them and shoot at them. The guidelines I will talk about are for systemic antimicrobial agents, not for topical antimicrobial agents. Then there will be a few talks from the FDA to follow which will go into more detail.

I think the two major areas that I would like to raise as issues as I go through the talk for you to consider are, one, the use of adjunctive therapy and how do you evaluate the success of antimicrobial agents and, two, osteomyelitis--do we include, exclude or simply treat these patients as a separate group?

[Slide]

We have guidelines for complicated skin and soft tissue infection. Why do we need separate

guidelines for diabetic foot infection, or do we need them? I think we do, and I think that patients that we enroll in trials of diabetic foot infection differ from the other patients in several ways, first of all, the risk factors which are vascular, neuropathic and diabetes itself and, secondly, the use of adjunctive therapy which, in the management of a diabetic patient with a foot infection, is major and part of standard care, and that is debridement and surgery, wound care itself or wound dressings and off-loading which is a term, by the way, I knew nothing about until I got involved with Ben Lipsky and Tony Berendt.

[Slide]

What are the desirable features of a study? Well, I think you want to optimize enrollment. The most recent trial we did enrolled 370 patients, which is a large number. I think it should include most types of diabetic foot infections. It should allow inpatient or outpatient therapy. It should allow intravenous or oral therapy if the agents are capable of doing this. And, it should allow additional antibiotic agents for organisms which are resistant to the study drug or comparator that are being tested.

[Slide]

Inclusion criteria--I am going to go through this and pause when we come to those things I think are real issues. Some of these are obvious and standard, over age 18; informed consent. The patients should obviously have diabetes mellitus by ADA criteria; and they should have an infected lesion of the lower extremity. You can see from the list that I have put here that these are much the same as Tony had, except that I have left osteomyelitis off and that is for purposes of discussion.

Clearly, we need to define an infected lesion and Tony has gone through that. The PEDIS classification I think is very helpful. I would only say that I second what he said, I think it is a clinical diagnosis, not a microbiologic diagnosis. Microbiology is important but I don't think you make the diagnosis of diabetic foot infection on the basis of the culture.

[Slide]

The infected lesion can require extensive debridement or surgery, but for purposes of a study it should not require complete resection or amputation. If that takes place, then clearly you

can't evaluate the effect of the antimicrobial agent.

It can be open or closed. It can be anywhere on the foot. You can have multiple lesions but you ought to select on as the study lesion, if you will. I believe it can have been treated with potentially effective antibiotics before the study, but only for 72 hours or less. Now, there is no magic about that. It could be 48; it could probably be 24; and it might be longer. I don't think we have any data as to how quickly antimicrobial treatment renders an infectious lesion no longer infectious or how long it takes to eradicate the organisms but, at least in my experience, you can go for at least three days without clearing a diabetic foot infection of bacteria.

[Slide]

The exclusion criteria--certain local conditions of the lower extremity; critical ischemia which we will come back to in a moment; the expectation that the entire infection will be resected or amputated; more than 72 hours of an agent active against the pathogen; an infected device that can or will not be removed; a patient

who required additional non-study antibiotics for any reason other than an organism resistant to the study drug; and I think the presence of extensive either dry or wet gangrene.

[Slide]

For ischemia, I think we can define this reasonably well. Critical ischemia would be defined as absence of palpable posterior tibial or dorsalis pedis pulses; absent or abnormal Doppler wave forms plus a toe blood pressure less than 4 mm Hg.

Can you enroll patients who have critical ischemia? Well, we know it affects healing. We know it affects outcome of infection. I think if you have a vascular surgeon who feels you can include this patient in the trial, you could but I think it is simpler if you use these criteria and say no.

[Slide]

Now, what about osteomyelitis? Tony touched upon this and Dr. Alivisatos is going to talk about it a bit more. But it occurs in more than about a quarter of diabetic foot infections. It can be difficult to diagnose. It is difficult to define. It can certainly be more difficult to

eradicate once osteo is present. It requires more prolonged antimicrobial therapy, and there really is no good clinical data on the required duration. Tony has suggested some good guidelines I think, but trying to get a group of clinicians or researchers to agree that you have resected bone back to blood bone or live bone, analysis and so on, is very difficult. So, to say that depending on the extent of surgery your optimal duration is such-and-such I think might work well with a small group of research scientists but won't work well in a clinical trial. The last point is obvious, that osteo requires surgical debridement or resection.

[Slide]

So, how do you diagnose osteo in clinical trials? Some of it easy, or at least we think it is easy. If there is an open wound and the bone is visible I think most people would agree that osteo is present. If there is an open wound and the probe to bone test is done and is positive, most people agree that that is osteo, although we will come back to that and others will talk about how that is based on one clinical study, done by Grayson and Kartchmer, in a group that had a high prior probability of osteo. Although the test is

very good, it has not really been validated in other studies.

More commonly, if you don't have an open wound and you can't see the bone or you probe it, we rely on either baseline x-ray or MRI which are read as active on osteomyelitis. I think you need to define the criteria for osteomyelitis very critically, and it should be standardized in the protocol. This is hard to do, and one of the things no one has looked at is inter-observer variability. If you gave the same x-ray or MRI to two or three radiologists, would they read it similarly? I have some experience with this as a fellow with urinary track infections and giving x-rays for pyelonephritis to a group of radiologists and the discrepancies where somewhat surprising to me at the time. They are no longer surprising I think. Nuclear scan is not sufficient to exclude osteo.

[Slide]

So, in order to set up criteria I thought, this being Washington, I would take one moment and just give you all a quote that I think most of you remember from the Supreme Court: I shall not today attempt to define the kinds of material--and

Justice Stewart was talking about pornography--but I know it when I see it. I think too often most of us are convinced we know osteo when we see it. For a clinical trial that doesn't work and you have to have accurate definitions.

[Slide]

So, what kind of studies would one do in a clinical trial? Plain x-ray; probe to bone for open lesions; culture and sensitivity testing; wound description and I think photography, if you could get it as a standardized thing would be very helpful; a wound score by a standard protocol; and a vascular evaluation. I am just going to talk about a few of these briefly.

[Slide]

Wound cultures--Tony talked about that already a little bit. We get them from all patients. They should be set up for aerobic and anaerobic culture. I think it is simplest to say that swab specimens are not acceptable. However, they are the norm in clinical practice and it is true that there was one small study where patients who had ulcers that were debrided and then had swabs versus tissue biopsy taken and there was great comparability in these two. However, in most

patients the swabs are taken directly from the basement ulcer and they are not taken from a debrided lesion, and I think it is simpler if you are establishing a protocol to say you can't do swabs.

Having said that, I think you then have to deal with the people who are doing the study. We would prefer to see curettage of the wound base or tissue specimens obtained at the bedside or the OR, or aspiration for secretions or cellulitis.

[Slide]

Wound scoring systems--Dr. Lipsky has put out one designed to give an objective wound score. It basically includes quantifying the wound parameters, peripheral pulses, wound measurements and the wound infection score itself.

[Slide]

Probe to bone--I am just going to say a few words about this. In one study, an excellent study I should add, by Grayson, et al., published in 1995, 76 patients at, again, a high prior probability of osteo; 66 percent sensitivity; 85 percent specificity; a very high positive predictive value and a mediocre negative predictive value. So, they concluded that if the test was

positive the patient had osteo. They compared this to bone biopsy as the gold standard, which I think was appropriate.

The technique of doing this is very important. You have to use a metal probe. You have to follow the technique that was described in the article. Too many people, for example, use the reverse end of a Q-tip or swab and put it into the lesion and try to feel for bone, and you can't get the same sensation which is what you want to feel, a gritty, metal feel as the probe hits the bone. So, you have to do it the way it is described. I think it is a good test, however.

[Slide]

What would we write for guidelines for treatment? For drug versus comparator, the comparator should be the gold standard. There are only three drugs right now that are approved for diabetic foot infection, piperacillin tazobactam, which does not have an oral form; trovafloxacin, which is no longer available or not widely used; and linezolid, which was just approved.

In the treatment you can add other agents for activity against organisms not covered by the study drug. So, if your drug has spectrum, for

example, only against gram-positives you want to cover for gram-negatives. Seven to 21 days of antibiotics I think would be allowed, and 14 days is the usual duration in most clinical trials.

[Slide]

Adjunctive therapy includes debridement and surgery; dressing changes; off-loading, and not allowed would be topical antibiotics, antiseptics or other antimicrobial agents such as Betadine.

I think the issue that comes up here, which is the second issue I wanted to bring up, is one that the FDA has raised, and I think raised appropriately. If you have all of these top three adjunctive measures going on, how do you know what the antimicrobial agent is doing? Might the patient do just as well if they only got the adjunctive therapies?

So, one of the suggestions has been could you do a clinical trial of adjunctive therapy plus placebo versus adjunctive therapy plus the antimicrobial agent in question? I would say I don't think you can. I think it would be very difficult to get any group of infectious disease people who would be willing--or diabetologists--who would be willing to treat infected lesions without

using antimicrobial agents unless they were absolutely the mildest of infections. So, I don't think you can do that, and I think you just have to assume in a clinical trial for diabetic foot infection that the adjunctive therapies are part of the standard of care. After all, in a sense we do this with intra-abdominal infections in clinical trials, everybody gets surgery as well as antimicrobial agents and we don't ask the question what is the role of surgery versus the role of the antimicrobial agents.

[Slide]

I am going to skip through most of these. Wound dressing--there are lots of types. None has been proven best. I think the bottom line is that the more you can standardize these adjunctive measures of therapy, the better but it is difficult to do in practical terms in clinical settings where institution A believes in one type of wound dressing and institution B in another, and there is no data to prove that one is better than the other.

[Slide]

The same holds for off-loading, which I have learned is invaluable in terms of curing infection. Many devices are used. None has been

proven best. Again, although we would like to standardize it in clinical trials, it can be very difficult to do.

[Slide]

I am almost at the end. In terms of efficacy evaluations, I believe that we should have a follow-up for test of cure at 14-21 days after the end of therapy. I think end of therapy evaluations add very little.

The clinical response to therapy is defined as resolution of pre-therapy clinical signs and symptoms of infection. In my belief, it does not include wound healing or lesion healing. Although they obviously move in parallel and obviously a wound that remains infected is unlikely to close, but the criterion should be the resolution of clinical sings and symptoms of infection. Final categories are cured, failed or indeterminate.

[Slide]

Surgical debridement is allowed during the trial and is considered part of standard care. Complete resection of the infected area would remove the patient from the trial.

[Slide]

The last slide, and I am very happy that we have at least two statisticians sitting at the table, how do you pick a sample size? I think most people would agree that 80 percent success rate for the comparator is reasonable. That obviously depends on what kind of patients you have in the trial and the severity of infection. A difference in cure rate of less than 10 percent would be considered equivalent. If we are trying to do trials of superiority, I think you need to decide what criterion you would use, and I don't really have a recommendation for that. I think you would like to be at least 10 percent better than the comparator but I think that is up to people designing the trial and the FDA.

I am going to stop at this point. Jim, I made it with two minutes to go, actually.

DR. LEGGETT: That will give us time for questions. Dr. Berendt, would you like to come up? Does anyone have a question for either of these two speakers?

DR. PATTERSON: Hyperbaric oxygen is being used as adjunctive therapy a lot these days. Would that be accepted as well?

DR. NORDEN: Well, I will answer that

first. I mean, it is being used. There is absolutely no data still to support it. It just complicates things immensely in terms of managing the patient and I would think I would not want to have it in a clinical trial.

DR. BERENDT: I know there are great enthusiasts about hyperbaric, and other people who don't have it available who are the unenthusiastic or don't know. All the views that I am aware of have still concluded that there is no real evidence for the role of hyperbaric and, therefore, I don't think we would know how to use it. The people who advocate its use would probably say it is about equivalent to an antibiotic in terms of what it adds so it probably should be considered in the same way as someone who elects to add another antibiotic to the trial and, therefore, that might not be allowed for those reasons.

DR. CROSS: Assuming that the vascular insufficiency doesn't impair the ability of the myeloid or white cells to enter the wound, what do we know now about the ability of diabetic white cells to produce pro-inflammatory cytokines which may affect the clinical appearance of the lesion?

DR. BERENDT: Carl very sensibly asked me

to do that. I am not sure I can give you a good answer to that question actually. There have been some studies done a long time ago on some of the more gross aspects of white cell behavior like chemotaxis, and so on, but I don't know whether there have been any systematic studies more recently so I would have to admit ignorance of that. Somebody in the room might know but I don't.

DR. LEGGETT: Dr. Berendt, would you have a single cut-off for when ischemia is enough? I think it was Carl who had an arbitrary 45 mL. I mean, I don't think it is an on/off phenomenon.

DR. BERENDT: No, it is not. That is difficult. The PEDIS scheme does set out absolutely specific criteria for ischemia. I can't quite quote them off the top of my head, but they are clearly laid down. I think I would agree with Carl that if critical ischemia persists during the trial, then you probably can't include the patient. You would have to make a decision about what to do if someone presents with critical ischemia and is successfully revascularized as to whether they can be enrolled or stay enrolled, as it were.

DR. LEGGETT: Don?

DR. PORETZ: One of the problems as I see

it is that in the diabetic foot you have a whole potpourri of physicians who are taking care of patients. You have general practitioners; you have general internists; you have infectious disease doctors; you have podiatrists; you have orthopedic surgeons; you have vascular surgeons and general surgeons, and plastic surgeons. So, you have at least seven or eight different disciplines. Any criteria I think is going to have to be agreed upon by all of these disciplines, which is really hard to do, but it seems to me if you don't do that you are not going to be able to have a reasonable system.

DR. NORDEN: I would agree with that, Don; I don't have any problem with that, and it is very hard to do it.

DR. PORETZ: The International Consensus was only diabetologists?

DR. NORDEN: No, it had others.

DR. BERENDT: The International Consensus does have representation from vascular surgeons, orthopedic surgeons, infectious disease specialists, surgical podiatrists as per in the States, as well as endocrinologists. So, that probably has a fairly broad grouping but whether

each of those people is then able to say there is an international consensus from their own specialty group that would feed into this particular version of the International Consensus is another matter. I mean, I think the consensus is there in a sense to be challenged and validated, and I agree with you, there is a huge number of people. That is probably why there are already so many guidances that deal with the general diabetic foot. So, you know, lot of different expert societies have their own guidance on diabetic foot in general.

DR. LEGGETT: If it is a follow-up, Don. Otherwise, if it is a new question, we have other people.

DR. PORETZ: Just quickly, it is just like the pneumonia guidelines. There are half a dozen pneumonia guidelines from various authorities, but maybe if it could be published in specialty journals and everyone agrees, that would be the best way to do it.

DR. LEGGETT: Dr. Armstrong?

DR. ARMSTRONG: As a follow-up on that, Dr. Berendt, you mentioned two definitions that you sort of proposed of diabetic foot infection. One was sort of general where it had a couple of

co-morbid factors associated with it. Of those, you were sort of non-committal. Which one would you prefer?

DR. BERENDT: Well, I think a lot of it comes down to this issue of sensitivity versus specificity really. The pre-meeting discussions I had with the FDA folk have helped me to understand that there is a special interest in having a very specific definition. If that is what you want, then I would go for the more specific version where, in fact, for example in your study which looked at the contributions of ischemia, depth and infection to amputation rates, I think if I have done the numbers right, over 90 percent of the cases in that study had ulceration with ischemia or neuropathy as part of it. So, I think if you exclude the people with intact skin you probably don't exclude all that many actually from the group you are interested in. But I think that is an area that people would want to debate because, you know, it all depends on whether you are taking a clinical view that a clinician seeing a patient with diabetes who comes into their room and has a foot infection would like to feel that the licensing of a drug and the guidance that has come through

covers that patient, and that is where the argument goes that from the clinical end you want a sensitive definition, whereas from the regulatory end, the research end, you want a specific definition.

DR. LEGGETT: Dr. Powers?

DR. POWERS: Dr. Berendt, I think that is exactly the point that we are worried about, the specificity of people getting enrolled into a trial. Because one of the things that Dr. Norden pointed out is--and this came up in the advisory committee back in 1999 regarding a topical drug called pexiganin, where the committee actually had this issue of did the people enrolled in this trial really have infections or not. In the pictures you showed, it seems that all these people have some degree of redness up around the lesion, some of which is chronic venostasis changes as well.

So, what I wanted to ask was could you and Dr. Norden give us an idea--many of these scales that you showed us say infection with whatever, and you gave us a pathophysiologic definition of what an infection is, and I think this gets back to Justice Potter's quote of we all know infection when we see it, but in terms of a protocol we would

need to put in specific definitions of what that means. Are these definitions specific enough in diabetic foot or even sensitive enough? Two-thirds of people aren't febrile. Leukocytosis may be absent. Are there some things, other than a diabetic with a break in the foot, such as new erythema that hasn't occurred in the last 48 hours; new drainage; some other things that would help us increase the specificity of diagnosis in these trials?

DR. BERENDT: I mean, you are right. It is definitely a problem. You could certainly add things like that I guess. I think that that PEDIS scheme at least makes it clear, you know, if a trial is reported according to the categories within it, then at least you are a bit clearer about what is going on. You could say, yes, as an improvement of that you want new things. And, there is some work done with other kinds of chronic wounds to suggest that there are some secondary characteristics that might be more useful than the classical definitions of infection which relate, as you have said, to sort of changes in drainage, or changes in smell, or changes in granulation tissue.

