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P R O C E E D I N G S

INTRODUCTION

CHAIRMAN CRAIG: I think we'll go ahead and start Friday morning's session. That way, we can hopefully get done a little bit earlier today and get everybody off.

We have no requests for the open public hearing, so we have already gained a half an hour there. So we will start with urinary tract infections, uncomplicated and pyelonephritis, and Janice Soreth will be doing the FDA presentation.

URINARY TRACT INFECTIONS

UNCOMPLICATED AND PYELONEPHRITIS

FDA PRESENTATION

DR. SORETH: Good morning. I'm Janice Soreth and I'd like to talk to you this morning about urinary tract infection. Perhaps before I start, though, Dr. Feigal, did you want to make any comment about--

DR. FEIGAL: Yes.

DR. SORETH: Do it later? Okay.

If you look at the description of urinary tract infection for categories to be studied, you'll find in the IDSA guidelines half a dozen or so that are listed, some of which I've indicated on this slide, acute uncomplicated UTI in women, acute pyelonephritis, complicated UTI and UTI in

men, asymptomatic bacteria, and prophylaxis for recurrent UTI, and furthermore, a separate section on the study of UTI in children.

By contrast, categories listed in the FDA Points to Consider document are just two, that of uncomplicated UTI or cystitis and complicated UTI and pyelonephritis, recognizing that pyelonephritis can be both complicated or uncomplicated, but that given that the regimens and duration of treatment are more similar for pyelonephritis, we tend to recommend that it be studied within the context of complicated UTI.

Just to give an example of a recent label that was given for an anti-infective with regard to treatment of urinary tract infection, it read as follows. Uncomplicated and complicated urinary tract infections, including pyelonephritis caused by a list of organisms with some mention of severity of infection, including cases associated with concurrent bacteremia with these organisms.

Now, I'd like to confine the rest of my talk to that of uncomplicated UTI, known by a variety of other terms, including cystitis, acute cystitis, and dysuria frequency syndrome. This is a clinical syndrome in women and it's characterized by the following. Dysuria frequency and/or urgency in combination with pyuria and bacteria with

no known underlying renal or urologic dysfunction or obstruction. The next slide.

The inclusion criteria are non-pregnant adult females with clinical signs and symptoms of a UTI, dysuria frequency, urgency, supra-pubic pain with the onset of symptoms 72 hours prior to study entry.

We require one positive pretreatment culture obtained by a clean-catch midstream urine within 48 hours of enrollment in the study and we have chosen to define that now and in the past as showing greater than or equal to ten-to-the-fifth colony forming units of bacteria per ml. In vitro susceptibility testing needs to be done for the uropathogen to both the test drug and the control drug.

By contrast, the IDSA entry criteria for women with acute cystitis include pyuria, defined as greater than ten white cells per cubic millimeter when unspun urine is examined in a counting chamber. And also by contrast, the IDSA entry criteria include and define a positive pretreatment urine culture as showing greater than or equal to ten-to-the-three colony forming units per ml.

Significant bacteria is defined depending on who you talk to. Certainly, not all experts agree on what the most reliable counts are for significant bacteria, and I'll just mention briefly, as Dr. Sousan Altaie will go into in

greater detail momentarily, that Kass first defined significant bacteria as the presence of ten-to-the-fifth or greater colony forming units of bacteria per ml in a clean-catch midstream urine sample.

If we go to the other extreme, Walter Stamm and colleagues have defined it as ten-to-the-three or greater colony forming units per ml demonstrated by supra-public aspiration or catheterization.

Exclusion criteria include males, women who are pregnant, nursing, or not using a medically accepted effective method of birth control, and three or more episodes of acute uncomplicated UTI in the previous 12 months. Further exclusion criteria are those of factors predisposing to the development of urinary tract infections, including things like calculi strictures, polycystic kidney or a neurogenic bladder, and the onset of symptoms 96 hours or more prior to entry.

Patients are not to be febrile, defined as a temperature of 101 or greater, and any sign or symptom referable to an upper-tract infection is excluded, flank pain, chills, et cetera. There should be no known or suspected allergy to test or control drug, and treatment with other intimate corpules within two days prior to study entry is prohibited.

Treatment duration can certainly range, and we've approved products now ranging from single-dose therapy to three days to the more traditional seven to ten days. The comparator agent should be an FDA-approved product with a similar duration of therapy so that short-course therapy is most appropriately compared to short-course therapy, and I would add preferably on the high range of efficacy to avoid inherent problems with biocreep.