But I wonder if I put those things up as

my criteria you would be equally critical of that because that would imply someone who has already seen the foot and who was reporting the change. And, you know, is that any more reliable? So, I am not sure whether that would take us further forward, but I am sure that what we need are studies that use some of these sorts of frameworks that try and validate it. I am also sure that one of the things you can't use as validation is the natural history because nobody is going to say, well, I'm not sure; I think that is infected but I'll wait a few days for it to get a whole lot worse and then I'll know that it was. So, I think some of your concerns are, unfortunately, unanswerable actually and we will be stuck with clinical definitions unless it turns out that using quantitative micro or some other thing is better.

DR. POWERS: Could I ask a follow-up question, and that is the idea of looking at the PEDIS scale where you have grades I through IV for infection. I guess it gets us into a conundrum there with you saying we need to validate those going forward. However, what we would need in a clinical trial is an already validated scale. This comes up in many infectious diseases, the idea of

how does one actually qualify severity. Again, it goes back to what is severity? What we have looked at is trying to define severity for these guidances as something that tells us that those clinical characteristics portend a worse outcome regardless of treatment. So, that doesn't need a placebo arm. I would refer to the patient outcome research treatment studies for community-acquired pneumonia where people get treated but certain factors portend a worse outcome, anywhere from 0.1 to 30 percent mortality. Have any of these scales been validated in that way? I know Dr. Armstrong's has been for wounds, but how about for the infectious component of that?

DR. BERENDT: I think the answer is no. I mean, it is the deficiency of the process really. It comes back to whether an agreement to all use the same thing, even if it is flawed, is better than an agreement for everyone to keep thinking up their own better version that is sort of personalized and impossible to compare.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: I just wanted to ask Drs. Berendt and Norden, in the inclusion of this definition of a diabetic foot that you have,

whether it was threatening the limb or not threatening the limb, where would that fit in? Because that is somewhat the definition that I see bandied around in Mandell and other sources.

DR. NORDEN: That is a good question, Dr. Maxwell, but again, like most of the others, there really is no good definition. It is used in Mandell and in most infectious disease textbooks. I think, well, we know a limb-threatening infection when we see one. You know, the patient looks more toxic. The deeper the infection, the more undermining there is. The greater the extent of the infection is more limb threatening than not limb threatening. A small ulcer is probably not limb threatening by definition.

We tried to look at that in one clinical trial and really didn't find it very helpful. Maybe we didn't have precise enough measurements but that would be my impression, that it doesn't help a lot.

DR. LEGGETT: Dr. Wald?

DR. WALD: I have a question about the exclusion criteria for osteo. The statement was nuclear scan alone is not sufficient to exclude osteo. That means normal is not sufficient? I

guess the question I would ask is, is abnormal enough to include a patient because it seems to me that a lot of these patients might have some contiguous inflammation which really didn't necessarily represent bone infection.

DR. NORDEN: Yes, Ellen, I think the slide isn't very clear and the way I wrote it isn't very good. Actually, a negative scan is so rare that it probably makes osteo very unlikely, but it is so rare to see a negative scan. No, I think a positive scan of any kind, whether it is technetium or indium, does not establish a diagnosis of osteo.

DR. LEGGETT: One final question--I assume you two will be around later this afternoon during our discussion session? Okay.

DR. CROSS: I was wondering whether in any of the previous studies a return to function has been used as a measure of efficacy, given what we heard about how many people who have these infections may be incapacitated for prolonged periods of time?

DR. NORDEN: I can only speak to the linezolid trial and the answer is no. It is a good measure but there wasn't enough follow-up available and sometimes people didn't have--I will leave it

at that, no.

DR. LEGGETT: Thank you. The next speaker will be Dr. Sorbello to give us a talk about lessons learned from previous review of drugs for diabetic foot infection.

Lessons Learned from Previous Review of Drugs for Diabetic Foot Infection

DR. SORBELLO: Good afternoon.

[Slide]

The focus of my presentation today will be on issues that were identified from previous submissions to FDA related to drug development for diabetic foot infections.

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The way I am going to structure my approach to my presentation is really to make it more of a conceptual discussion of some important issues, which we have already heard a fair amount about but still are very critical issues in trying to evaluate clinical trials and clinical study results in relation to not only drug development but looking forward to trying to develop a guidance document for drug development for diabetic foot infections.

[Slide]

We have already heard some discussions about developing a definition of a diabetic foot infection so some of this will be repetitive, but there are just a couple of points that I do want to again bring to your attention.

First, looking at the issue of developing a definition of diabetic foot infection, as of yet there is still no generally accepted definition, and both a definition as well as a classification system for diabetic foot infections remain an area of controversy and discussion and an area of a considerable amount of work.

It is important to remember that foot infections in diabetics can be either ulcer or non-ulcer related and that statistically about 15 percent of diabetics are at risk to develop a chronic non-healing ulcer in their lifetime. But even amongst those who develop chronic non-healing ulcers not all are infected. It gets back to one of the prior discussion issues of how do you define and determine whether a chronic foot ulcer is actually actively infected.

Regarding clinical trials that have been submitted to the agency, many of them are submitted under the complicated skin and skin structure

infection guidance, and these are broad, large studies with a broad mix of different types of complicated skin infections, of which diabetic foot infections are one subgroup. These are usually supplemented with studies limited to diabetics with lower extremity infections to provide more specific data.

The eligibility criteria for many of these studies relate to either specific disease entities, such as cellulitis, paronychia, deep soft tissue infection; discrete clinical findings such as drainage, redness, warmth, swelling of the infected limb; and sometimes the presence or absence of a foot ulcer. Again, there is not any uniformly applied or clearly described definition of what a diabetic foot infection is or even what constitutes the different specific disease entities that are being studied.

[Slide]

There has been obviously discussion about making a clinical diagnosis of diabetic foot infections, and I just wanted to reiterate the point that diabetics do tend to have other problems that can affect their lower extremities which can produce signs and symptoms that may appear similar

to some of the changes that you may see in a lower extremity infection or may actually predispose to lower extremity infections. Certainly, diabetics can have significant developmental foot abnormalities, hammer toes, valgus deformities that, combined with sensory peripheral neuropathy and inability to appreciate and feel pain in their feet, they could develop into lower extremity ulcers and not be aware of them for considerable periods of time, that get colonized with bacteria and chronically and slowly smolder and become infected and become a more complicated infection.

Patients develop significant soft tissue changes from chronic lower extremity edema, stasis dermatitis, dependent redness, and they certainly are at risk for neuropathic joints, Charcot joints with advanced peripheral neuropathy. Certainly their vascular status is important because the significance of peripheral vascular disease in diabetics and the potential effect on wound healing becomes an important complicating factor in ability to get some of these infections to heal successfully.

[Slide]

With this slide I wanted to just show you

some data from a study which looked at diabetics with osteomyelitis of the foot. A long list of different features were evaluated to try to see if any of them, or any combination, would be good prognostic factors for those who had a good outcome versus those with a poor outcome, and poor outcome usually portended amputation.

As you can see from the list of features and the comparator percentages there, the only two findings that were statistically significant as far as prognosticating factors were the presence of swelling and the absence of necrosis in patients who had a good outcome.

As was alluded to earlier, findings such as temperature occurred in very few patients. I think overall about 17 percent of the population that were studied had fever and most of the others did not. Other findings, such as redness, drainage, warmth and presence of a foot ulcer were comparable in both studies and really were not good distinguishing characteristics. Again, it tends to underline that physical findings can certainly be of clinical value but they are of some limited value, especially with respect to not only looking at prognosticators for responsiveness to infection

but possibly also to even evaluating the severity of an infection.

[Slide]

I wanted to kind of use those concepts to look at a framework for defining a diabetic foot infection. We have obviously heard definitions for diabetic foot infections. What I thought I would do is basically just propose certain concepts to at least think about in developing a definition. There is obviously some overlap between defining and diagnosing diabetic foot infections but I think there is a need to do that.

I think first deciding about whether the presence or absence of some type of lead point, an open wound, a foot ulcer, or any type of break in the skin, is that really a necessary or should that be a necessary part of defining a diabetic foot infection in a clinical trial? Clinical findings themselves--I suspect probably a constellation of findings would probably be of more benefit than looking specifically at evidence of erythema or swelling or foot ulcer individually.

The anatomic location or site of infection probably would be important, not only defining it, as was mentioned earlier, to sites in the foot

distal to the malleoli line but also possibly the location within the foot as there are certain areas, such as the areas beneath the metatarsal heads, which are more prone to being sites of ulcer development.

I think depth of infection is a very key aspect here because, in many ways, diabetic foot infections are contiguous infections, that is, a high risk of spread and extent of infection from skin to soft tissue to the deeper structures and especially the distinguishing of skin soft tissue versus bone and joint infections is a critical one because bone and joint infections probably should be considered in separate studies because the pathophysiology is different; the ability of drugs to penetrate into bone is different. They involve different endpoints, different durations of treatment, etc.

I would also consider in the definition the issue of isolating pathogenic bacteria. This obviously would be more specific to a person who has an open wound or foot ulcer but, again, distinguishing not only that the bacteria are there but that you actually have pathogens as opposed to colonizers, and obtaining these cultures from what

would be considered an appropriately obtained specimen.

[Slide]

Classification systems is a second and, again, important consideration in developing a guidance document for diabetic foot infections. We have certainly heard important information about ways to classify diabetic foot infections but, in general, there have been two approaches. One has been to look at the severity of infection and the other have been approaches centered more on the status of the foot ulcer and the progression of the foot ulcer with disease.

To date, there is not a generally accepted classification system. They do differ in the criteria that is utilized, the complexity of the parameters that they are being assessed and, certainly, they would require some type of validation to be applied full-scale in a clinical trial.

[Slide]

To talk a little bit about the classification systems, the two main types of classification systems have been mentioned based on severity or either limb threatening or non-limb

threatening which basically, again is looking at extent of disease. Localized disease is not limb threatening, which does not have clinical signs and symptoms of sepsis, without evidence of any osteomyelitis, with no or very minimal vascular compromise, as opposed to limb-threatening infections which are more extensive, high risk of osteo, usually associated with ischemia or gangrene, usually aggressive deep infections. Mild, moderate and severe basically can be thought of as graded progression from superficial to deep infections, from minimal to no ischemia to progressive ischemia, from no osteomyelitis to evidence of osteomyelitis and, obviously, from no systemic symptoms to persons who appear clinically septic.

[Slide]

I just wanted to list some of the classification systems that are in the literature. These include the Wagner system, which is one of the earliest; University of Texas system; the S(AD) SAD, which stands for size, area depth, sepsis arteriopathy and denervation and simple staging; and we have heard today about the PEDIS system.

Again, if anything, it is just to point

out that there remains controversy, debate about how to think about classifying these infections; what would be the appropriate parameters to include in a classification; and how to use these then in the context of a clinical study and clinical trial.

[Slide]

Again, kind of as we did we definition, just to consider some concepts as a framework to try to classify diabetic foot infections, I think as we have already heard discussions today earlier, standardized definitions are needed so that investigators in the studies are really looking and evaluating these infections with some uniformity. The clinical disease entities that would be studied should be delineated. There should be some kind of a uniform consideration of how to approach evaluating these patients for ischemia and neuropathy and what would be considered significant or profound ischemia versus lesser grades, and the same with neuropathy.

Classification systems that might correlate with the extent and natural history and the prognosis of the infection would be important because certainly, especially in infections that are treated for longer periods of time, you might

be able to correlate the status of the infection from baseline to points later on and end of therapy and follow-up where patients had a course of therapy, and it would be another way to objectify what has been happening in response to treatment.

Again, distinguishing skin and soft tissue from bone and joint infections is an important consideration, as I already mentioned, and I think in many ways bone and joint infections probably should be examined in a separate trial because of all the fundamental differences from skin and soft tissue.

Lastly, as has been described, a classification system probably would need validation before being adopted.

[Slide]

Moving on to some other concepts within the development of a guidance, another one would be characterization of the study population. This is a very critical consideration because there are a number of demographic and co-morbid factors that need to be assessed on patients who are enrolled. Baseline assessments need to be performed and clinical diagnoses need to be developed for the patient depending on the extent of their disease.

[Slide]

I have listed here some demographic parameters that should be assessed in enrolled subjects, and these would include age, gender, race, weight, country of origin for an international study or the study center or site, and co-morbid factors, whether they have insulin dependent or non-insulin dependent diabetes, evidence of peripheral neuropathy, peripheral vascular disease or renal insufficiency which may be complications from the underlying diabetes, any history of osteomyelitis affecting the limb or any history of lower extremity surgery, be it podiatric, orthopedic or vascular which, again, may involve treatment of prior osteomyelitis or revascularization procedure to improve blood flow.

[Slide]

Baseline assessments should include both laboratory as well as various other types of imaging procedures. Labs should include routine hematology and chemistry and hemoglobin A1C to give some idea of recent glycemic control and, obviously, appropriate cultures, either wound, tissue and/or blood. Radiologic imaging would be important in evaluation for concomitant

osteomyelitis, and this will be discussed later on this afternoon. Neurovascular evaluation, as was already mentioned, and, lastly, assessment of the wound or the ulcer size or dimensions either through measurements or wound score or as appropriate.

[Slide]

Clinical diagnoses in diabetes really reflect on the heterogeneity of the disease. This slide illustrates for you just a little bit about the complexity of a diabetic population with foot infections. The small box on the left-hand side which says "CRF tabulation" is basically seven diagnoses utilized in one study to categorize patients with diabetic foot infections. These were basically extracted from the case report form.

On the right-hand side is just the kind of breadth of types and complexity of infection from the FDA analysis, really to show you that patients with diabetic foot infections tend to have multiple concomitant processes going. They have an infected ulcer. They have cellulitis. They have an associated septic arthritis and/or osteomyelitis. So, their infections tend to be complex. There is a greater risk of depth and extent of infection

which tends to be complicated. Trying to identify those with bone or joint infection becomes important, again, because they may well need to be assessed in a separate trial, in a separate study with parameters, etc., that are more appropriate for those types of infections.

[Slide]

I wanted to spend a little bit of time on adjunctive treatments and this was mentioned previously. Adjunctive treatments are, in many ways, the standard of care in the treatment of patients with diabetic foot infections. These can involve a multitude of different types of interventions, from off-loading to reduce edema, from dressing changes, other types of local wound care, medical therapy including antibiotics, putting patients on insulin coverage, etc. to get blood sugars under control, and various surgical interventions which can range from debridement to revascularization of the lower extremity to improve blood flow.

So, there are a number of different interventions that are being done and it is important within the protocol to try to specify what treatment should or should not be permitted

because, most importantly, they do augment wound healing and resolution of infection which is a very important response in all this. But there are some other effects of these adjunctive treatments that need to be considered in analyzing efficacy data. In particular, whether or not they are used equally in all the subjects in both arms of a comparator trial for example, and whether adjunctive treatments may have a beneficial effect as far as clinical success and outcome, possibly making dissimilar drugs appear more similar or more indistinguishable.

[Slide]

This is data which is basically an FDA analysis of a submission of a drug for a diabetic foot infection indication where the assessment was to look at surgical debridement as adjunctive treatment, and if there was any relation of that to the clinical outcomes observed.

The debridements were broken down by those which had no debridement; those which had one to two; and those which had three or more. As you can see, it was broken out by the number of patients who received study drug or comparator and their outcome as far as cure at end of therapy.

The main point here is that although the numbers are small, as the number of debridements increased the overall trend was a trend of improvement in the cure rate. Increasing number of debridements tend to be associated with an improvement in the cure rate and the cure percentage. These percentages were not statistically significant but certainly it is an important observation which may underscore that adjunctive treatments may be having a contributory effect to the clinical success that is seen, and they probably should be considered in efficacy analysis.

[Slide]

I want to finish up with just a couple of concepts on microbiologic considerations. This will be discussed later on this afternoon but, again, there are some important points. One is the need to identify pathogens amongst polymicrobial infections and distinguish them from colonizers; two, the need to standardize methodology as far as what are acceptable and appropriate specimens, in particular the issue about swabs; and microbiologic outcomes.

This really underscores the point that

many times diabetic foot infections are clinically driven and that patients who have pre-therapy wounds which then heal during the course of therapy, obviously, don't have an accessible site for reculture at end of therapy and their outcomes are presumed or extracted based upon the clinical response.

[Slide]

In summary, issues to consider for guidance development for diabetic foot infections: Number one, definitions and classifications of diabetic foot infections and diabetic foot ulcers; appropriate characterization of the study population; recognition that the primary focus tends to be on clinical outcome; the need for standardized microbiologic methodology; to consider the effect of adjunctive treatments on clinical outcome; and drug development for bone and joint infections probably should be addressed with a separate clinical trial, possibly with a separate guidance due to their differences in pathophysiology and treatment. Thank you.

DR. LEGGETT: Thank you. Unless there are any really specific questions we will move on. The next speaker will be Dr. Albert Sheldon, who is

going to talk to us about microbiologic diagnosis of diabetic foot infections.