Assessments are as follows. An entry assessment, including the usual history and physical, et cetera. An on-therapy assessment used to be required years ago but we now consider that optional, and certainly a telephone contact with the patient is really, I think, all that's necessary, with patients then coming back in to the clinic or office only if their symptoms are not very much better or anything untoward is happening.

As far as post-therapy visits are concerned, we like to see the patient back at five to nine days after the last dose and consider this the test of cure. It is not exactly clear to me whether or not we should require a four- to six-week post-therapy visit. I think there are reasons pro and con. Certainly, I like to see some of the patients come back at that point, but we may talk about that in the discussion.

Outcome measures are alluded to in the Points to Consider document and I've mentioned them here. An evaluable patient should be both clinically and microbiologically evaluable, and generally, the primary efficacy parameter is microbiologic outcome at the five- to nine-day post-therapy visit. The study should also, however, show the general correlation between clinical cure and bacteriologic eradication.

Definitions of microbiologic outcome include the following. Eradication, defined as a urine culture taken within the five- to nine-day post-therapy window that shows that the uropathogen or pathogens present at enrollment at a level of greater than or equal to ten-to-the-fifth have now been reduced to less than ten-to-the-fourth, and here, I think there is also some wiggle room for variation on where you might put the cutoff and I think we might hear more about that from Dr. Altaie and Dr. Reller.

Persistence, we have defined as a urine culture taken anytime after the completion of therapy that grows ten-to-the-fourth or better colony forming units of the original pathogen.

Just a moment on the eradication persistent point. I guess it is a fair enough question to say, why not require a sterile culture? We do for most other things where we

have a microbiologic endpoint that we emphasize, and it has to do with the obvious way that clean-catch--put "clean" in quotes--midstream urines are gotten and there probably isn't a heck of a lot that's clean about them, as much as patients may try. So to get around the issue of contamination, we have set the bar as I have mentioned.

Superinfection is defined as a urine culture growing ten-to-the-fifth or greater organisms of the uropathogen other than the baseline pathogen, and if it is noted during the course of active therapy it is called superinfection and if the same pertains after therapy is completed we have variably called that new infection or reinfection.

Recurrence, on the other hand, is a urine culture that grows greater than or equal to ten-to-the-fourth organisms of the original pathogen taken anytime after a documented eradication in the five- to nine-day window, and if we include that later visit, up to and including the four- to six-week post-therapy visit. And I have already mentioned reinfection, also known as new infection.

Clinical outcome, I think in the briefing packet, and the document is available on the Web, these micro and clinical outcomes are separated for five to nine days post and four to six weeks post, but for the sake of brevity, I

combined them here. A cure is simply the resolution of pre-therapy signs and symptoms within a reasonable period of time with no evidence of their resurgence at the follow-up visit at five to nine days or at the longer window of four to six weeks.

Failure, conversely, is no or little response to therapy, continuing or worsening of most or all pre-therapy signs and symptoms at the follow-up visit five to nine days after the last dose of drugs.

Another point to be made here is that in treatment trials in which the test drug and the comparator were of different duration, what we have asked sponsors to do is to look at the five- to nine-day window after the last dose of the longer arm, although that point is also controversial.

Improvement really has meaning only in the context of the five- to nine-day window in which you would see most but not all of the pre-therapy signs and symptoms gone.

A relapse is defined as a resurgence of signs and symptoms after the four- to six-week post-therapy visit.

Just a little bit about the rationale for requiring what we feel are strict criteria for bacteria in new drug trials. I had the good fortune to talk briefly with Dr. Reller yesterday and he pointed out to me that Dr. Cal Kunin has just recently published his fifth edition on

urinary tract infections, prevention, diagnosis, and management, so that gave me the opportunity to steal from a better writer.

Not all clinical investigators have adequate experience in obtaining clean-voided urine specimens and are capable of differentiating low-count bacteria from contaminants.

Secondly, drugs are certified by us for UTI regardless of the bacterial count.

Thirdly, low-count bacteria might respond differently, and presumably, more favorably, to shorter courses or lower doses of drugs.

Urinary tract infections are common and we don't really think that there is a recruitment problem inherent at leaving the definition at ten-to-the-fifth or greater.

Last but not least, and I think this is probably a good segue into Dr. Altaie's talk, it's difficult to define the endpoint for microbiologic eradication when patients with low-count bacteria are enrolled in trials because uropathogens may continue to colonize the periurethral zone even after bacteria are eradicated from the bladder.

So I think I'll stop there, and unless there are any burning questions, turn the podium over to Dr. Altaie.

CHAIRMAN CRAIG: Any burning questions?

[No response.]

CHAIRMAN CRAIG: Dr. Altaie?

COMMITTEE PRESENTATION

DR. ALTAIE: Good morning. I'm Sousan Altaie, a member of the Clinical Microbiology Group at the Division of Anti-Infective and I'm trying to attempt to justify or explain why the deviation from the IDSA recommendation and how we feel about the UTI and the entry criteria.

Our approach in the Division when we label drugs is to label a drug for a specific indication in conjunction with a specific organism, with the exception of, let's say, neutropenic patients, for neutropenic patients. But otherwise, we try to label the drugs for specific indication associated with a specific microorganism.

When we look at the evaluability criteria, we are trying to have a 100 percent diagnosis of a disease and deal with the populations that there is no bias or there is no doubt about them having the condition.

Then to define the clinical and microbiological cure or endpoints in order to determine efficacy rates in comparison with an already approved drug, we need to keep the base intact when we are comparing drugs to look at drugs as they come on the market, which one is probably more efficacious in a given case versus the other one.

Today's situation, as far as our evaluability criteria is concerned, as Dr. Soreth mentioned, is a patient--we enter patients with a symptom and these are dysuria frequency or urgency and supra-pubic pain with the period of onset less than 72 hours, equal or less than 72 hours, and identified uropathogen at greater than or equal to ten-to-the-five colony forming units per ml in a clean-catch urine specimen, and we do want to see the in vitro susceptibility testing on those isolates.

To determine clinical and microbiological cure after therapy, the patient must have resolution of symptoms and have clean-catch urine specimen with originally identified pathogen at counts less than ten-to-the-four.

Now, how did we get here? The history goes back to Kass and his colleagues in '56 and '57 and they collected asymptomatic patients and women with acute pyelonephritis and they did quantitative cultures on clean-catch urine specimens collected from this group of people. When they analyzed their data, they came up with two groups of individuals in that population, a group that had significant pyuria as they defined it, greater than ten-to-the-five colony forming units per ml, and they were associated with morbidity.

The other group were the ones that had

insignificant bacteria and they defined it at less than ten-to-the-five and those were considered as contaminated urines because they were not associated with morbidity in the patient.

The sensitivity and specificity that came out of these studies was that if you take one clean-catch urine specimen from a given patient and you isolate a uropathogen at ten-to-the-five colony forming units, you will pick a patient with an actual UTI 80 percent of the time and you will be 100 percent specific in your population. If you take two or greater specimens from the same population and you isolate the same uropathogen twice at this count, your sensitivity comes up to almost 100 percent and you are still 100 percent specific.

Thereby, the goal of having clear-cut population with UTI is achieved 100 percent of the time, and if you get less than ten-to-the-colony forming units in a specimen, you are more likely to be looking at vulvo/vaginal and urethral and vaginal skin flora in a given urine, a clean-catch urine.

Also, Jackson in '58 did this clinical study. They picked up clinically manifested pyelonephritis patients and they did quantitative cultures on the clean-catch urine specimen and they came up with the same sort of sensitivity

and specificity as Kass did when they did the cutoff at greater than ten-to-the-five colony forming units.

Little and his colleagues in 1980 picked up asymptomatic women and did quantitative cultures, although a slightly different method. It's a pour plate. It's as accurate as our regular loop calibrated methods, which I go in more detail before, but the technique is acceptable and they did clean-catch urine cultures and they had the luxury of comparing it with supra-pubic aspirates from the same individual.

When they looked at single Gram-negative rod at greater than ten-to-the-five colony forming units, 92 percent of the time, the clean catch was confirmed by the supra-pubic specimen. If it was a discounted clean catch, it was 92 percent of the time present in the supra-pubic aspirate. When they looked at the Gram-negative at lower counts, their sensitivity dropped to 72 percent.

When they looked at the Gram-positive cocci at greater than ten-to-the-five counts, their sensitivity dropped to 70 percent. For some reason, the sensitivity always is for Gram-positives is less than Gram-negatives and that comes in different studies and it seems to be consistent from study to study. When they dropped the counts to ten-to-the-five, they were only 30 percent

accurate when they were looking at a clean-catch urine.

When the clean-catch urine specimen in the same studies contained more than one organism in the urine at this high of counts, there were only 11 percent of the time when they could confirm the infection in the supra-pubic aspirate, so now there is another player in the game and it's not just the counts but how many in the urine are present. If you look at more than one organism being present in a clean-catch urine, you're only 11 percent of the time diagnosing a true UTI.

When the clean-catch specimen contained greater than one in the lower counts, their specificity dropped to two percent, and now these will be coming in a range of unacceptable non-specific population.