Microbiologic Diagnosis of Diabetic Foot Infections

DR. SHELDON: Good afternoon, ladies and gentlemen. I am absolutely delighted to be here to talk to you about the microbiology of diagnosis of diabetic foot infections. I can tell you that as a microbiologist, this is one of the more difficult indications that we have to address.

[Slide]

During this discussion I will focus on the controversies that exist in the acquisition and interpretation of microbiological samples obtained from decubitus ulcers and, hopefully, you will find that this presentation will complement those that have come before me to help you answer the questions that you are going to have to address this afternoon.

[Slide]

Before I proceed, I think what I would like to do is to give you some insight into our thinking regarding the guidance that has been created within the agency to develop drugs for the treatment of foot infections in diabetic patients. These include that all patients should have

pre-therapy cultures. We would like to see gram stains and cultures obtained from acceptable sources using acceptable methods. These methods will include leading edge needle aspiration, soft tissue and joint aspirations, bone biopsy and/or surgical debridement. The microorganisms isolated should be assessed as true pathogens, colonizers or contaminants. Finally, only microorganisms designated as true pathogens should be considered in determining microbiological evaluability of enrolled subjects.

[Slide]

In order to understand the microbiology of decubitus ulcers, I think we need to understand the factors that influence the risk of infection. These were actually articulated by Altemeire in 1965, where he stated that the risk of wound infection varies according to the following equation, that is, the dose of the bacterial contamination involved, the virulence of those organisms and the resistance of the host to that infection.

[Slide]

The host factors that influence infection rates include diversity and abundance of

microorganisms present in the wound, and include the wound type, depth, location and quality. They include the presence of nonviable exogenous contamination; peripheral blood insufficiency and the immune competence of the host, as already stated.

[Slide]

In doing the microbiology of decubitus ulcers, the "Manual of Clinical Microbiology," published by the American Society of Microbiology, in obtaining the use of specimens says, "the use of specimens for bacteriological analysis requires that specific clinical material be collected, stabilized, and transported according to exacting specifications to insure valid results."

[Slide]

Implicit in this definition are two issues that are of interest to the discussion of decubitus infections. The first is the methods used to collect the clinical sample and the other is the validity of the results to assess the involvement of an organism in the etiology of that disease.

[Slide]

Now I will address the first, which is methods used in collection of microbiological wound

samples. These can be basically divided into two types of techniques. The first is deep tissue techniques, and they include biopsy and surgical debridement; leading edge needle aspiration; joint fluid or synovial fluid; bone specimen and blood. The surface sampling techniques include the swab; curettage; dermabrasion; velvet pad surface imprints. There are actually others but these are the most prevalent.

Also, the methods that are most frequently used in published literature are the biopsy, leading edge, swab and curettage. The methods recommended in our guidance document are all deep tissue techniques.

[Slide]

What I would like to do now is to give you an example of studies that have been performed to compare the sampling methods that are used in decubitus ulcers. Here we have an example of a study that was done by Sapico where he compared the ability of ulcer swabs, curettage, needle aspiration and deep tissue to be able to determine the types of organisms that could be isolated by each of these methods in decubitus ulcers.

You can see that using deep tissue or the

biopsy method as the gold standard, we see that they were able to isolate approximately three aerobic species and two anaerobic species using this technique. Compared to the ulcer swab method, we see that the values are actually much larger, that is, the number of species that can be sampled using the swab sample method are greater than with the deep tissue method.

[Slide]

Then what they did was to try to determine quantitative concordance between these two methods. Again you can see that using the biopsy method as the gold standard, needle aspiration was considered to have the highest concordance, followed by curettage and then the ulcer swab technique. One of the things that they concluded from this study specifically was that the ulcer swab method was not a method that should be used in these kinds of studies.

[Slide]

A study was also performed by Thomson to determine the relationship between a swab culture method and a tissue biopsy method. Their conclusion was that there was concordance or there was a correlation between the two methods. If you

look at the biopsy numbers of two and three, that is, 102 and 103, they had a swab culture relationship of plus 1. If you look at organisms that had 107 organisms or 106, a plus 4 was considered to be concordant with that quantitative number.

I think that one of the things that we need to remember here in looking at establishment of concordance between methods is that one of the critical aspects is that we also need to establish concordance with the clinical outcomes. In other words, we need to correlate what these methods are telling us clinically and what that clinical outcome actually is.

[Slide]

This is actually what Breidenbach and Trager tried to do in their particular study. Here they tried to determine the relationship between the quantity of bacteria and infection in complex extremity wounds. They compared the predictive value for wound infection of qualitative cultures versus other factors considered to have predictive value for wound infections. I am only going to focus on the last purpose.

[Slide]

They evaluated 50 patients with complex wounds. These were defined as soft tissue defects that required flap for closure. They did quantitative culture biopsies. These were compared to clinical parameters. These were factors that had predictive value in wound infection and included wound position, mechanism of injury and fracture, fracture type.

They also did a comparison to laboratory tests, primarily the swab culture method. Twenty-eight patients had quantitative cultures obtained after debridement and high pressure wash prior to flap closure. Sixteen patients had swab cultures, and two to five samples were obtained per wound, depending on the wound size.

[Slide]

These are some of the results that they got. Here, what they did was to determine what kind of criteria, using the positive test criteria and the negative test criteria, correlated with clinical outcome.

Looking at the first line, the quantitative, we see that positive test criteria were considered 104 organisms per gram of tissue. In eight of nine situations they were found to have

a high prevalence of infection, for a prevalence of 89 percent. The negative test criteria were considered less than 104 colony forming units per gram of tissue. In only one case did they have infection out of 19 cases, for a prevalence of five percent. So, there was reasonably good concordance using this method in the analysis.

[Slide]

Now let's look at the swab method. Again, the same kind of study. In this particular instance they defined the positive test criteria as having positive organisms in the swab. In this particular instance, in only 5 of 13 cases did they have infection, for a prevalence rate of 38 percent.

The negative test criteria were the presence of no organisms, and here they had an infection rate of one in three, for a prevalence of 33 percent. This is a very small number so I don't know how much we can really extrapolate from that particular negative test criteria.

[Slide]

What was different in this study from others is that they then did predictive values, sensitivities and specificities of the previous

study. What they found was that the positive predictive value for a quantitative culture was 89 percent, with the confidence intervals presented in brackets. The negative predictive value was 95 percent, and the sensitivity and specificity were 89 percent and 95 percent respectively.

[Slide]

Using the swab culture method in comparison, the positive predictive value here was 38 percent; the negative predictive value was 67 percent; and the sensitivity and specificity were 83 percent and 20 percent respectively.

[Slide]

The one point that I want to make about the previous slide is that we must have good positive predictive value and we must have good specificity in a method that is used in a clinical trial.

[Slide]

Now I would like to talk a little bit about the interpretation of microbiological diabetic foot infection samples. This is qualitative microbiology. I only have one slide. I think that this has already been discussed by previous speakers. Most diabetic foot ulcers are

polymicrobic in nature. In the study that was done by Sapico 25 of the 30 samples were polymicrobic in nature. The predominant organism is Staph. aureus, followed by Staph. epidermidis, streptococci, P. aeruginosa, Enterococcus and coliform bacteria. The predominant anaerobic species are Bacteroides and Prevotella.

[Slide]

Now I would like to discuss some of the schools of thought that I encountered in my reading of the published literature. Although microorganisms are responsible for wound infections, there is controversy regarding their role. The published literature is rather inconclusive, and I think that has been brought out by some of the other speakers. Some believe that the density of microorganisms is the critical factor in determining whether a wound is likely to heal. Other published literature suggests that the presence of specific pathogens is of primary importance in delayed healing. Further others believe that microorganisms are of minimal importance in delayed healing, and there is debate as to whether a wound should be sampled, the value of the results and the methods that should be used.

[Slide]

In conclusion, there is widespread controversy regarding the exact mechanisms by which microorganisms cause wound infections; regarding the significance of microorganisms in non-healed wounds that did not exhibit signs of clinical infection; regarding the best microbiological techniques to monitor the microbiology of wounds; and the ASM Manual of Clinical Microbiology states, "a swab is not the specimen of choice...since a swab specimen of a decubitus ulcer provides no clinical infection."

[Slide]

A regulatory agency must require microbiological methods that provide us with confidence and data necessary to assess the response of antimicrobials for their indented uses. We describe, in our guidance document, what we consider to be relevant methods, and these are the deep tissue techniques that were discussed in a previous slide.

[Slide]

I leave you with one final thought that was articulated over a hundred years ago, "the germ is nothing. It is the terrain in which it is found

that is everything." That concludes my presentation.

DR. LEGGETT: Thank you. Any specific questions?

[No response]

We will move on then to the next speaker, who will be Dr. Alivisatos on ruling out osteomyelitis in trials of diabetic foot infections.

Ruling out Osteomyelitis in Trials of Diabetic Foot Infections

DR. ALIVISATOS: Good afternoon.

[Slide]

I was asked to address the issue of the imaging assessment of diabetic foot infections with you this afternoon.

[Slide]

The initial question is why? Why are we discussing imaging techniques within the context of complicated skin and soft tissue infection in clinical trials that have as a goal to obtain not only the complicated skin and soft tissue infection indication, but a specific mention of diabetic foot infections in the label?

As you all know, subjects with

osteomyelitis, an infectious process that requires a more prolonged course of antimicrobial treatment and often surgical intervention, should be identified in order to ensure not only that they receive the most appropriate course of treatment but, within the clinical trials context, to ensure a relatively homogenous efficacy population. Subjects with osteomyelitis are usually excluded from the protocol populations of complicated skin and soft tissue infection trials, and often the preclinical development programs do not support the labeling for the long-term administration necessary to treat osteomyelitis.

I would also like to point out that despite the attempt at exclusion of such subjects from these trials, between 7-14 percent of enrolled subjects have osteomyelitis and are subsequently excluded from the protocol populations. Additionally, as per the protocol, these subjects are usually classified as failures in the ITT analysis.

[Slide]

So, does it matter if there are subjects with osteomyelitis within the study population of complicated skin and soft tissue infections or

within the subset of subjects with diabetic foot infections? The inadvertent inclusion of such subjects may not be an issue in double-blind, randomized trials as the distribution of these subjects should be equal between the treatment arms. However, this is not always the case.

And, what happens if that distribution is not equal? As we know, clinical success is defined as total resolution of all signs and symptoms of the infection or improvement of the signs and symptoms to such an extent that no further antimicrobial treatment is necessary. So, subjects with osteomyelitis who receive further antimicrobial treatment could be, and usually are, classified as clinical failures, leading to an inaccurate assessment of the true efficacy for one or both of the treatment arms.

In trials where there are small numbers of subjects with diabetic foot infections, the exclusion of subjects with osteomyelitis from the per protocol population leads to a decrease in the size of the efficacy database. As cure rates potentially decrease, confidence intervals widen and difficulties develop in drawing conclusions about efficacy.

So, the questions of which imaging procedure or procedures should be recommended, if any, and is this enough of an issue to justify the cost associated with the more sensitive and specific procedures are raised.

[Slide]

I would like to review what we have seen at the agency to date in studies of complicated skin and soft tissue infections, and these are seven applications. In all of these, subjects with osteomyelitis were excluded in the protocols. In the two oldest, which are A and B on the slide and which were from the late '80s and early '90s, the method of assessment of such subjects was not specified.

In later applications, C and D, x-ray of the infected area was performed at the investigator's discretion if the skin and soft tissue infection was proximal to bone and how the determination of proximity to bone was determined was not specified.

In one application all subjects had to have baseline radiologic evaluation, and that is F, whereas in another, more recent protocol, all subjects also had to undergo probe to bone. If the

probe was positive, a confirmatory x-ray was performed.

In another application, and that is G, if osteomyelitis was suspected clinically, and the clinical suspicion was not described, at least one of the following studies could be performed, and those included x-ray, bone scan, indium scan, MRI or bone biopsy. So, no procedure was uniformly recommended or applied and this makes comparisons across trials difficult.

[Slide]

What complicates the interpretation of study results in patients with diabetic foot infections or determination of infection of diabetic foot is complicated because of superimposed neuropathic osteoarthropathy and peripheral vascular disease. These complicate the images that can be obtained not only with x-ray but with the other techniques. Neuropathic disease can lead to fracture, deformity, bone production and hyperemia which can mimic infection on an MRI and bone scanning and increase the number of false positives. Peripheral vascular disease can prevent contrast material or tracer from reaching the site of concern and lead to an increased number of false

negatives. So, the simple and cheaper tests are often not sensitive or specific enough to correctly identify these subjects.

[Slide]

Before reviewing the currently available techniques, I would like to reiterate that the goal in obtaining an accurate diagnosis is not only to ensure that the clinical trial population is appropriate but, more importantly, to ensure that each individual patient receives the most appropriate course of treatment.

As a reminder, the presence of osteomyelitis impacts on the failure rate of soft tissue infection where failure is defined as the need for additional antimicrobial treatment within the follow-up period. With regards to diagnostic methods, the diagnostic gold standard is bone histology and culture through non-infected tissue.

The procedures I am going to go over include plain films, radionuclide scans including the triple phase bone scan, gallium scan, indium-labeled leukocyte scan, also MRIs and probe to bone.

[Slide]

First I am going to talk about plain film

radiographic examinations. This procedure remains the initial tool because these films are easily obtained, relatively inexpensive and, even if non-diagnostic, they provide anatomical information that may be useful in the interpretation of other tests that may be performed. Demineralization, periosteal reaction and bony destruction are the classic triad of findings and usually appear after 30-50 percent of bone is destroyed. These changes can take as long as two weeks to appear, and they can be found in other conditions such as fracture or deformity. Sensitivity of plain films is usually around 54 percent, whereas specificity is approximately 80 percent.

Just quickly regarding CAT scans, CAT scans were used in the past to diagnose osteomyelitis but today have mostly been replaced by MRIs. They do give good images of the cortex and can be used to aid in the determination of cortical extent of infection.

[Slide]

After plain films, the question is whether to proceed to one of the available radionuclide imaging techniques or to an MRI, and I am going to quickly go over the available to most clinicians,

in clinical settings, radionuclide techniques.

[Slide]

First, triple phase bone scans which may be positive as early as 24 hours after the onset of osteomyelitis, so it is a much more sensitive indicator of early changes. A dynamic scan over the region of the suspected osteomyelitis is obtained during the first minute following administration of the technetium-99 phosphate compound, followed by an immediate blood pool image and then delayed images at two to four hours. Both osteomyelitis and cellulitis demonstrate increased activity in the early images due to increased vascularity, whereas only osteomyelitis tends to have increased activity in the delayed images.

This pattern though also can be seen in fractures, neuropathic joints and in some cases of cellulitis. So, the specificity of the test is decreased. The addition of a 24-hour image can increase the specificity because diphosphonate accumulation ceases in normal bone after four hours, while it presumably continues to increase for several more hours in abnormal bone. Generally though in situations where bone remodeling is increased, a second imaging test that can help

localize the site of infection, such as a gallium or an indium scan are recommended in order to increase specificity.

[Slide]

As an example of the high sensitivity and low specificity of the triple phase bone scan, in a retrospective review of 20 reports of 1,166 patients, by Schauwecker in 1991, the sensitivity and specificity of the triple phase bone scans in subjects who did not have prior bone abnormalities--and here they had normal plain films--were 94 percent and 85 percent respectively, whereas in subjects with complicating conditions that increased bone remodeling the sensitivity was again high, at 95 percent, but the specificity decreased to 33 percent. In this, as well as some other slides, the methods of confirmation of the osteomyelitis diagnoses are not referred to so we don't know if they had biopsy or not.

[Slide]

Gallium uptake in infected foci is due to many factors, including direct bacterial uptake; direct leukocyte uptake; and binding to local proteins released from leukocytes. Osteomyelitis is distinguished from cellulitis by focal

localization to bone with or without a soft tissue component. Images are obtained at 24-72 hours following tracer administration and, in general, osteomyelitis is diagnosed when the gallium uptake exceeds the technetium-99 phosphate uptake at a specific site. In other words, the results of the two scans are discordant. Often however, the opposite occurs and the technetium-99 uptake is greater than or equal to that of the gallium.

In a compilation of results of 15 studies, the sensitivity with the gallium scan was approximately 81 percent and the specificity was 69 percent. So, a major drawback of this type of scan is the added cost of the gallium and the triple phase bone scan together that may exceed the cost of a single more sensitive and specific test, such as indium-labeled leukocyte scan or an MRI.

[Slide]

Of the scans available, indium-labeled leukocyte scans provide the highest sensitivity and specificity in patients with and without prior bone abnormalities. The patient's leukocytes are labeled with a radionuclide tracer, such as indium-111 oxine and after readministration to patients, images are obtained at 4 and at 24 hours.

The laborious process of labeling the patient's leukocytes in conjunction with the later image may be less practical within the context of outpatient clinical trials.

Localization to the site of infection by direct leukocyte migration and a diagnosis of osteomyelitis is made when labeled leukocyte uptake is moderately or markedly greater than that in a comparable adjacent or contralateral bone. Indium does not accumulate at sites that are not infected, and a compilation of sensitivity and specificity for 142 diabetic subjects from 5 studies revealed a sensitivity of 88.6 percent and a specificity of 84 percent.