In this situation in his study, pyuria did not help to confirm the diagnosis of UTI because patients that were not infected had no different in pyuria amount than the ones who were actually infected, and otherwise telling us the pyuria has other reasons but the bug in the bladder.

Roberts also did studies in 1986 and they had bacteremic pyelonephritis patients. They did quantitative clean-catch urine counts and they went back to the same kind of 82 percent having greater than ten-to-the-five colony forming units. However, they came out with this around 18

percent of the population that did have bacteremic pyelonephritis but their counts were lower and that is the population, obviously, we will miss if our counts are hold up to ten-to-the-five.

It is a tradeoff. Do you want to keep the 20, 18 percent population and deal with the biased non-specific population that might not have a UTI or do you want to be very specific and have a clean-cut diagnosis of the disease and then take a look at the drug, does it treat or not?

Now, that was, at that time, or the old class urologists believed that you don't treat a patient if they don't have counts greater than ten-to-the-five and that obviously is not the case because the previous Roberts studies showed that the individuals, 20 percent of them do have UTIs and they have to be treated.

So Stamm initiated studies and his coworkers in 1982 to try to promote treatment of those patients even though they had less counts. Now, this is clinical management. It's not clinical trial. I want to emphasize that. This clinical management of this patient is totally a different issue than clinical trials. You want to take care of a patient and make it feel better, but in the clinical studies, we don't want to confuse the ones that do not have the disease and include them in our population.

He did an elegant study and he had 187 symptomatic patients and he did some clean-catch urine specimens with the supra-pubic aspirates and he also did white cell counts, a very defined method of having the unspun urine being counted in the counting chambers, which is, I want to add, not a usual practice in any clinical laboratory.

He also, to prove his point and have the studies drive his point of treating these patients, sampled a larger sample, 100 times larger than a regular standard technique of culturing the urines if they are clean catch and ten times larger than the sample if it was a supra-pubic aspirate.

Otherwise, I want to emphasize that the standard technique nowadays in clinical laboratories, if you have it, it's sample related. It's a specimen related. If it's a clean-catch urine, you take a calibrated loop that carries 0.001 ml of the urine and put that on the plate and count, and the colonies that will grow, if one colony grows, you say I have 1,000 colonies per ml of urine.

So he went up to his sample size as 0.1 ml. Otherwise, he could detect up to ten colonies in--down to ten colonies in his samples. One of his colonies on this plate represents ten organisms and one in here represents 1,000 organisms. I want you to keep this in mind and down

the road I will say why he is able to go down, because his sample is larger.

Then they were able to identify with their methodology 98 out of 187 that had Gram-negative rods in their supra-pubic aspirates at counts ten-to-the-one to ten-to-the-five. Now, all the results from now on are the results in the supra-pubic aspirates. There is no comparison with the clean-catch urine in that paper because he had the luxury of having the supra-pubic aspirate and being able to diagnose the disease by having this kind of sample.

So this is the emphasis again. With his technique, he was able to count one to 10,000 colonies on their plate. Of course, this is a consolidated growth. He also was doing dilutions to be able to count this high in actual colonies.

If he had done the way the other laboratories would do, he would have been only able to pick up 91 patients with a Gram-negative in their supra-pubic aspirate because the detection limit would have gone up. Otherwise, the missing numbers were the ones that had this kind of count.

Eighty-nine percent of these patients had no Gram-negatives in their urine. From this 89, 26 had

non-Gram-negative rods and the breakdown is like what you see, Staphylococcus saprophyticus, Staphylococcus aureus, enterococcus, and other organisms, one each in six patients.

The remaining of the 89, the 63, were sterile urines. They were sterile supra-pubic aspirate urines, and 38 of them had pyuria. Half of the sterile specimens, supra-pubic aspirate sterile specimens, had pyuria and 15, almost half of those, had chlamydia trachomatous, so if you incorporated pyuria, you are dealing with patients that do not have UTI. This is just half of them. The other half have non-infectious reasons for having pyuria and they could have stones, they could have malignant tumors, they could have objects that don't belong in the--otherwise, instrumentation of whatever else that causes the pyuria.

So from the 98 that had Gram-negative, they all had pyuria, so specifically, pyuria is good to detect Gram-negatives.

Of the Gram-positive ones, they also had pyuria, so pyuria is specific when you have actual true UTI but it becomes also--it is sensitive in detecting UTI but it is not specific, so you give up specificity for the sake of sensitivity. I don't want to have that tradeoff when I'm looking at clinical trials.