[Slide]

Now to discuss MRIs, MRI with gadolinium contrast enhancement is recommended as often as indium scanning or combined triple phase bone scanning and indium scanning in subjects with preexisting bone abnormalities. Decreased signal intensity of marrow and T1 weighted images and increased signal intensity on Y2 weighted images with marrow enhancement after injection of gadolinium contrast are strongly suggestive of osteomyelitis.

Associated findings such as soft tissue mass, cortical destruction, sequestrum formation and sinus tracts with ulceration increase the diagnostic certainty. An additional benefit is the very good anatomical detail provided with this method. Sensitivity and specificity are comparable to those with the indium scan.

In a review of 129 diabetics with foot infections, cited in the American College of Radiology's appropriateness criteria for the imaging diagnosis of osteomyelitis in patients with diabetes, the sensitivity and specificity of MRI were 86 percent and 84 percent respectively. Again, the method of confirmation of the osteomyelitis diagnoses in these reports was not specified.

[Slide]

In a publication entitled, "Osteomyelitis in the Feet of Diabetics," published by Morrison in Radiology in 1995, the authors described the prospective evaluation of 62 feet from 59 subjects, 27 of which were diabetic. Confirmation of the presence of osteomyelitis was obtained, primarily by histologic evaluation and biopsy specimens. In the 27 diabetic feet, 17 feet had osteomyelitis and

the sensitivity and specificity of MRI were 82 percent and 80 percent respectively. Overall accuracy did increase with contrast-enhanced studies as opposed to non-contrast studies.

[Slide]

In this table of reports of sensitivity and specificity, taken from the Morrison publication and modified slightly by the addition of the MRI data at the bottom, when triple phase bone scan was combined with indium scanning in a number of studies, the overall results were comparable to those of MR imaging.

The authors concluded that the use of the triple phase bone scan is an excellent way to rule out osteomyelitis in uncomplicated situations because of the low false-negative rate. But both triple phase bone scanning and gallium scanning have low specificity in the diagnosis of osteomyelitis in diabetic feet because of the uptake of radiotracer by neuropathic joints. Triple phase bone scanning with indium scanning has a higher specificity in this setting and would be the optimal scintigraphic method.

The authors concluded that with MRI there is an initial cost savings because the MRI can be

more rapidly obtained and, in general, they are competitively priced as compared with the combination of the triple phase bone scan with an indium or with a gallium scan.

[Slide]

I would like to briefly presentation some information about another technique that has been used to identify subjects with underlying osteomyelitis, that Dr. Norden also mentioned earlier, and this technique is probing to bone in infected ulcers, which was described by Grayson in JAMA, in 1995.

This was a single-center study. There were 75 subjects with 76 ulcers. They were prospectively assessed. A diagnosis was confirmed histologically if possible. There were no cultures performed. If bone was not available for histology, then radiographic evidence of bony destruction in association with a purulent ulcer or identification of friable, nonviable bone by the surgeon during debridement were also acceptable. Osteomyelitis was diagnosed in 50 of the 76 ulcers, or 66 percent. In 46 of those there was histologic confirmation. It was excluded in 26 ulcers, or 34 percent.

Among the 50 ulcers with continuous osteomyelitis, bone was probed in 33 or, again, 66 percent, and bone was visible in only 3 of the 33. In the 26 ulcers without osteomyelitis bone was probed in 4. So, as an indication of underlying osteomyelitis, the sensitivity of the positive probe was 66 percent and the specificity was 85 percent. Palpable bone on probing had a positive predictive value for underlying osteomyelitis of 89 percent, while the predictive value of a negative probe for the absence of underlying osteomyelitis was 56 percent.

The authors concluded that palpation of bone is strongly correlated with the presence of osteomyelitis, and that probing should be included in the initial assessment of diabetics with infected ulcers. I would like to reiterate though that this was a single-center study and, until I saw Dr. Berendt's slides a few days ago, we were at least unaware that these findings had ever been reproduced, and the data is not published from the second study and so hasn't been reviewed.

[Slide]

I would like to touch on the issue of cost briefly. As you can see, we don't have recent data

but plain films are the most inexpensive test, whereas indium-labeled leukocyte scans and MRIs are both relatively and similarly expensive. Issues such as the sensitivity and specificity of a test, availability, as well as cost aid in the determination of which test a clinician would order, as well as which test should be broadly recommended within the clinical trial setting.

[Slide]

To conclude, I would like to show you this table of sensitivities and specificities of the various imaging procedures discussed, and stress that the methods with which these data were obtained are not necessarily comparable and are highly dependent on the use of the bone biopsy as the gold standard to diagnose the disease. Again, I would like to remind you that the goal is to recommend a procedure that has as high a sensitivity and specificity as possible not only to ensure that the clinical trial population has the disease under study, but to ensure that the patient receives the most appropriate course of treatment.

In a clinical trial setting, if we wanted to study osteomyelitis one would opt for studies with high specificity, whereas if one is studying

complicated skin and soft tissue infections and excluding subjects with osteomyelitis, high sensitivity is paramount.

A number of sources continue to suggest that conventional plain film should be utilized as the initial screening procedure in all patients. This test is the most readily available and reasonably priced, but the question of are the results good enough to ensure that osteomyelitis is ruled out remains. If positive, yes; if negative, then the diagnosis cannot be excluded.

At this juncture, and given that most diabetics have underlying bony abnormalities, most sources recommend either an indium scan or an MRI, both of which have high sensitivity and specificity. The costs of both are similar given the rapidity with which the MRI can be obtained compared to the indium scan where the patient has to go through the initial labeling of the white cells followed by a 24-hour scan.

In subjects without underlying bone lesions on plain films, a triple phase bone scan is highly sensitive and specific. Finally, probing to bone in conjunction with plain films is also an option in the initial approach of the diabetic

subject. If the probe or the film is positive, then the patient can be excluded. However, if bone cannot be probed and the plain films are negative, then the diagnosis of osteomyelitis cannot be excluded. Thank you.

DR. LEGGETT: Thank you. Yes, Don?

DR. PORETZ: I am not sure of something, getting a bone biopsy is obviously the gold standard if it shows histologically osteomyelitis. What percent of the bones that show osteomyelitis on histology grow an organism?

DR. ALIVISATOS: I don't know that, Don. Maybe some of the experts know.

DR. PORETZ: Does anyone know?

DR. LEGGETT: It is not 100 percent.

DR. PORETZ: Because I have seen numerous biopsies that show osteomyelitis under the microscope, yet half of them grow. What is the experience?

DR. ALIVISATOS: Dr. Norden seems to know about that issue.

DR. NORDEN: I can make an educated guess--

DR. LEGGETT: You need a microphone.

DR. NORDEN: You are absolutely right that

a certain number of patients don't grow an organism with positive histology. I would say it is anywhere from 30-40 percent. Whether that is a sampling error--you know, the organisms are obviously not homogeneously distributed throughout the bone. But I think most of us would accept either histology or a culture, a positive culture as a positive bone biopsy. So, it is the best that we have at this point.

DR. LEGGETT: Yes, Janet?

DR. ELASHOFF: I would just like to comment that in both this talk and the preceding one the sample sizes that estimates of sensitivity and specificity were based on were, generally speaking, too small and many times far too small to have any real idea of the comparative sensitivity and specificity of these techniques.

DR. LEGGETT: Thank you. Why don't we go on to the next speaker? David Ross will give us the implications for clinical trials.

Implications for Clinical Trials for Diabetic Foot Infections

DR. ROSS: Good afternoon. I know everyone is waiting for a break so I will try and talk quickly.

[Slide]

We have been talking a lot about the distinction between clinical trials and clinical practice, and I think that is extremely important to keep in mind. Having said that, I would like to move to a clinical case because I think that is ultimately what is driving the trials, the need for more knowledge for how to treat diabetic foot infections.

[Slide]

This is a gentleman whom I saw about three weeks ago. He is a 74-year old veteran in a nursing home. I was called because of a stage IV pressure ulcer which was thought to be infected. As you can see, this patient had a complicated medical history, type I diabetes, peripheral vascular disease and chronic renal insufficiency. On exam he was afebrile. He actually was not complaining of a whole lot of pain.

He had a large ulcer distal to the left malleolus with clearly exposed bone. There was a smaller ulcer on the dorsum of the left foot with an eschar and surrounding erythema. He had a white count of over 18,000. Interestingly, a plain x-ray did not show any bony changes suggestive of osteo.

He had been started on piperacillin tazobactam, actually for nosocomial pneumonia but also with the thought that this would cover a diabetic foot infection. He did not show improvement of the erythema on this, and vancomycin was added because of worsening cellulitis. He was transferred to the vascular surgery service. He continued not only to show no clinical improvement but actually deteriorated and is currently in the SICU for hypoxemia.

Just before this afternoon's session I spoke to the second most reliable source of information about patients. The first most reliable, of course, is the primary care nurse. In this case she wasn't available so I spoke to the fourth year medical student. The patient's hypoxemia has improved but his foot has deteriorated and they are talking about an AKA.

[Slide]

I won't belabor the public health impact of this sort of patient multiplied many fold. Dr. Berendt did an excellent job of outlining that. But I will just mention that, as Dr. Soreth mentioned, we have over a million cases of diabetes mellitus a year that are newly diagnosed, and this

has increased from the '90s when it was more in the neighborhood of 700,000 to 800,000. There are roughly about 140,000 hospital admissions for diabetic foot infection every year in this country, a quarter of all admissions for diabetes; over 80,000 lower extremity amputations due to diabetes; and over a billion dollars a year in direct costs for LEA associated care. That does not include costs for things like rehabilitation, prostheses and so on.

The patient I just described, if he undergoes the AKA, his odds of being alive in three years are around 50 percent. In five years, his odds of being alive are less than a third. Five-year mortality after LEA is 68 percent.

[Slide]

Did those antibiotics that he was receiving actually help him? It is hard to say. In looking through the literature to see what I could find about randomized, controlled trials for diabetic foot infections that were specific to that entity and not part of complicated skin and skin structure infections, I was not able to find a whole lot, probably about 350 patients in these sort of trials. I am sure there are some that I

missed, but the point that I would like to make is that there are relatively few trials. They have varying populations, varying regimens and it is very hard to put them together to say anything meaningful.

For example, the study by Grayson looked at limb-threatening infections, whereas the study by Chantelau, in 1996, looked at much more superficial infections and in this study placebo actually beat amoxicillin clavulanic acid.

[Slide]

So, why don't we pose the question what antibiotics really work in diabetic foot infections? To address that we need to think about some issues. What should the clinical definition of diabetic foot infections for a clinical trial be? How should we identify true pathogens in diabetic foot infections in such trials? How should such trials handle osteomyelitis? Finally, how do we take into account adjunctive therapies and other confounders?

[Slide]

Let me start with the question of what the clinical definition of diabetic foot infection should be. My first sub-bullet there, thanks to

the wonders of Power Point, should be clinical trials do not equal clinical practice. We want high sensitivity in practice. We don't want to miss a patient whom we want to treat. But in order to adequately define a patient population we need high specificity. Obviously, you have to have an appropriate balance if you want to have generalizability from clinical trials.

Nonspecific definitions run the risk of allowing enrollment of patients without disease, potentially obscuring differences between drugs. One possible definition, and there are many others and I am just drawing this out is a defect in epidermal integrity with new erythema and/or swelling and/or fever and/or leukocytosis and/or loss of glycemic control.

[Slide]

How should true pathogens be identified in diabetic foot infections? Dr. Sheldon spoke about some of the data underlying different methods and the sensitivity, specificity and predictive values of those methods. It is clear that we need accurate microbiologic data to assess the strengths and limitations of clinical efficacy data. In order to be confident that a drug really works in

diabetic foot infections clinically, it should be active in vitro against the organisms that are the true pathogens. We have had applications in which claims have been sought for organisms for which there was no in vitro activity.

It is also important to remember that a particular drug, in order to guide practitioners, is labeled for an infection due to specific organisms. In order to get maximum possible specificity and most reliable information, we would suggest curettage or biopsy with semi-quantitative culture.

[Slide]

How should we handle clinical trials as far as osteomyelitis? Rather, how should clinical trials handle osteomyelitis? As Dr. Alivisatos pointed out, this is not just a clinical trial issue. We know that inadequate treatment of acute osteo or even chronic osteo runs the risk of converting one infection into a more chronic form with a poor outcome. It is important to remember that imbalances in osteomyelitis patients across arms, which is certainly possible in a relatively small study, confound assessments of differences in drug efficacy. We would suggest excluding

osteomyelitis patients, potentially by MRI. If the study drug is topical or has no bone penetration they could be rolled over to a separate trial if the drug does have bone penetration.

[Slide]

Finally, how do we take into account adjunctive therapies and other confounders? I will just mention that the most recent issue of The Annals of Internal Medicine has a study by Landy and coworkers reporting on the use of nerve growth factor in treatment of neuropathic ulcers. This excluded diabetic patients but we will certainly see this sort of technology applied. I will also note that in looking for controlled trials in diabetic foot infections I found more studies dealing with adjunctive therapies than I did with antibiotics.

Confounders may contribute to differences in apparent efficacy, either adjunctive therapies or other confounders. For this reason, we need to define patient characteristics potentially affecting outcome, and some of these have been mentioned, such things as transcutaneous PO2, demographics, co-morbidities and so on. Wound classifications are potentially useful but they

need to be validated for trials and they don't, by themselves, define infection.

[Slide]

I just want to give this quote, and I want to thank Dr. Powers for pointing me to this: "Thus, it is easy to prove that the wearing of tall hats and the carrying of umbrellas enlarges the chest, prolongs life, and confers comparative immunity from disease; for the statistics shew that the classes which use these articles are bigger, healthier, and live longer than the class which never dreams of possessing such things." G.B. Shaw had some things to tell us, I think, about what to think about as far as clinical trials.

[Slide]

So, I am going to leave you with some questions. Actually, since writing this we realize there are even more questions so those will be on the agenda and I won't go over these in detail. But we look forward to your discussion of these issues and for your advice and recommendations. Thank you.

DR. LEGGETT: Thank you, David. Any specific questions?

[No response]

Then I suggest we take a 15-minute break and be back here at 3:45.

[Brief recess]

DR. LEGGETT: The next item on the agenda is the open public hearing. We did not have anyone contact the FDA about wishing to speak during this open public hearing. Is there anyone in the room who would like to use this time to read us a statement? Seeing no one wishing to give a statement, we will pass on to the next item on the agenda which is the charge for the committee that will be delivered by Ed Cox.

Charge for the Committee

DR. COX: Thank you, and I will keep my comments brief. I just wanted to start out by thanking all the presenters. We have had a series of excellent and very insightful presentations on some of the issues in diabetic foot infections, including issues regarding the microbiologic evaluation, diagnosis of diabetic foot infections, evaluations for osteomyelitis.

There is no question that managing diabetic foot infections is challenging clinically and many of these challenges from the clinical arena carry on over to the clinical studies of

antimicrobial drugs that are being evaluated for their safety and efficacy in the treatment of diabetic foot infections, the issues of other chronic conditions underlying skin disease and vascular disease that may also impact upon the outcomes in patients with diabetic foot infections. Fortunately, the presentations do mesh very well with the questions that we have for the committee today.

Without further ado, I will just move on to the five questions at this point in time. The questions are being asked in terms of clinical trial design and clinical study design, so that is just one point to keep in mind as we move through them.

What I will do is give the Reader's Digest version of the questions because I am sure we will come back to them as we progress through them. But essentially the first question deals with the definition of diabetic foot infection and asks also how we should handle the issue of breaks in the skin in the setting of diabetic foot infections.

The second question deals with how we should handle infected ulcers and whether the ulcers are infected or not infected, and how to

handle the diagnosis of infection in the setting of ulcer.

The next question deals with the microbiologic methods that should be used for the diagnosis of diabetic foot infections.

Question four moves on and looks at evaluations for osteomyelitis and the methods that should be used there. We will be able to use a lot of the information that was presented here today in the earlier presentations.

Then the final question, question number five, deals with how we should define clinical success or failure in the setting of diabetic foot infection clinical trials.

So, we look forward to the committee discussion on these questions and, once again, I would like to thank all the presenters for really excellent presentations on the topic of diabetic foot infections. With that, I will turn it back over to Dr. Leggett.

Committee Discussion

DR. LEGGETT: Thank you. I had cut people off who had questions of Dr. Berendt and Dr. Norden before, but I think if there are questions we can, hopefully, ask them in the context of trying to

answer these questions.

So, number one, how does one define a diabetic foot infection? Who wants to start? Don?

DR. PORETZ: Well, you can be very simplistic I guess or you can be very erudite, but the way I think about it is a person who has diabetes who has an infection in their foot is not equal to a person who does not have diabetes and has an infection in their foot, i.e., I always take a diabetic patient with an infection more seriously, no matter where the infection is. So, to be simplistic, I guess, diabetes mellitus and cellulitis in the foot or ulcer in the foot or closed wound in the foot, I would consider that a diabetic foot infection. I don't know if you have to go more advanced than that or not, but I am always more aggressive in treating those patients than non-diabetics.