Ninety-eight out of 98 with Gram-negative in

supra-pubic aspirate had--this is the only time when he refers to clean-catch urine. He says all the 98 that had Gram-negatives in their supra-pubic had similar counts in their clean-catch urine. There is no mention of what else was in that clean-catch urine.

Obviously, it wasn't a mono-organism because you are dealing with a clean-catch urine. It had other organisms, and typically when you look at a clean-catch urine, you see one or two colonies of, let's staff, staph, one or two colonies of lactobacillus, one or two colonies of enterococcus, and you see ten-to-the-five colonies of Gram-negative rod. Well, which is the culprit?

He could tell which was the culprit because he had the luxury of having the supra-pubic aspirate that had only one organism and he could tell which one was the pathogen, and if you're looking only at clean-catch urines, you are actually not able to say who is the pathogen if your counts are down to ten-to-the-three. That is one single colony on the plate. And then he says only half of those people who had UTI had counts greater than ten-to-the-five.

Now, to compromise, we say ten-to-the-five or greater. Otherwise, we include some of these patients that--some of these 40-some-odd patients that were not correlating with the supra-pubic and we include them in the

populations just because there is a possibility that they do have UTI. I don't want to go below ten-to-the-five because then I would lose specificity.

To continue with their findings, ten-to-the-two to ten-to-the-four colony forming units is often associated with the infection of lower urinary tract and they will say they have a sensitivity of 95 percent and specificity of 85 percent. This is the catch.

However, I'd like to quote a sentence from his paper that he graciously acknowledges the only way he could diagnose his UTI was because he had the luxury of supra-pubic aspirate. Contamination can be identified unequivocally only by demonstrating that urine collected by supra-pubic is sterile whereas mid-stream urine culture grows one or more organisms.

But his effort was not lost and most of the urologists now follow this format for treating their patients. This is clinical management. Nitrate is important, these are dipstick tests, and symptoms are important. If your dipstick nitrate and esterase is positive and you have symptoms, you really do not need to do culture. The result would be probably greater than ten-to-the-five and your diagnosis should be cystitis or pyelonephritis. You don't even need to culture if these

things are positive.

If you have the nitrate and you have the esterase but you don't have the symptoms, you're dealing with an asymptomatic patient that has bacteriuria and you probably don't need to culture because the result is going to be ten-to-the-five or greater.

If you have a negative nitrate and you have a positive esterase, provided the esterase test was not one of the finicky ones and that it was a morning urine and you have symptoms, then culture. The result is probably greater than ten-to-the-five and your patient still has cystitis or pyelonephritis.

If nitrate is negative and esterase is positive and patient is symptomatic, do culture. The result will be probably less than ten-to-the-five and you're dealing with chlamydia trachomatous or GC or uroplasma uryliticum.

If you have don't have a nitrate and you have an esterase and you have no symptoms, do culture the patient. The result is probably negative and you're dealing with tuberculosis or non-infectious agents, hence the pyuria aspects right here.

If the nitrate and esterase are both negative and your patient is symptomatic, you're probably dealing with a viral or chlamydia. Don't even attempt culturing the

patient. And if everything is fine, the patient is okay.

This was valuable, because now patients who had less counts and have the other conditions were being able to get treated and get relief two or three days ahead of time.

Sometimes we say it is important to treat these patients because if you don't treat them, they come back two days later with counts greater than ten-to-the-five. So you use the other two, esterase and nitrate, to treat the patient two days ahead of time.

The American Society of Microbiology has the guidelines for how much a specimen should be worked up in a laboratory, and as I tried to demonstrate to you, it's not just the counts but it is the density of the isolate--it's not just the density of the isolate but it's the number of the isolates, the kinds of organism and also the clinical information you get and the type of the specimen. Is it supra-pubic? Is it a clean catch? Is it a catheterized specimen? So there are guidelines of how much you work out and how real the picture you see on the plate and how it correlates with the patient.

So in summary, I would like to say our thoughts are not to drop the criteria for positive culture down to the ten-to-the-three like the IDSA recommends and the reasons are as follows. Standardized techniques for

culturing clean-catch urine uses 0.001 ml of specimen. The ten-to-the-three colony forming units will appear as one colony on the plate and increases the margin of error.

Was that colony actually from the patient? Was it from the air when they were culturing the specimen? Was it from the plate that they put the specimen on? Was it splashed from other sample under the hood on this plate? So one colony is really not appropriate to judge a clinical condition with.

We also lose the ability to identify the true pathogen, because if you're going down to one colony of enterococcus and one colony of Gram-negative rod, which one is the culprit? I can't tell. There's one of each.

We also lose the ability to measure--what's happening here?

[Pause.]