DR. LEGGETT: David, what would you care to add to that?

DR. ARMSTRONG: Well, I must say that when I came in here I was favoring that view. I think it was very simplistic and that is really the way that I would think about it. I would say maybe using the ADA criteria for diabetes, then we define

foot as that which is below the malleoli and then an infection based on the criteria that you heard Dr. Berendt and Dr. Norden describe. But after hearing some of the concerns in clinical trial design, I am wondering whether we should consider going for more specificity and adding in something like the presence of neuropathy, or an open wound, or something else. I have not really come to any conclusion. I am still looking at that first as the thing I am favoring but I would open it for discussion amongst those who have so much more experience in clinical trial design than us clinicians and clinical investigators.

DR. LEGGETT: I can just think of the most recent patient I saw with diabetes who had bad tenosynovitis from Staph. aureus and no lesion. He lost part of his foot. So, I think you can have a severe infection without necessarily requiring there to be an ulcer.

DR. ARMSTRONG: Absolutely.

DR. WALD: In children with diabetes we don't see these infections. So, I think that it is not enough to be a diabetic. I think that probably there has to be some component of either neuropathy or ischemia or both.

DR. LEGGETT: Don?

DR. PORETZ: Yes, I think that is a problem. I think the difference between a diabetic and a non-diabetic are those exact things, and all things being equal, diabetics don't do as well as non-diabetics drug for drug, treatment for treatment, infection for infection. Because of the neuropathic changes and the vascular changes, which I think you have to presume are present in a diabetic who has one of these infections, that is why I think they need to be treated more aggressively and that is what I would call a diabetic foot infection.

DR. LEGGETT: Go ahead, Ellen.

DR. WALD: I guess I would just ask are there adult diabetics for whom your statement is not true, that they really do the same as other comparable patients without diabetes because, in fact, they don't have neuropathy and they don't have ischemia so they are healthy diabetics in their 20s, 30s or their 40s who don't have any component of ischemia or neuropathy and they do just fine.

DR. PORETZ: I think a lot of them do have small vessel disease and, maybe that is the case,

but in general I think if you are a diabetic and you have an infection in your foot you don't do as well as a non-diabetic, period.

DR. LEGGETT: John?

DR. POWERS: Maybe I can try and clarify what it is that we are looking for here, and it is something Dr. Wald just pointed out. If you took a 30-year old, well-controlled type I diabetic who has no problems and no foot issues other than this, and comes in with cellulitis on their foot the size of a quarter, that is not the same kind of person in the pictures that Dr. Berendt was showing earlier today. So, if you go for that broader definition, both kinds of patients get enrolled in the same clinical trial and that is a problem for us, if they are unequal across the arms of the trial, in determining the efficacy of the drug.

The first kind of patient, you don't know how much the drug contributes because those kind of people might get better spontaneously. What we are trying to get to is a more specific definition, and again, because of the things that the speakers have raised about adjunctive therapies, etc., who is the kind of patient we would be pretty sure where that adjunctive therapy isn't going to cut it? In other

words, you know, we all know the patient that comes in with redness from the tip of their toe up to their knee that wasn't there two days ago--that is the kind of definition we are trying to go for, something that allows us a little more specificity in picking those people.

DR. LEGGETT: Jan?

DR. PATTERSON: Well, the PEDIS classification I thought was very useful in the sense that it quantifies the severity of perfusion, extent and size of the ulcer, the depth, tissue loss and so forth. So, if that was used in terms of the definition of infection, you could quantify the severity and, thereby, in terms of the clinical response, you could quantify how much it gets better if it goes from grade IV to grade II.

In terms of cellulitis, I don't see that it really fits into the PEDIS classification. Correct me if it does. But I would see a diabetic foot infection cellulitis as a cellulitis in a diabetic that is in the foot.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: I kind of like the classification that I saw in Mandell where it seems to me, and I could be wrong, that they are really

calling a diabetic foot infection an infection that actually has an ulcer that you can ascertain is penetrating beyond the subcutaneous tissue; that it has not just cellulitis but extensive cellulitis; has a lymphangitis; and then ischemia and polymicrobial or not type of bacterial growth. So, I think it is more than just a cellulitis. It has to actually penetrate behind the borders. So, that would be my feeling for the definition.

DR. LEGGETT: David?

DR. ARMSTRONG: Maybe then to sort of steer the discussion toward that, just as Dr. Powers said, we are not looking for all of these patients with cellulitis or maybe an infected ingrown toenail. I think maybe something that will confer some specificity might be just what Dr. Maxwell said, which is perhaps an infected break in the skin and an infected break in the integument, that being a diabetic foot ulcer. Maybe that is your touchstone that you use for your definition for clinical trials. Will it exclude a number of what we might still consider as diabetic foot infections clinically? Absolutely. But perhaps then something like a wound would make it a little bit easier to standardize these things across

strata, using something like you saw Dr. Berendt show in terms of the International Consensus classification on infection as well.

DR. LEGGETT: That would certainly make the population more homogeneous. Allan Tunkel?

DR. TUNKEL: I was thinking why wouldn't we include those people? I mean, this is how it begins. This is really where they first get their first infection that winds up progressing and you start chopping away little bits of their feet until you wind up doing that below or above the knee amputation.

So, part of my definition of diabetic foot is if I am going to treat the patient with antibiotics, I think they have a diabetic foot infection and maybe that isn't a great definition--

DR. LEGGETT: You mean somebody with an ulcer?

DR. TUNKEL: Well, I guess whether it is that quarter size area of cellulitis with a tiny break in the skin. If I am giving them antimicrobial therapy to resolve it, they have a diabetic foot infection.

DR. LEGGETT: That leaves things open to having a predominance of folks in your trial if you

want your new drug to work. Alan Cross?

DR. CROSS: I think part of the problem is we have been saying if a patient has an infection, but, yet, we really are begging the plan. I think one of the problems we see is these patients do have chronic stasis changes. They do have erythema and I think what John suggested earlier is that there has to be perhaps a new finding; perhaps a new erythema or tenderness or swelling that hadn't been there in a defined period of time. Otherwise, you are always going to be stuck with how to deal with these chronic stasis changes.

DR. LEGGETT: Ken?

DR. BROWN: I think what the FDA is asking is an impossible question because what they really want the group to do is to tell them how to define when a patient has microvascular disease. If they just have a neuropathy the patients do very well, as in leprosy, and in leprosy patients with a terrible ulcer on the planter surface--you wash it once, wrap them up for six weeks and immobilize them, and at the end of the six weeks they are fine.

So, I think what we need is a way to define these people, at least the young versus the

not so young, in terms of their vascular ability to deliver the goods to the site.

DR. LEGGETT: Good point. I don't think you would get any disagreement from anyone about that. Dr. Elashoff?

DR. ELASHOFF: It seems to me that part of what is happening here is not so much a definition of what is a foot infection or not, but a definition of a person who has a situation that is serious enough to make sense to have an indication for it. So, we are kind of mixing definitions of this and with a definition of poor prognosis or severity, or something, and I think it might help if we kind of separated those two issues a little bit more clearly.

DR. LEGGETT: Barth?

DR. RELLER: To extend what Dr. Brown said, this is inherently a dynamic process that is heterogeneous and we will never come to a definition that is comprehensive enough if we want one definition. It seems to me what Dr. Poretz pointed out is sort of the bare necessity ofwhat Dr. Norden put in, over 18; and then there is no substitute for categorization of the patients in terms of extent, severity, neuropathy, vascular

status. Rather than trying to reinvent all of those items, since in the end the people doing the trials are going to be those clinicians who are actively involved in this area and to get collaboration to apply drugs that would be approved, involves many different disciplines.

So, the way I would go about it is to take what Dr. Berendt presented in terms of the stratification, take the base definition that we could agree on, and then one has to stratify the patients between comparator and study drug. They have to be distributed comparably according to severity, etc., according to vascular compromise, etc. Then we could get into the details of what kind of microbiology we want; what is valid, etc.; what kind of imaging we want, etc. But I think there is no substitute for differentiation of patients so that they are comparable in the groups, but it is impossible to put all diabetic foot infections in one definition.

DR. LEGGETT: It seemed that Dr. Elashoff had a good point. If we are going to give a specific indication, it really should sort of be weighted towards the more severe folks at risk. There would be an easy way to do that if you want

to say that we have a drug that is very effective; it is given parenterally; that can be transitioned to oral; and we are going to have a trial that enrolls patients who are of grade II/III or grade III or IV severity. Or, it is effective in those with this degree of severity and assume that if it is effective in that it would be effective in those that are less severe. I think in the end the patients have to be comparable and there have to be objective definitions of the degree of the severity because I think we all agree on the principles--no blood supply; it is not going to heal. You know, if it is dead, it has to be taken out or taken off, etc. Keith?

DR. RODVOLD: I agree a little bit with what Barth was saying. Looking at grading of II, III and IV is that one of the things where, at least from an agency point of view, you are going to have to have a comparator? You only have two comparators that are legitimately used on the market that have this labeling at this point. For example, linezolid being the last one that was approved, how many of the linezolid patients that were in that trial fit into that grade III/IV versus II? You know, if most of them are III and

IV, is that a lead to you to find out that maybe everything that you need in this indication is III and IV?

When I look at grade II in this definition--and I may be wrong; I am not a physician, I am a pharmacist--I look at grade II and I kind of read a little bit of complicated skin and skin structure infection for the recently approved daptomycin because 30 percent of their patients were diabetic. They try to remind you of that in their advertisement a lot to get you enticed to use the drug. But they weren't really what I think most of us would think of as diabetic foot and they don't have that labeling specifically. So, I kind of see grade II here bordering on just the typical definition of complicated skin and skin structure infections and III and IV lead you up to diabetic foot that I think everyone in this room would be comfortable with. If you could treat III and IV with a new agent, then you should be able to slip down to a little bit more tricky case of II. But from a regulatory point of view, III and IV would fit the bill of having spelled out criteria that this is the target you have to hit to get the data.

But I think at the same time that you are thinking that, you have to back up and look at what comparators--will they be a legitimate comparator to the new guy coming up.

DR. LEGGETT: Ciro?

DR. SUMAYA: I am thinking similarly with the last two comments, being more comfortable with the PEDIS classification to try to categorize people to some level of severity. I like that one in particular because it does touch on the neuropathy, and it does touch very well on the ischemia aspects. So, I think we could hit the cellulitis for mild disease and then go into more severe levels.

Just one other modification perhaps, it could be as in rheumatoid fever where one has minor and major components, and perhaps out of those five there may be two we want to consider more major criteria and the other three would be more minor. But they could be manipulated I think to categorize into different levels of severity to do the clinical trials.

DR. LEGGETT: Don?

DR. PORETZ: Would it be reasonable for any prospective study to consider the concept of

digital photography where prospectively you could have an independent review of a reading person? You know, they do this in ophthalmology where there are independent reviewers, that have nothing to do with the patient per se, who read the fundoscopic pictures. They do it in neuropathy with nerve conduction times where independent neurologists, having nothing to do with the case, read the nerve conduction times. Maybe there could be a standardized digital photographic way of doing things where independent readers look at it and then you can prospectively go forward and get some idea of what is going on.

DR. LEGGETT: In our hospital, in the last ten years I have never seen a podiatrist see a patient without having plenty of pictures.

DR. PATTERSON: Well, I think a digital picture would be very helpful as supplemental information, but it wouldn't tell you, for instance, about the depth of the ulcer and some of these other things that are in the PEDIS classification, the ischemia and so forth. So, I think it would be helpful supplemental information but I think you would still have to have some other, more objective criteria.

DR. LEGGETT: John?

DR. BRADLEY: I too am interested in trying to stratify these patient groups based on all the different factors because you are getting a 3 X 3 matrix of vascular disease, peripheral neuropathy, and something that people haven't brought up and I don't know if it has not been studied or is difficult to quantitate, but the control of the diabetes because, certainly, that may impact the wound healing.

The other thing that Don and I were talking about is burn patients. After you clean a wound, you biopsy the wound and you can get an idea of histology and quantitative cultures which leads you to believe that it is truly infection as opposed to just colonization. To me, that will enhance the quality of the data. So, if you have nice histologic data you need fewer patients to actually show benefit. Then, of course, Don said a lot of people would be reluctant to do biopsies because these wounds may not heal. So, it is putting the patient at additional risk.

DR. LEGGETT: Any further discussion about this? Can we take up that second phrase in number one and, ignoring the people without breaks, what

do we do with the preexisting breaks in the skin? Ellen?

DR. WALD: I think in clinical practice we do this all the time. We look at something and we say it is clean and dry; it doesn't look infected. When we think it is infected it is because there is new onset of erythema and oftentimes there is accompanying discharge, and it may be warm to the touch. And, if the patient has sensation, it may be painful. So, I think those classic findings of inflammation, accompanied by discharge, are what persuade us clinically.

DR. LEGGETT: David?

DR. ARMSTRONG: Maybe just to clear some of those initial diagnosis issues, and we have been mulling over this issue for sometime now; maybe for too much time, some might say, but Dr. Berendt has some knowledge of that committee and what is coming out of there, and maybe you could share some of that about the specific diagnosis of infection and what is being used. Is it greater than two cardinal signs of inflammation? Is it presence of purulence, advancing erythema? Is there any way you could share some of that perhaps to clear some of this up?

DR. BERENDT: I think the thing to say is that generally speaking the IDSA guidance was worked out very similar to the International Consensus guidance. So, yes, from my memory, it is two or more of the clinical signs of infection that you have really been describing. I mean that, of course, is a clinical classification and is slightly different to the research type classifications you have been describing.

DR. LEGGETT: Did you want to say something? Any other thoughts? Yes, John?

DR. POWERS: Dr. Elashoff asked me a question at the break that I kind of wanted to address because it has come up now several times around the table. That is, stratifying people according to severity. Dr. Elashoff asked me what did the FDA mean by validating the severity scores.

I think one of the issues we get into is the idea of do these severity scores really predict severity? By severity, what we have interpreted that to mean is that patients with these given characteristics do worse than patients with those given characteristics regardless of what therapy they get. So, this does not require a placebo-controlled trial.

Speaking with Dr. Norden too at the break, we were saying we don't have the answers to this. That doesn't mean we can't go forward, but these could be incorporated in future trials. But the question I ask myself is does somebody that has 1.9 cm of erythema really differ from somebody who has 2.6 cm of erythema round their ulcer? And, that is the way this reads. The difficulty we get into in the setting of a non-inferiority trial is that drugs may come out looking the same and a drug sponsor may say to us, oh, but look, I have more patients with grade II. So, we want in our label that we are better than this guy, over here." If those severity scales haven't been validated it is very difficult for us to know what to do with that information going down the line.

DR. LEGGETT: The only easy one is going to be I versus IV. Joan?

DR. HILTON: I wonder if there isn't a registry that exists in which you could choose some outcome, whether it is time to death or some other very severe endpoint, and figure out the relative weight of these different prognostic factors, like the PEDIS classifications. I don't know if you can resolve this with opinions. It seems the data have

to speak.

DR. POWERS: I think one of the reasons why we are bringing this forward to the committee is also to raise the question that there are pieces of data that are missing about very commonly treated diseases that we need folks to do research on outside of the clinical trials of the FDA, but we need help on answering these questions.

DR. LEGGETT: Carl, do you know if there is any such registry or any ongoing trials to try to validate the PEDIS system or any of the others?

DR. NORDEN: The simple answer is no, I don't know of any trials that are ongoing. But I think it is critical but I don't think it should stop us from doing clinical trials. I mean, you can within clinical trials try to validate things and get answers to prognostic questions and you can look, for example, at other diagnostic tests. You can do a lot of things within trials if the drug company is willing to do it and if they sense that this is an appropriate thing to do. But, no, I don't know that there is any data at all.

DR. LEGGETT: What about the University of Texas system which has been around far longer?

DR. ARMSTRONG: Well, the answer to that

is that I think we may be comparing apples and oranges when we talk about stratifying based on severity of infection versus looking at the wound as a whole. I mean, a large number of wounds we shouldn't even be talking about because they are not infected. They may be treated just with good debridement, off-loading and coming back frequently for care. But something like the UT system is probably a good system for assessing wounds as a whole but when it came to the issue of infection, I can tell you that we had a very difficult time, just as we are having a very difficult time here, and we just decided to dichotomize it, saying it is infected or it is not. That was how we sort of skirted the whole issue of infection. We did include things like depth so certainly probe to bone might confer a higher risk for osteomyelitis. Some of the data supported that if you had a deeper wound, then one was at higher risk for developing osteomyelitis in that 360 patient study. But, again, I think to use a system like that would be inappropriate for looking at infection.

DR. LEGGETT: Alan Cross?

DR. CROSS: I was impressed by the presentation of Dr. Ross when he actually showed

the slide of the published DFI randomized clinical trials. Of the five he found, there was only one that had more than 100 patients, and that was 108. So, here we are having some discussion about stratification, and we are having all these other discussions about how do we handle all these confounding variables that we will not be able to control for.

I think at least one approach to this is to have a large enough trial, such that it allows these confounding variables, hopefully, to be handled through a large trial. The implication of that is that we have to come up with perhaps some definitions and treatment endpoints that would allow one to do a large enough trial in order to have an assessment of all the concerns that have been voiced here.

DR. LEGGETT: Janet?

DR. ELASHOFF: Also, the issue of whether certain severity classification is predictive of prognosis brings up the issue of what we are talking about with respect to prognosis? Are we talking about cured, not cured in eight weeks? Or, are we talking about a year from now how the patient is doing? If we are talking about

longer-term prognosis, then we would have to be talking about an entirely different kind of trial in order to validate these things than if we are talking about a shorter-term yes/no cure.

DR. LEGGETT: Could we leave that until we get to question five, which I think addresses that? Jan?

DR. PATTERSON: Well, I was just going to say that the PEDIS classification--I mean, whether or not grade IV or grade III is actually more severe than grade II, maybe we don't really know the answer to that in terms of the prognosis. But it does give us an objective way to assess the infection at baseline and to give us objective criteria for improvement. You know, if it goes to a lesser grade, that is improved.

In terms of the criteria, I mean, it is just like with any other study. If you have a criterion that, you know, you have to have a fever greater than or equal to 100.4 to be in the study, if you have 100.3 you may clinically fit but you can't get into the study. So, it is just like anything else; you have to have a cut-off somewhere.

DR. LEGGETT: And it certainly looks like

clinically people who do this can tell the difference between grade II and III, looking at whether it involves other structures and other sorts of things. So, it is not just one factor involved. It is not just 1.9 cm versus 2.1 cm. David, you look like you want to say something.

DR. ROSS: The thought that came to mind, and this is really a question for Dr. Armstrong, I was thinking about the process by which Fine and coworkers defined prognostic categories for community-acquired pneumonia. Obviously, we have to start somewhere in terms of defining grades of severity, but the question is to what extent is there a difference between 1.9 cm and 2.0 cm, square centimeters. I guess one way to define that, not putting everything on hold while we do this, is to prospectively follow patients and collect data. I was just wondering if I could ask Dr. Armstrong, since there is such a huge concern for the VA health system, if that is anything that is even a twinkle in the VA central office's eye.

DR. ARMSTRONG: Certainly not speaking for Secretary Principe, by any means, but I think that it certainly should be a twinkle in the Department of Veteran Affairs' eye. It is certainly common

enough. I think that the trouble with doing a VA-wide study is while I think care is excellent at a lot of VAs, if you have seen one VA, you have seen one VA and there may be differences in approaches to care. Even though there is a nationwide pact program that has been excellent, I think standardizing things is still a little bit difficult. But I think that would be certainly of interest to the VA health services research and development and other grant-making agencies to look at. I think it could be done.

DR. LEGGETT: Basically, Dr. Berendt and Dr. Norden, this PEDIS thing is still just a bunch of old fogies getting in a room in Hawaii, right?

[Laughter]

DR. BERENDT: In fact, the PEDIS thing is considerably more than that actually. That is to say, it is a bunch of old and young fogies getting together in a number of rooms over a very long period of time, actually. The International Consensus process that Carol Backer initiated, has been on the go for about 12 years. They have had four quadrennial meetings during that time. The Consensus guidelines on sort of management and prevention of diabetic foot in general were issued

four years ago through a process of international consensus, with a working group of about I think 30 or 40 people from, literally, all over the world and from multiple disciplines.

The infection subgroup was a smaller subgroup, once again specifically required to be international in its composition. It has sort of authoring members and corresponding members. Ben Lipsky was on the chair of that group and I was involved in that, but widespread, people sort of across Europe and the world. Then that was signed up to by this much larger group who met at the Holland meeting earlier this year. In fact, David Armstrong was one of the people whose signature is on that piece of paper.

So, I am not saying that it has total legitimacy at all, but I think it does have a reasonable degree of face validity. The criterion validity remains to be established, and that is accepted, and for that reason in the outdated version of the consensus it is listed as a report on progress rather than as a final version of a classification.

From your point of view today, it is perhaps a shame that it is a classification system

for research on foot ulcers because that meant that people without ulceration were eliminated from consideration. So, unfortunately, the cellulitis in the diabetic is sort of unclassifiable by PEDIS. I think that is a pity. Whether one could get that changed over time is an interesting issue. I think it is worth saying that, based on your deliberations here, even if PEDIS could classify those sort of cases, the sort of cellulitis cases, they would, as long as your stratifying the reporting of the trial be an obvious difference between the cellulitis case, who would be a sort of P1 which would be, you know, normal perfusion; P0 for no area; D--let's say--0 if it existed; I3; S1 for protective sensation present. So, that is kind of our uncomplicated diabetic person with infection. That is dramatically different from the kind of P2E 25 cm, or whatever it is, you know, D2/I3/S2. You can see how different they would actually come out, and that might help you duck the issue of having to make the definition, if you want to duck it.

The other question in my mind, having heard you debate this, is whether those individuals who don't yet have complications of diabetes and

don't have a wound are covered anyway by the cSSSI or SSSI definition. I am assuming diabetes is not an exclusion to be licensed under those. So someone has already thought about them; you have.

So, those are the main things to say. Trying to come back to the legitimacy of PEDIS, which is, yes, designed mainly for research, the authors, or some of the authors involved in the UT system, the S(AD) SAD system and the clinical staging system are also signatories to that. So, in that sense, some people have accepted that their own personal systems that they have already advocated in the literature would be superseded by the development of this system. I mean, that is just sort of a sales job on that. But I think everyone accepts that it needs to be validated. Clearly, if the agency requires that before they adopt it, or ask other people to do it, then you can't sort of turn up to it now but we hope you might later.

DR. LEGGETT: Janice?

DR. SORETH: I just wanted to say that Dr. Berendt raised a good point, which was that most drug manufacturers don't seek diabetic foot indication in a vacuum. They do it in the setting

of having usually two large, multicenter--at least one, sometimes two large, multicenter trials of complicated skin and skin structure infections fairly well defined in a broad spectrum of patients, some of whom may be diabetic and have a cellulitis, let's say, on the thigh. To augment that experience, they then go to another trial, which we like to see as a comparative trial, in which they enroll the various spectrum of patients that we discussed today, diabetic foot infections with what we expect are the complicating factors of not normal vasculature, not normal neuropathic system. So, we feel that in the intact patient the drug is studied within the organ of skin in a complicated setting.

DR. LEGGETT: Barth?

DR. RELLER: Dr. Berendt, what do you mean by validation? This word has been used multiple times but what exactly are we seeking here?

DR. BERENDT: My understanding of any classification system that is being used for clinical work is that it should have what is called face validity and it should have what is called criterion validity. Face validity I understand to mean that there is a common sense basis to the

classification and that a clinician looking at it would say, yes, that makes sense to me; I can see where you got to that and I can see how I can use it.

Criterion validity would be about the fact that classifications inevitably also attract people into wanting to assume that there is a prognostic significance to that difference. That specifically addresses the issue of 1.9 versus 2.5 and is that, in fact, a prognostic factor or not.

So, the kind of validation that I think one would like to see the PEDIS system go through, as any other, would be, one, would anybody use it. If no one will, it has clearly lacked face validity and it is gone immediately.

Secondly, when people did use it, was there some kind of obvious difference in outcomes when one looked at the different groups within it. Clearly, the goal of expert treatment would be that there aren't any differences in outcome because your treatment would be tailored to your classification. That is a common difficulty with all classification systems, that the worse the scoring, the more intensive the treatment and, therefore, sometimes the better the outcome.

DR. RELLER: Well, the reason I ask--and I like the PEDIS concept. I mean, it sounds plausible. These are the things we know affect outcome. So, I should think that there is a high probability of pretty widespread--given the tremendous amount of work. I mean, this is an enormous effort that has already been undertaken. So, the face validity may be pretty close.

Now, the validity as regards prognosis, outcome, etc., how can one possibly get at that in the pure sense unless you treated some people and didn't treat others, or you just watched the natural history of these things without doing anything? Or, if this face validity has an element of does it make sense, maybe the validation in terms of prognosis and outcome has to have a common sense element of how can we do that unless we get an adequate number of patients and get them into trials, categorize them and see. I think it is pretty likely that if drug A is better than drug B, the people in comparable categories--that everybody is going to do better if they are down the PEDIS ranking and they are going to do worse if they are up the PEDIS ranking, and there may be differences between two drugs. Now, you can argue about how

big the difference is, etc., but it is hard for me to imagine that somebody with a lousy PEDIS score is not going to do worse on balance than good if you have enough patients to be able to show a difference.

So, I don't know how one could, without using it, establish pre-use validation unless--I mean, it becomes so artificial. I mean, what one needs to have is something that people can buy into so they would be willing to enroll sufficient numbers of patients and accurately categorize them, including digital image but not limited to that because it is not sufficient, but in this categorization there is, you know, depth.

The thing that is really appealing to me about the PEDIS approach is that it doesn't have so many categories that you have so many little subsets that, as Dr. Elashoff talked about, you end up not having enough people in the cells. I mean, it is pretty straightforward. I particularly like the sensation. I mean, it is grade I or grade II; you can feel or you can't feel. I am sure they have in there how you assess the feeling. Similarly with the perfusion.

So, no matter what we do or what the FDA

does, I should say, in the end it is going to have to have buy-in. To take something and tweak it that already has considerable buy-in, it seems to me that it would get us there a lot sooner to get to the point that we really need, and that is a lot of patients who are properly assessed that we could actually see for clinical trial purposes whether one agent contributes more than another agent does for comparable patients.

DR. LEGGETT: Janet?

DR. ELASHOFF: Yes, I would agree with a great deal of what you said. I just wanted to add two things that haven't been mentioned about using a severity classification. Before I start, I want to say that generally speaking some classification is better than none and a small number of categories is generally good. But the important thing is whether people are going to actually use it. So, if it is easy to use will people who are doing the clinical trial, or perhaps even people who are looking at a patient and deciding whether to use a particular antibiotic use it?

Also, the issue of inter-observer variability ought to be low. If you have two different people look at patients, will they agree

a fairly high proportion of the time as to which category the patients are in. So, those are some other things to think about in choosing and evaluating a system.

DR. LEGGETT: Ellen?

DR. WALD: I just wanted to ask a question. It seems to me that maybe you could do both things at once. We clearly need a score because we need to make sure that patients are stratified so that one therapy isn't overloaded with more severe patients than the other. The validation though is really another thing. You like to validate something according to something relatively objective, except clinical outcomes are not so objective. But we could look at things like requirement for amputation, or certainly mortality although it may be that some patients who adverse event grade IV will die as opposed to patients who are grade I or, again, either amputation or long-term outcome in terms of not eradication of infection maybe but time to overall healing, and we could define healing however we wanted to that. Would that be the way to validate the score?

DR. ELASHOFF: Well, it is basically what people agree on as being important aspects of

prognosis. I don't think the objectivity or lack of it is as important as long as things are randomized and double-blind. The essential issue is--I mean, if you think the quality of life down the line is the important thing, even though it is kind of subjective, that is what we should be looking at to see this correlation with. It is what is the really important outcome that you want to find out about that we should be looking for, and not so much objective, non-objective, although it ought to be somewhat correlated with pretty much any measure that you use of outcome. If it is not correlated at all with some and really correlated strongly with others, then that it suggests some issue that we haven't looked at hard enough.

DR. LEGGETT: Celia?

DR. MAXWELL: I just have a question and I don't know the answer. But shouldn't the degree of disease--let's say a diabetic that has always been well controlled versus someone that is not well controlled--wouldn't the degree of disease that you find in the limb be different depending on the control or the lack thereof, and should not that be part of the criteria? Because it seemed like it would make a difference. Someone spoke earlier

about the young diabetic versus someone that was more mature.

DR. LEGGETT: David?

DR. ARMSTRONG: I am sure that that makes a difference, certainly the degree of glucose control, whatever metric you use. But I think we are charged with defining a diabetic foot infection right now, and I think you can look at that continuous variable as regards a certain outcome when more people are enrolled in a trial. I am not sure that validating this system is of primary importance right now. What it strikes me as is that it is a framework for discussion and for definition of potential severity. At least it is talking points, if you will.

I think it maybe gets back to how do we define a diabetic foot infection. I think the question is are we going to have a broad definition, as Dr. Poretz mentioned, an infection below the malleoli in a person with diabetes? Or, is it going to be someone with an open wound? I think that is the fundamental question. Personally, I think there is more buy-in for this PEDIS classification, speaking again as someone who took part in this. There is buy-in worldwide

amongst people who will be doing these trials. So, I think it might be worthwhile using this as just a framework because if I look at this, this looks to me like a lot of our inclusion or exclusion criteria for the bulk of projects, at least the local inclusion and exclusion criteria, personally.

DR. LEGGETT: One last comment because I don't think we are ever going to get an answer today and we still have five or six more things to do. Joan?

DR. HILTON: I was also thinking about the validation that I mentioned as being driven by the need to define the eligibility criteria. So, some of these PEDIS categories, say three categories, some are continuous like size and such. So, the objective that I had in mind is to try to find where to draw cut points for each of these five and possibly for a few additional factors like cellulitis and control of infection.

Then in the analysis of the clinical trial each of these could be analyzed as individual prognostic factors. But what I was thinking that you needed to get to right now was how to define a homogeneous subgroup of subjects, with sort of a homogeneous risk of quality of life, or amputation,

or whatever some important outcome is rather than including all patients with diabetic foot disease.

DR. LEGGETT: Thank you. Why don't we move on to question two, which we have sort of addressed already, in patients with preexisting skin ulcer, how does one define infected versus non-infected ulcers? Jan, I think you made the comment before of two or more criteria.

DR. PATTERSON: Well, I think the PEDIS classification, in terms of criteria for grade II, grade III infection, I would think that would be a pretty objective way to do that. Grade IV has systemic inflammatory response, signs and symptoms as well.

DR. LEGGETT: Any other comments, other than what we already mentioned?

[No response]

Number three, what is the most accurate way to obtain microbiologic information in patients with diabetic foot infections? Alan?

DR. CROSS: I guess a question I have is that looking at the data, the most impressive data was from a supplement. That is, the Trager study looking at quantitative bacteriology looked like it really was able to separate out what was probably

infection from non-infection and avoid problems of swab and other things. I am just puzzled. That was done a while ago and there certainly is a lot of precedent for doing quantitative cultures certainly in burn patients. I am just curious why that hasn't been followed up by other studies in peer reviewed journals.

DR. LEGGETT: David, could you address that again? Do you think the people who would be doing these trials would all be adapt at and willing to enter somebody in a trial with a quantitative culture?

DR. ARMSTRONG: I am not sure that it is even as important as who is taking the culture because I think that could be standardized. I think that is not very well standardized right now, but I think that could be standardized. I think while I would love to see quantitative cultures taken everywhere, I think there might be a mutiny in a lot of microbiology labs if a lot of these were taken. We try to get them--I am just speaking from our center, and I think trying to get them and trying to get those standardized is somewhat problematic.

That said, it would be wonderful if that

were done. But I would personally just want to try to work to standardize things on the front end, that being that we take good quality biopsy from the actual wound. I am not talking about a giant biopsy where you take a big divot out of the wound. I am talking about a biopsy from the actual wound which is relatively easy, or taking wound base curettage which is also easy to teach and do. I think that is just not done enough. I think in most of these studies you sometimes have a technician that is just swabbing the wound and then it will sit on the desk for three or four hours. Then, when it gets down to the microlab, as Ben Lipsky often says, it is a Rodney Dangerfield--you know, it doesn't get any respect. So, I don't think we get a true estimation of what we are growing out of these wounds.

DR. LEGGETT: Barth, would you like to address this from a microlab's point of view or any other way you want to address it?

DR. RELLER: I am hesitant to do this but while these were being presented I jotted down ten aphorisms about microbiology.

[Laughter]

First, many are colonized; fewer are

infected. Two, unlike people, all microorganisms are not created equal. Three, the less secure the meaning of the microorganism, the more rigorous the need for quality of the specimen. Four, quantitation may be important but it can't replace the quality of the specimen. Five, transport is important but a dog in the first class seat is still a dog.

[Laughter]

Six, infection yes/no is a clinical enterprise. It can be supplemented by imaging. For example, physical exam is important but chest x-ray is also important for diagnosis of pneumonia. So, it is a clinical enterprise. Seven, not all clinicians are Osler. Eight, histology is historic but it is still relevant. This is for the osteomyelitis. Nine, microbiology can help with the etiology. Indeed, it is crucial for therapy susceptibility testing but it doesn't make a diagnosis of infection. Ten, just thrown in for clinical trials, specificity is more important than sensitivity.

So, what does all that mean? Our laboratory accepts swabs but it only looks for Staph. aureus and group A streptococcus. You don't

have one of those two, that is all you are going to get from an aerobic culture of a swab. There is a greater intensity of effort depending on the quality of the specimen. You know, we get to the other end and get a bone biopsy and you have a pristine--you know, the ultimate in specimen and whether you request it or not you will get aerobic and anaerobic culture. We know that there can be a mixture of organisms in some of these infections but we still think Staph. aureus and group A streptococcus in the early stages--and these things, as we know, may evolve. What starts out as one thing, with treatment and you don't take care of the vascularity, etc., may down the line get into something worse, sort of the elevation in the grades in the PEDIS scheme.