DR. ALTAIE: And we lose the ability to measure eradication of uropathogens because when you drop your count to ten-to-the-three, your loop is going to only detect one colony. What is cured, no colony, one to none? That is a very tight limit. Actually, if you repeat the same urine twice or three times, you're very likely to get no colony on the next slate. The technique is so that it is reproducible but not 100 percent of the time.

Not necessary to include pyuria, and I hope that I illustrated, we lose specificity if we include pyuria.

I would like to leave the enrollment criteria as it is, with patients being systematic and having a clean-catch urine that has equal or greater than ten-to-the-five colony forming units per ml and leave the cure as less than ten-to-the-four or we can drop it even lower because you could go down.

If you look at a regular laboratory--I can give you some statistics from a previous lab that I was running. If you look at the urine specimens that come in the laboratory and you do the standard technique of 0.001 ml, a calibrated loop on the plates, 50 percent of those samples are sterile. So it is possible to get a sterile culture. And from the other 50 percent, half go trash and the other half will demonstrate a true UTI.

So there is room for wiggle to go below, depending on how the Committee feels, but as a microbiologist, to me, ten-to-the-nine colonies is the same as three colonies on the plate if they are the same. If they're different, that's a different story. Then they all are trash.

So I leave that open for discussion, and that would give us advantages when we keep the situation, to have a uniform and standardized culture technique and it will

allow for uniform and standardized culture result interpretation by the reporting microbiologist who is used to doing that that way and doesn't have to do something different and the physician that ten-to-the-five colony forming units will be seen on the plate as 100 colonies, eliminating the margin of error. When you see 100 colonies on the plate, you have no doubt it came from the patient, not from the air, not from somewhere else. The next slide, please.

The other advantage is the ability to identify the true pathogen. The one that has the higher count is the pathogen you're looking at and you don't need to worry about the enterococcus at less counts. The ability to measure eradication of the uropathogen, because ten-to-the-four or less is within the detection limit of the technique.

With that, I would like to thank my colleagues on my clinical microbiology team, Peter Dionne, Harold Silver, James King, Linda Uthrop, Fred Marsik, Robert Whitten, and our team leader, Dr. Sheldon. I'm willing to answer questions.

CHAIRMAN CRAIG: Direct questions right now?

[No response.]

CHAIRMAN CRAIG: Okay. It's Dr. Reller now.

QUESTIONS AND COMMENTS

DR. RELLER: Bill, if it's all right, I would like to lead the commentary and the questions from where I am. My notes are intact and the slides that I would have made if I could make them have already been made by Drs. Soreth and Altaie better than I could myself.

CHAIRMAN CRAIG: Okay. Go ahead.

DR. RELLER: There are four issues that I would like to focus on for additional discussion and they relate to the differences between what has been presented and the IDSA guidelines.

The first is the categories of infection. The second, entry criteria. The third, issues regarding test of cure. And then a few comments about the follow-up period four to six weeks after treatment.

First, the categories. The clinical entities described in the IDSA guidelines are real and valid, but several of them are ordinarily or specifically excluded from clinical trials. For example, the antimicrobial prophylaxis in recurrent UTI, one of the exclusion criteria is that there haven't been those recurrences frequently in the preceding enrollment.

Secondly, the asymptomatic bacteriuria, the only place that it has been proved that this is worthwhile seeking and important to treat is in pregnant women who

would not be subjects for the clinical trials.

So I think they are important descriptions so that in the future if there be changes, one could utilize these categories. But what I'm saying is I support the simplification into the two categories of acute uncomplicated and complicated.

Now, what about pyelonephritis, urinary tract infections in men included in the complicated? Dr. Kunin and others, but you might say the text for my sermon is this fifth edition. It's a wonderful book and gives ample credit to all of the fine investigators, including those notable persons who wrote the IDSA guidelines, so that there is full acknowledgement of the importance of their work but different practical conclusions which have already been presented.

One interesting issue in a follow-up, a long-term follow-up study of women with acute pyelonephritis is actually a striking years later higher risk for problems related to the urinary tract, so that I think it's perfectly reasonable to include acute pyelonephritis in the complicated. Even though in an individual patient there may be ready response and things look quite uncomplicated, that's not necessarily true when one looks at the whole population ten to 20 years later, which has been done.

So those are points, I think, to consider in support of the condensation into the two major categories as regards clinical trials.

Second, the entry criteria. In the IDSA guidelines, there are three entry criteria. The lowest hurdle for the cystoureteritis low colony count coliform infections at ten-to-the-three and symptomatic women. For acute pyelonephritis, it is ten-to-the-four and for urinary tract infections in men and acute pyelonephritis, and ten-to-the-five with complicated urinary tract infections.