So, if you are going to ascribe significance, and there are published reports of this, for osteomyelitis you had better have a very good specimen and swab won't hack it. So, I think although these are not ironclad, I think that they can be translated. You know, swabs are not acceptable unless you isolate the Staph. aureus or group A streptococcus. So, those are some of my thoughts.

DR. LEGGETT: What about swab of a purulent drainage? In other words, there is frank pus. Put your swab into that area.

DR. RELLER: Colonizing organisms love pus.

DR. LEGGETT: Is that number eleven? John?

DR. BRADLEY: It was nice to hear David say that the biopsy wouldn't be the problem but the microbiology lab would be. Having done investigations in appendicitis, if you want to see a microbiology lab go crazy just have them isolate all the organisms from drainage from a ruptured appendix. I think the best way to define whether there is an infection present--and I have looked at biopsies from burn wounds--is a quantitative culture and histology on a biopsy. If you think that the biopsies can be done, then that is defined evidence. You can have a pathologist look at all of the histologic samples. You can look for evidence of invasion as opposed to the organisms sitting on top of the skin. You get some idea of whether the skin is viable or not. So, you can find out whether it is invasion of viable tissue, which would meet your definition of infection as

opposed to just a soup that is necrotic tissue in which organisms are growing. So, if a biopsy can be done, I think that is clearly the most quantitative, non-subjective way to document infection.

DR. LEGGETT: Just as an aside, we are headed towards an awfully expensive clinical trial if now we have the pathologists and our indium scans and our MRIs and da-da-da-da.

DR. PORETZ: I agree that Staph. aureus and group A strep. if isolated is significant even from superficial draining changes. But if you saw osteomyelitis, what was read as osteomyelitis on an MRI or a bone scan and you grew Staph. aureus from the pus, would you make the pronouncement that the osteomyelitis was due to Staph. aureus?

DR. RELLER: You are aware of the literature as well as I. I think that it is possible that you have the right organism but it has more to do with the pre-test probability of what would be causing it in a patient with diabetes in the first place. In other words, I am not so sure that from a poor specimen growing the organisms is what makes it more likely than simply that Staph. aureus is an important player in

osteomyelitis in these patients. If one has a contiguous osteomyelitis with a longer-standing ulcer, we know those things are often mixed, and my empirical therapy is often, for example, piperacillin tazobactam or something comparable to that.

So, I think Staph. aureus from the draining pus from something--if you have an osteomyelitis and there is persistent drainage, I mean, you think it is osteo there. If you have Staph. aureus growing out of that with a little bit of epi. and other things and it is relatively acute, I think the credence of the aureus also has to do with how fresh this thing is. So, if they have just broken through and you are draining pus and you have a few other things there and you get a Staph. aureus that is on a gram stain smear--that is the other thing, whether it is there on the gram stain smear--and they haven't seen a lot of antibiotics, I think it is pretty likely, along with the pre-test probability. If you have had somebody that has been around a long time, they have a chronic ulcer; the thing stinks; and just because they are in the hospital and they have MRSA growing out of the soup, along with other things, I

am not so sure. That is the patient I would like to image and biopsy. What do you think about that?

DR. PORETZ: I think you are right.

DR. LEGGETT: Jan?

DR. PATTERSON: I don't remember what number it was but I agree with Dr. Reller that quality is more important than quantity. I think that the most accurate and practical way, in terms of what can actually happen in microbiology labs, to get the information would be deep tissue curettage or biopsy or an OR debridement sample. I think quantitative cultures are not really going to be a practical way to do it. If you have some center that is interested in it and you want to do a little side study out of interest, that is one thing but I don't think across the board that would be a practical thing to do.

DR. RELLER: In the specimen that Jan is talking about I don't think one can overemphasize the importance of the gram stain smear, correlate of that. So if you have poly and you have lots of organisms and you grow something, even if there are a few other things around, I think you have infection.

DR. LEGGETT: It is not like there is not

consensus to go for what I think was called the deep culture techniques in the presentation.

The next number, and we have already sort of been approaching this but let's take a direct investigation of it, what are the considerations for clinical trials for ruling out osteomyelitis in patients in trials of diabetic foot infections?

DR. POWERS: Jim, can I ask you a question to start off with that?

DR. LEGGETT: Yes.

DR. POWERS: One of the things that Dr. Alivisatos showed in her slide was that what we see in clinical trials is all over the place. One of the other things that she said was that except for one trial, it left it up to the clinician's discretion as to whether or not to even examine the patient for osteomyelitis. When we reviewed this lit it appeared that there is a fair number of people that end up having osteomyelitis that the clinician never suspected they had in the first place. So, one of our initial questions would be should everybody in these trials get some kind of imaging study and, if so, which one?

DR. LEGGETT: Just to put up the whole range of stuff before we start talking, if we were

to just dictate a plan x-ray, realizing its sensitivity and specificity, are there statistical methods that would allow you to determine an N big enough, if we had some way of differentiating preexisting osteo or failure of a drug and developing of osteo in a clinical trial, would you, as a statistician, be able to tell us that we need 15,000 or 1,000 people? Can you overcome that noise that the x-ray is going to tell you? On the other end of the spectrum, if we get MRIs on everybody they are almost too sensitive and, you know, the same thing could apply. Is that possible?

DR. ELASHOFF: Well, certainly if you can lay out some scenario of assumptions, then it is straightforward enough to do sample size calculations. What I was thinking about myself with respect with this is to use some relatively easy definition of osteomyelitis and simply stratify patients on that basis. If the proportion of people having it is not too large, it won't dilute your trial too badly even if you are not really careful about having done it. But as long as you have some system that you have agreed on for classifying them, then you can learn a little

something by the end.

DR. LEGGETT: Ellen?

DR. WALD: It seemed to me that anybody in PEDIS classification III or IV would need to have a study because certainly duration of therapy is very dependent upon whether or not you have an osteo. So, we wouldn't want to fault a drug because we hadn't used it long enough because we hadn't made the right diagnosis. From what we heard today, it sounded to me like either indium or MRI.

DR. LEGGETT: Just as an aside, at our hospital if you use indium you need a separate explanation and a separate thing. I mean, that is going to be hard. So, you have to get not only consent for the trial but you are going to need to get a separate consent to do the indium study. Jan?

DR. PATTERSON: I think everybody ought to have a plain film and then for grades III and IV, if you can probe to bone I think you should assume they have it, or they have a plain that is positive, then have it. But if both of those are negative they should have MRI.

DR. LEGGETT: I don't know about your radiologists but our radiologists can't tell

diabetic osteolysis from osteomyelitis. Allan?

DR. TUNKEL: I agree with Jan because I think it is a step-wise approach so we should do whatever we can first to prove that the patient does have osteomyelitis. So, you see the bone, or probe, or do a simple radiographic study. Even if maybe there is controversy, that at least excludes a group of patients from the study that you don't have to consider. Then either the MRI or perhaps the technetium bone scan or indium, whatever is better, or maybe the investigator could have a choice on one of those studies if we think the sensitivity or negative predictive value is relatively good for all of them.

DR. LEGGETT: David?

DR. ARMSTRONG: I don't know if I am speaking for other people but I am very worried about this aspect of trial design, not from an academic perspective but from a practicality perspective. I am really concerned about the cost of a huge number of MRIs, the lack of dedicated musculoskeletal radiologists in various centers with the expertise and interest in looking at these, and the difficulties perhaps in getting nuclear scans in some of these centers, just by the

vagaries of protocols.

I think maybe for a large number of these infections sometimes, just for simplicity sake, serial radiography seems to have some benefit. But, again, I think as we look at those data, I don't think there are good data to guide us in that area, seeing as they are very insensitive. But for someone where there is not a high suspicion of osteomyelitis, why not have everyone get a serial radiograph? Obviously, you will be probing to bone as that is part of a local physical examination. If, indeed, the patient can probe to bone one may proceed with another investigation, perhaps an MRI, at that point and then, perhaps at the end of the study or at some point at the end of the study, get another radiograph, giving them point A and point B to compare. That would seem to reduce the cost of this versus getting blanket exams on all these patients. I don't think that is perfect by any stretch. In fact, I think it is not so good but I think this is going to be very difficult in thousands and thousands of patients.

DR. LEGGETT: Alan?

DR. CROSS: While it is true that having an MRI would add to the cost, I don't know if, as

Ellen suggested that you restricted at least as part of the protocol to grade III and IV, how much extra it would be over what would be good clinical practice. I would certainly agree with Jim that just doing plain films in the case of just diabetic osteolysis has provided more misinformation than information, and I think that would be a big mistake. So, I would simply echo that in the more serious cases it really is imperative that we rule out osteomyelitis and requiring some type of thing like MRI would not add that much over what would be required by good clinical practice.

DR. LEGGETT: Celia?

DR. MAXWELL: Just to echo the concern about cost, certainly in a population like what I see most people have no insurance. So, even getting an MRI might be difficult. It is my understanding that if you can probe to bone, isn't that one of the definitions of osteomyelitis, if you can actually touch the bone? So, it seems to me that if you can probe to bone there is a strong possibility that there is osteo and it is only when you can't really do that that you should look to some of these more definitive and definitely expensive tests. I mean, not to mention the cost

of the antibiotics. So, I think that that has to factor in when trials are done because what happens is that once a trial is done guidelines are put forth and then you are held to these standards and oftentimes it might end up costing patients access to care because you just can't provide it. So, I think that that should be considered.

DR. LEGGETT: David?

DR. ARMSTRONG: Well, just to make this more complicated, the probing to bone may not be all it is cracked up to be. You heard I think some excellent concern by Janet, and I think there may be data over the next year or two from some of the larger trials to suggest that maybe it is the pre-test probability of having osteomyelitis in your given center that confers the positive predictive value on this probe. Maybe if you have a much lower prevalence of osteo than, say, 66 percent which was in the Grayson study, then the positive predictive value may be no better than flipping a coin. I don't mean to badmouth the probe because I really believe that it is a very useful tool, with that in the back of your mind, but I think that you have to maybe combine common sense and some of these instruments. As was said

by Jan and others, that might be the way to go and maybe stratifying patients, as was said earlier, might be the way to go. I just don't think there is a good answer to this though.

DR. LEGGETT: John and then Ellen.

DR. POWERS: I think what our issue is here too is what you are going to do with patients who eventually you think have osteomyelitis. If you have a drug and the sponsor decides they don't want to study osteomyelitis, or they have a drug that, say, is a topical agent, or one that from preclinical testing has absolutely no penetration into bone, then your goal there is to exclude patients with osteomyelitis.

What we want there is almost the opposite of what we have been saying all day. We want high sensitivity because we don't want them in the trial. We are not saying don't treat them, don't do whatever you do in clinical practice but we don't want them in the trial. If, on the other hand, you are going to roll them over into a separate trial, now we want both. Now we want high sensitivity and we want to be sure that the people actually have osteomyelitis when they get into the osteomyelitis trial.

There are all the issues you said about probe to bone. I think about our earlier discussions about surrogate markers. It may be that is just a coincidence, that they had probe to bone and that you are really just picking the population that has it. So, the other issue is probe to bone may be okay in the sense that if you can probe to bone, fine; they are out of the trial from the complicated skin aspect. But if you then want to roll those people into an osteo trial, is that good enough by itself to get you in?

DR. LEGGETT: Question, does that level of discussion need to be in a guidance or can that be on a drug case-by-case basis when you work it out with the company?

DR. POWERS: I think what we are trying to do is to formulate a guidance that would address--as Dr. Norden said today, he addressed his to just systemic drugs. What we were trying to do is say how would you stratify this into, say, topical drugs versus a drug that doesn't have bone activity versus one that does. Because you would hate to see those patients just get excluded and not get studied for osteomyelitis when, in fact, the drug may have activity there. You could

examine those patients and the drug's efficacy.

DR. LEGGETT: Allan Tunkel?

DR. TUNKEL: David, I just have a question for you. If this is a person who needs to go to the OR for debridement, if a podiatrist goes in, can they make a determination in the OR and say the bone is definitively not infected?

DR. ARMSTRONG: Well, we would like to think we can. You know, podiatrists tend to think that if they cut something and it bleeds, then it looks intact. But, in fact, I think our eyes are not petri dishes or microscopes. But I think that also raises another issue. In some of those higher grade infections perhaps those patients will have a higher incidence of intraoperative debridement. Therefore, we will have a more definitive diagnosis of those patients as well. So, maybe an MRI in those patients may not be needed because we will have already taken that patient to the operating room and taken a good bone biopsy. I think that is probably what you were alluding to.

DR. LEGGETT: David?

DR. ROSS: Two points. One, certainly we are very mindful of the cost. I will just mention the patient whom I described in my presentation.

The day that we saw him we recommended an MRI. Three weeks later he still has not gotten it.

The other thing I wanted to say though is that if one is studying osteo, especially chronic osteomyelitis because we do not think that is a disease, obviously, with a high placebo response rate, that might be a setting where a small number of patients who are rigorously characterized could yield very important information on drug treatment effects and give rise to a label claim in terms of focused development.

DR. LEGGETT: I want to bring the discussion around to something called clinical cure or clinical failure. If we are doing diabetic foot trials and we are only looking at the soft tissue part of it, why does the osteo, and how can we tell the development of an osteo on therapy versus preexisting osteo, and can't you make a case, to play either devil's or angel's advocate depending on what side you are on, that improvement in that soft tissue, whether or not anything happens in the bone, is what we are after? So, I would like some discussion if people have some ideas about how we address that issue. This is assuming that we are not going to be a perfect situation and, no matter

what route we go, we are going to have at least one person in a clinical trial who has an unrecognized osteo when we sign him up for the soft tissue diabetic foot infection protocol.

DR. ARMSTRONG: All right, I will give this a try.

DR. LEGGETT: Good.

DR. ARMSTRONG: I think that when it comes to diabetic osteomyelitis and the diabetic foot we often have a little time to react. It may be sacrilegious to say that but I think sometimes we have time. In the acute limb-threatening diabetic foot infection we don't. We have to go after those patients very aggressively with antimicrobials and I think with adjunctive means like intraoperative debridement. I am certain that there are patients that will have a smidgeon of osteo after some of these acute infections are resolved. But I am not sure how critical that is from the initial endpoints that we are looking at, and I am not certain how much of--

DR. LEGGETT: I don't know we know the endpoints yet. That is the next question.

DR. ARMSTRONG: But if we are looking at resolution, say, of cardinal signs of inflammation

or recession of erythema, those will happen very frequently even if someone has, say, an osteitis or a superficial osteomyelitis, or something along those lines.

DR. LEGGETT: What if we don't realize that the drug doesn't penetrate into bone, and then we say that the soft tissue improved and, therefore, we can use this in all diabetic foot infections? Ellen?

DR. WALD: I think we will get to know because the patient will become symptomatic again. I mean, isn't that what happens? You stop therapy and two weeks later they have pain, or redness, or swelling, or drainage just starts again. So, I think, you know, you have healed the superficial part that you are looking at with your eyes but something is going on underneath and that is how you find out. I don't know of any laboratory parameters that are particularly helpful.

DR. LEGGETT: But I don't know how long we are going to be following these people to find that. In diabetic osteo it can show up three months later.

DR. WALD: Yes, when we talk about when we should look at outcome, you know, I think this is

one of those infections where you don't want to only look at the end of therapy but you do want to select some arbitrary time--one month, two months, three months, I don't know what that would be. But, certainly, we wouldn't be content with end of therapy as the complete evaluation.

DR. LEGGETT: John?

DR. POWERS: Dr. Wald, you said something earlier about we wouldn't want to discard a good drug or say that one drug is inferior to another, and that gets to the case of if you didn't know that there was an imbalance at baseline between the arms. So, that goes back to Dr. Leggett's question, is development of osteomyelitis in somebody where we are studying a drug for soft tissue infection, would we consider that a failure? So, we are looking three weeks, four weeks down the line and their soft tissue infection doesn't come back but now the person develops a draining sinus that has osteomyelitis. Is that a failure? Would you consider that a failure for the initial soft tissue infection? And, should we consider that a failure in those trials?

DR. WALD: No, I would consider it probably a failure of diagnosis. So, what you

would want to know is if the two groups were comparable, if you are comparing two drugs, we expect a miss in a certain number of cases in both groups but if you had many more misses on one side than the other, then it would suggest that it was in effectiveness of treatment rather than misdiagnosis.

5:15 p.m. DR. LEGGETT: Janet or Joan, what sort of proportion of missed diagnoses--obviously it is based on the number of the N that you have, but what is the range of mistakes that can sort of be taken care of? You made the comment before, Janet, that it often wasn't that important if it was small.

DR. ELASHOFF: Of course, that is under the assumption that you have a fairly sizeable trial. I guess it is also to some extent under the assumption that you are looking at a superiority trial because if you are looking at these kind of equivalence things where you are thinking that maybe a ten percent difference is important, then if you are talking about misdiagnosis rates of three percent or four percent, that is a pretty big piece of the outcome. I don't know what to do there but that, of course, is another reason for

finding it problematic to do a non-inferiority trial.

DR. LEGGETT: Wouldn't clinical cure or clinical failure also be depending on what the company was trying to look for? If a company wanted to include osteo in that category, then the drug would have to be considered clinical failure. If the company was only going after a soft tissue portion, could that in another situation be looked at as a clinical cure? Or, is that not possible with guidance and with those kind of considerations?