I know of no data that support different break points based on whether the infection is in men, women, or complicated. Rather, the different concentrations of bacteria have more to do with the reproducibility and correlation, as Dr. Altaie has pointed out, with supra-pubic aspirates.

From a clinical standpoint, a pure culture of ten-to-the-four organisms in a well-hydrated person that would be confirmed by supra-pubic aspirate, no one is in any way denying that that lower count is just as important as a higher count but it has to do with the practicality of reproducibility in clinical trials.

So I think that from a trial standpoint, there are very good reasons for retaining the higher hurdle of

ten-to-the-five.

The pyuria as being a very sensitive but not specific, that is, one can, in the absence of pyuria, for practical purposes, sensitivity SNOUT, one can rule out with high sensitivity, where specificity rule in, SPIN, I think that this is a convenient marker for those who want to be efficient in clinical trials to use pyuria not as a criterion for establishing infection which it does not, but it screens out--it is potentially a very nice screen for eliminating enrollment of patients who turn out not to have the disease.

So I think there is utility in capturing that information, but the diagnosis, as all of the investigators and Kunin emphasized, the yes/no depends on a quantitative culture of urine.

Additionally, the guidelines emphasized of wanting to have--be certain that there are adequate numbers of *Escherichia coli* infections because that's the most common cause of acute uncomplicated and outside of catheter-related infections and so on. It's still important in all patients.

Because the nitrate test for practical purpose, that is, reduction of nitrate to nitrite, is a cardinal feature of all enterobacteriaceae, the convenience strips can pretty much assure you that if they be positive, that

is, the leukocyte esterase and the nitrate to nitrite positivity, that one has the kind of infection that one is looking for in the clinical trials.

The IDSA guidelines emphasize the importance of ten white cells per microliter by hemocytometer counting. As has been pointed out, this is very impractical to do in today's automated laboratories. Kunin and others have pointed out that actually, the leukocyte esterase correlates quite well, a sensitivity and specificity in the order of 90 to 95 percent with those hemocytometer counts. Moreover, in a patient with symptoms where the pretest probability is high, those turn out to be very useful in selecting patients who would be good candidates for enrollment and likely to yield the organisms that we are looking for.

Kunin also emphasizes that the ten white cells actually is perhaps too sensitive. He likes 20 because in this population group, it is very difficult to avoid any white cells when one looks at large numbers of women in the target population, so that the leukocyte esterase positivity, I think, is a good substitute for the quantitative chamber counts which are impractical.

The third issue, and perhaps potentially one of the more contentious ones, is what should be the specific quantitative count that one should achieve after effective

therapy in a clinical trial? The guidelines of the IDSA as written is that one would enter based on ten-to-the-three or greater and one would have a persistence or failure after therapy of ten-to-the-three or greater and that success or eradication would be based on less than ten-to-the-three. We are talking about a wiggle of one colony in practical terms that is simply, to me, you know, an unacceptable separator for assessing effective therapy.

Now, I always like to go back to what is the natural state of things. The natural state of things is that women and men, but particularly women acquire asymptomatic bacteriuria in rough terms at one percent per decade of life, so that in the reproductive age group where most urinary tract infections occur, 15 to 45 years of age, one could expect a three to five percent background asymptomatic bacteriuria and that's exactly what's found in studies of pregnant women in first trimester pregnancy where screening is not only recommended but is a part of good practice.

So the flip side of that is 95 percent of women in this age group ought to have a urine culture and with a reasonable collection is flat out sterile using a thousandth of an ml loop. That is, they have less than ten-to-the-three organisms per ml.

And, in fact, as has been pointed out with reasonable collection and transport, most--you wonder why they're being sent--but most laboratories find that at least half of their urine cultures are flat out negative. So I don't think a negative culture after therapy is too rigorous a hurdle to achieve.

Now, why would Dr. Altaie want to have three or possibly more organisms per ml, that is, less than ten-to-the-three, a flat out negative plate? Well, there are a couple of reasons. One is one might have one or a couple of organisms that, in fact, because of even under the best of circumstances with the periurethral colonization, one might have a single organism.

The reason for three is the critical issue and I think ought to be defined is are the organisms present among those three, for example, the same organism and are they the same one that was there before. So one needs more than one colony to tell whether it is a pure culture and whether it is the same organism by genus and species as was there, the uropathogen that was there in the first place, so that one really needs to have a break point that is set in such a way that one can accurately assess persistence of the organism bacteriologically in an accurate way, so that if one had a single colony and called that persistence, as the current

guidelines suggest, that is, ten-to-the-three or greater, it may be that if there were three organisms present, they would all be different and one would discount the whole lot, as Dr. Altaie has stated.