DR. POWERS: I think that is the question that we are actually trying to get at. When we look at other diseases, so if you have a child with otitis media who then develops meningitis two days into therapy, is that because that child had meningitis when they came in the door and it was, as Dr. Wald said, a failure of diagnosis? Or, does that mean the drug wasn't working in those people? It is a question in almost all trials, this one more so than others because the diagnosis of osteomyelitis is so delayed into the person's treatment that by the time you find out the person is on day 10 or 12 of their treatment and it is

hard to figure out.

DR. LEGGETT: And that is the lag phasing with MRIs, by the way.

DR. PATTERSON: Well, I think we agree that with grades III and IV we would do some type of definitive test for osteo. I guess I would just like to ask Drs. Armstrong and Norden, in your experience, people who have grade II infection, how many of those people end up having osteo?

DR. ARMSTRONG: As you are ambling up, Dr. Norden, I think a rather low percentage in people that have a superficial wound that does not initially involve bone; that may not have a long chronicity, although chronicity is notoriously difficult in these patients as well; who have a negative radiograph. The prevalence of osteo in that population, say in a grade II if you are using this PEDIS system, is quite low and the rate of misdiagnosis, at least in our experience, has been quite low. When you get higher up into these categories I think you have a greater risk for misdiagnosis, depending upon your style of treatment.

DR. LEGGETT: Dr. Norden?

DR. NORDEN: I just have a couple of

comments. I agree with David's answer to that. I think it is very low. I just want to comment on bone penetration because people keep talking about it. I have studied osteo for a long time and I have never seen a drug that doesn't penetrate the bone in all of the studies that we did. So, I don't think that is really an issue. They penetrate in varying amounts and percentages, but unless the MIC of the bug you are looking at is very high, that is not going to be an issue.

I think in terms of the question both John and David raised, if you can argue that somehow you have to say this patient has osteo, you have to make up your mind, and if you use probe to bone is positive as one of the best tests we have now and say, okay, those patients who were positive have osteo and we are going to take them out of the trial and put them in another trial, if you are going to do a definitive trial with those patients for osteo I think they should have bone biopsy. That is the definitive test. It is still the best test. You may get an organism out and then you at least know what you are treating.

I wouldn't like to mandate MRIs for everybody. I think it is prohibitively expensive

and the yield--you know, although the sensitivity and specificity may be very high, as we say, sometimes they are over-read and, as David pointed out, you need a radiologist who understands musculoskeletal radiology. We had one person in our institution that we took all bone MRIs to because he was the only one who could read them well.

DR. LEGGETT: Dr. Berendt?

DR. BERENDT: Yes, my answer would be concordant with the others, very low for the grade II type infections.

DR. LEGGETT: What kind of numbers would we be talking about in terms of what you would envisage in a trial in grades III and IV? What kind of numbers of people would we be sending to the orthopedic surgeon or the podiatrist or somebody to get an intraoperative bone biopsy or a biopsy through intact skin? Any idea of that at all?

DR. ARMSTRONG: Well, I would weigh in that clinically most of the patients that fall under those definitions by any community standard of care ought to be either taken to the operating room or at least into an area where they can be

washed out and have it investigated. So, I think I would say a large number of those patients should go for a biopsy or some form of definitive kind of investigation. Whether that happens or not, I don't know. There are a lot of times where patients will go to the operating room for a washout, say, by someone who may be tangentially associated with the study. Let's just use an example. That person would just forget to get a biopsy, and that happens a large percentage of time. This would have to be very well coordinated, but I think that that is what should be happening.

DR. LEGGETT: So, for the FDA, it sounds as if the people that are going to have osteo are going to get biopsied anyway. Then, no matter which way we do the trials, if you develop osteo that we missed it should probably called a failure.

DR. POWERS: Let me read to you an example of why we are worried about this. This was a trial that was published in JAMA in 1991 by Newman. So, this predates the PEDIS trial. How these patients apply in PEDIS, I have no idea. When you look at the patient inclusion criteria, it is 54 patients that had diabetic foot ulcers. We can't tell what kind of grading they would fit into. These are

people who had osteomyelitis determined by bone biopsy and culture, a very small number of people. But osteomyelitis was found to underlie 28/41, 68 percent of diabetic foot ulcers. Only 9 of those 28, or 32 percent, were diagnosed clinically by the referring physician, and 19 of those 28, or 68 percent, occurred in people that did not have ulcers exposing bone. When we read things like that we say, wow, gee, well, if there is nothing to stick a probe into and it is not near the probe, how is this going to help us?

The other thing is when we talk about ruling out osteomyelitis, it seems like if you stick a probe in there and you hit bone, okay, it is pretty good. If you stick a probe in and you don't hit bone, there are an awful lot of those people, according to the Grayson trial, that still have osteomyelitis.

DR. LEGGETT: Ellen?

DR. WALD: Those sound like they are patients who are grade III or more. Right? So, I think this grading system is going to be very helpful. If we say those are patients who probably do require debridement, then I think it is very logical to say that they will go to the OR and we

will get some tissue, and we will get a good culture and we will get histology.

DR. LEGGETT: Barth?

DR. RELLER: It is hard for me to imagine, at least at our place and I would be interested in Don's and others' comments, of someone going to the OR for a biopsy for osteomyelitis in this situation without imaging. I mean, it just doesn't happen at our place.

DR. LEGGETT: Why do they get the MRI? They get it because they want to know where to get the biopsy so as not to miss it and have a false negative. Ergo, I am all for Jan's approach, that people need to have an MRI and if they have osteo, then they need a biopsy to give us the histology for the histologic diagnosis and then we get a good sample so that we can get an etiologic diagnosis, which is different from a histologic diagnosis. Dr. Berendt?

DR. BERENDT: Thanks for allowing me to comment. I just wanted to say that in relation to that study by Newman that was quoted, quite a lot of people in the field also find that study worrying and, as with any other study where there is only a single study showing such a surprising

result, are anxious to understand how that fits in to what they actually see, and I don't think there is a resolution on that matter. So, I just wanted to say that, you know, that is an N of one and it ought to be ranked alongside other kinds of N of ones, recognizing that it does raise a concern.

DR. LEGGETT: Don?

DR. PORETZ: Should we eliminate the bone scan completely?

DR. LEGGETT: I vote yes.

DR. PORETZ: I do too. I just find it more irritating than anything else. We end up doing a bone scan and then we do an MRI. It seems to me that bone scan, which has been promulgated for years and years, should be abandoned for osteo as long as we have access to an MRI.

DR. LEGGETT: Ellen?

DR. WALD: I would just be cautious to say that for this kind of contiguous osteo I would absolutely agree with you.

DR. PORETZ: No, we are talking about--

DR. LEGGETT: Diabetic foot, yes. Go ahead.

DR. ARMSTRONG: Just to respond, while I am certain that there are many centers that will

get an MRI on patients that are going to the operating room for an acute diabetic foot infection, I would say that that is probably not the majority of centers throughout the country. We will do that on many occasions but not on every occasion. Why? There are a whole host of reasons why. Most of the time it is time. The other reason for common sense because most of these infections--I mean, you are often looking at the bone preoperatively and we can see where that contiguous source of presumed osteo is so we have a good idea about where we are going to go when we take that biopsy. So, I wouldn't just say that we mandate MRI in all these patients. I would vote for an approach that says maybe an and/or kind of concept, quite frankly.

DR. LEGGETT: Jan?

DR. PATTERSON: Well, I was just going to reiterate that I think it varies very much by center. As David knows since he used to be there in San Antonio, we are very fortunate to have aggressive podiatrists who will go in and biopsy without an MRI when it is appropriate. You know, we talked about having an MRI for grades III and IV anyway, so I would think that you would want either

an MRI or a bone biopsy in grades III and IV.

DR. LEGGETT: And I don't think that we are going to come to a consensus about whether we call them cures or failures. That ought to be another day I think to end that one. That is part of number four, I am talking about.

In number five, how does one define clinical success or failure in a clinical trial of diabetic foot infections? This will probably only take 30 seconds.

[Laughter]

Don?

DR. PORETZ: Well, for the soft tissue infections you can know failure quickly. For the bone infections you are right, it may take two, three or four months because some of those things do exacerbate later on. So, soft tissue infections, you will know fairly soon.

DR. LEGGETT: When we talk about clinical success or failure, what do we mean by clinical? It is only going to be those two or more symptoms of inflammation. Or, is it going to be return of the function? Is it going to be appearance goes back to where it was? Is it going to be some wound healing? That is sort of what I was trying to get

at. David?

DR. ARMSTRONG: Yes, I would vote rather strenuously against those other, softer criteria, strictly because I think that the thing that is going to confer success in the long term in terms of wound healing, in terms of quality of life, other whatever instrument you want to apply to that, has nothing to do with the antibiotic. It has everything to do with the adjunctive care, as you heard very eloquently from all the lecturers about off-loading, debridement, activity modulation, things of that nature.

DR. LEGGETT: Do we require adjunctive therapy of everyone and then do we make it the same for everyone? What kind of leeway do we give?

DR. ARMSTRONG: I think we have more leeway here than we would, say, in a wound healing study where I think the criteria have to be much more stringent. But I think there should be guidance on regular debridement of necrotic tissue on some regular basis. We saw some data to suggest that the more we debride the better these patients do. I think that is very true, and I think there are other data to suggest that too, and I think there are center effects there too.

In terms of off-loading, that is also very important. I don't think we should mandate that these patients be placed into total contact casts. Although those are rapidly becoming what many would call a gold standard based on randomized, controlled trials, I think that most patients with infections are not going to go into total contact casts. That is a relative contraindication. But I think attention to off-loading, meaning being in a brace or something other than their shoe that caused the ulcer, that caused the infection in the first place is very important and that should be stipulated for all of these trials.

DR. LEGGETT: And do we let everybody use normal saline or do we let people use whatever the heck their wound care nurses want to use?

DR. ARMSTRONG: I will try this one. I think that as we move on over these next several years we are going to find actually fewer and fewer centers using just normal saline wet to moist dressings. Whether or not we believe there are any data to support this, while important, I think is beside the point from a pragmatic standpoint. I think maybe what we should stipulate is that there not be any active agents in the dressing that may

be antimicrobial or antiseptic in nature, or anything in there that may be bioengineered like, say, a cytokine or bioengineered tissue which are becoming more and more popular, depending on where you go, but something that is a passive dressing rather than a so-called active dressing, and there are good definitions of that now.

DR. LEGGETT: Alan Cross?

DR. CROSS: I would like to ask Dr. Berendt, among patients who have grade III or IV PEDIS classifications, what percentage of them may be expected to have loss of function? For example, unable to ambulate?

DR. BERENDT: I think that is a difficult question to answer because you would need to know the other elements of the prognostic features. So, the answer is that it doesn't depend just on the infection. Again, the data from the University of Texas showed quite well that ischemia is a massive confounder in terms of the likelihood of amputation, so that when you get into severe ischemia complicating infection, amputation rates become very high. I mean, so it wouldn't be just about infection or not. So, I am going to sort of duck it in terms of giving you percentages. It

becomes kind of multi-dimensional really but the more adverse prognostic factors you notch up, quicker you end up with very high percentages of that group requiring amputation at some point.

DR. CROSS: The point I am getting at is that it may be possible, on the one hand, to have a cure of the cellulitis but have a clinical failure in the sense of what was defined at the outset about the number of people who actually are going to amputation. On the other hand, it seems like we will have a very difficult time trying to have an agreed upon adjunctive therapy since those criteria for success and failure are even looser or more difficult to achieve. So, I think at least one thing is to try and come up with a clinically relevant, perhaps composite endpoint over and above simply a response to the cellulitis.

DR. BERENDT: I sympathize with what I think you are driving at because how can you have an endpoint that is so easy that you could have mega-trials on this kind of stuff? I can see where you are coming from. Whether that is something that is going to work for this committee in terms of new drugs which, by definition, are not going to be put through mega-trials to register them, I

don't know. I like the ambition, but I am not sure how it works for here.

DR. LEGGETT: Thank you. Ellen?

DR. WALD: It probably goes without saying, but I am going to say it anyway, that the adjunctive therapy, of course, has to be standard across all the studies that are done. Whatever it is you decide you want to have done, it really must be meticulously standardized across groups within a study and across all people who are embarking on studies.

DR. POWERS: I think the question we would ask is are there adjunctive therapies which would even affect the outcome of just the cellulitis, like raising your foot up? We have all seen people where that makes the swelling go down tremendously regardless of the antibiotic. So, those kinds of things, it would seem, would need to be standardized across the arms.

DR. LEGGETT: Agreed. Ciro?

DR. SUMAYA: A question from a pediatric mind set, but as you are looking for the clinical outcomes, I realize the adjunctive type of modalities that are used are important and a uniform assessment of that, and the type of drugs

you are assessing, and realizing that this is a long-standing problem with ischemia and neuropathy in the more severe patients, where does the glycemic control fit into the assessment of that? I am assuming that if they are wildly out of control they are not going to be doing as well. Is that assumption not correct?

DR. POWERS: The problem is it is very circular. Having a bad infection makes your glycemia get out of control. Having your glycemia out of control is a risk factor for getting an infection. How one sorts that out, using that as an endpoint in a trial, is very tricky.

DR. SUMAYA: But does it need to be assessed at least?

DR. SORETH: Yes, it needs to be assessed, and we are at such a basic level of data capture that we cannot even say across different drug development programs that have this as an indication what the underlying glycemic control was in any given program because, if it was captured, it wasn't put on the case report form so you can't even tell, treatment versus control group, what that information was.

DR. LEGGETT: A couple of points I would

like to bring up that sort of tie in with this clinical success or failure, what do we do in the person that we want to enter into the trial--this is the osteo/not osteo--who has had some bone debrided? So, now the podiatrist or the orthopedic surgeon tells me he has bleeding bone and there is no osteo, what do we do about that, David? So he had a biopsy and the biopsy is negative?

DR. ARMSTRONG: And that raises another issue. Often this can be a quasi-excisional biopsy because we are talking about small bones. Often those small bones are the same thing that caused the ulcer in the first place. So, the clinician, when he or she is in the operating room, may say, well, I want to do something that may help cure this area of pressure as well as help cure this infection. I think if you remove all of the bone and you have a margin, I think it is fairly standard to take a biopsy of the residuum of, say, a metatarsus, for instance. Then, that person cannot be considered to have osteomyelitis.

DR. LEGGETT: Going back to Dr. Norden's hypothetical thing, you made the point--if I understood this right--that there may be multiple lesions but you should select one study lesion. I

don't know how that fits in with what the FDA or other people are saying because I can envisage a couple of different ulcers, one of which improves and the other doesn't. So, do you count them all, and how does that get factored in, in terms of success or failure? Joan?

DR. HILTON: It is actually possible to study more than one within a patient as long as you use longitudinal models that account for that.

DR. POWERS: I think what we are worried about here is getting back to something Dr. Armstrong said earlier, the difference between healing an open wound versus healing the signs and symptoms of the active infection. In that case, it probably doesn't matter how many holes you have in your foot. It is the surrounding erythema, swelling and those other things that we want to see go away, not the healing of which hole.

DR. LEGGETT: But that is what I am saying. Under your foot metatarsal the erythema gets better but on the dorsum, your unrecognized tendinitis, that doesn't get better.

DR. POWERS: I think though since we are talking about systemically administered drugs, one would have to consider that failure because the

drug is going to all of those sites.

DR. LEGGETT: So, the drug company is going to have to give us data about each particular lesion. Did I interpret what you were saying, Carl?

DR. NORDEN: Fine.

DR. PORETZ: Can I just ask one question? I was very surprised to find out that there are only three drugs that are approved for diabetic foot infections, of which one drug is not even on the market anymore. Those drugs are approved for diabetic foot infections including contiguous osteomyelitis?

DR. POWERS: No.

DR. PORETZ: So, tissue diabetic infections?

DR. POWERS: Yes. There is a caveat to that though. Well, let me make one correction. Trovafloxacin is still on the market.

DR. PORETZ: It is not being used.

DR. POWERS: I know it is not being used but it is still on the market. But one of the issues is there are a number of drugs that have been studied for complicated skin and soft tissue infections. The question is how many have actually

looked at the specific subset of people with diabetes and foot infections? That is what David showed, that there is a much smaller subset looking at that group of people.

One of the things that we are trying to get at too is could we actually, in terms of what we talked about for streamline drug development, look at an overall complicated skin and soft tissue infection trial and then examine a subset of people that have diabetic foot infections within that trial so we wouldn't require separate trials across the board for this as well?

DR. LEGGETT: Any other comments about this? I don't think we are going to get much further today.

DR. COX: I just want to thank everyone on the committee. I think we got a lot of very helpful discussion and a lot of very helpful advice today, helping us navigate through some of the challenges here in clinical trial design for diabetic foot infections. So, my thanks to everyone for the discussions and advice today.

DR. LEGGETT: Great. So, 8:30 tomorrow.

[Whereupon, at 5:40 p.m., the proceedings were recessed, to resume on Wednesday, October 29,

2003 at 8:30 a.m.]

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