What we are talking about, then, is that ten-to-the-five down to what's tantamount to ten-to-the-three and a 95, 99 percent reduction in organisms and with the concentrations of these active agents achieved in the urine and with the usual state, I don't think that is too much to ask, whereas if we get down to ten-to-the-four, we are not asking for very much eradication of the organism from the urine.

The last issue that I mentioned was the four- to six-week follow-up. One of the potential pitfalls in putting too much microbiological emphasis on the four- to six-week follow-up is that it enables the return and recolonization with the women who are risk in the first place owing to periurethral colonization with E. coli and certain secretory and receptor group issues, that antimicrobials that do not dramatically alter that periurethral colonization, one may pick up a few organisms. So I think there can be some false interpretation or over-interpretation of persistence of the organism the further one gets out from the acute therapy.

The last thing related to that that I think nowadays might be helpful is when one has E. coli as the initial uropathogen and at follow-up if one had two or three colonies or three colonies or more of an E. coli, it could readily be assessed to be a failure, particularly for persistence out at four to six weeks.

With the ready availability of typing techniques now, it seems to me that it might be worthwhile to have the possibility, if the sponsor wanted to go to this effort, with the initial isolate and the later one, given the frequency of recolonization of the urethral flora, and it may be with a different organism, we know in recurrent acute uncomplicated infections in these women, most of them are reinfections and have no pathophysiologic significance as regards intrinsic underlying renal disease.

If the sponsor had three or four colonies of an E. coli, for example, at four to six weeks that it looked like it was the same organism as the earlier one and they had specific molecular typing, as one would do for epidemiological purposes that showed that it was a different organism, I don't think that that presence late on should count against them in terms of persistence of the organism because reinfections are so common.

So those are the points for discussion and some of

my own viewpoints about them, largely derived from, I think, a masterful synthesis of the data as has been referred to in the 1997 edition of Dr. Kunin's work.

CHAIRMAN CRAIG: So let's start, then, going back to the first one, which is categories, of lumping everything down into two. I guess the question I would have is do you think that urinary tract infections in males is different from what one sees in females, taking aside the complicated, because I think that's what tends to happen, is it's lumped in there with the complicated. Is it the same, or--

DR. RELLER: I think the pathophysiology is different. I think most infections in men are related to or result in difficult to eradicate problems with the prostate, and given the investigative imperative that most people feel with a first urinary tract infection in otherwise healthy men that's clearly documented, I think they are complicated issues relative to the lack of problems long-term associated with acute uncomplicated infections in women.

CHAIRMAN CRAIG: So if you were designing a study for complicated urinary tract infections, you would want to make sure you had a certain percentage of males in there which you stratify for?

DR. RELLER: I think that would--I think that complicated infections, if we lump them by definition, are a

mixture of different things and it would, I think, be an ideal trial that had diversity in the complicated infection group, so that you wouldn't have only people with acute pyelonephritis, one wouldn't have only males. I'd want to see the whole lot. I think that would be a more rigorous test of how a given therapeutic regimen acts.

CHAIRMAN CRAIG: Okay. So you're require and not allow them to, let's just say, just do pyelonephritis?

DR. RELER: I would.

CHAIRMAN CRAIG: Dr. Melish?

DR. MELISH: Well, once again, I have to speak up for children. If we're going to have two categories, which I actually do support because I agree, I would like to see that there be a requirement for a certain number of children in the complicated urinary tract trials. If the trials are going to be mixed, they need to be mixed down to that age group.

I would put children per se in the complicated group because young children, it's very difficult to distinguish between pyelonephritis and cystitis and they're usually febrile. Children who were afebrile could be included also in the acute uncomplicated. But it's an important infection for children and I think we in pediatrics are more and more impatient with the fact that

children are under-represented in clinical trials.

CHAIRMAN CRAIG: Wouldn't that, though, be difficult initiating when you don't have much knowledge on the toxicity of the drug, since urinary tract infections are some of the first ones done?

DR. MELISH: Well, I would say that's one of the reasons why I think that children should be involved in pharmacological studies. This is absolutely a national disgrace. About 90 percent of--we are all used to, in pediatrics, adapting drugs that have never been tested in children to the use of children. Not only do we have to get used to it but we have to do it for years on end. So I understand. Yesterday, we heard that it's important to include the elderly. Well, it's important to include the children.

DR. HENRY: Henry. I support that. I think it gives an opportunity to look at closely what the pharmacodynamics are. Some of the inclusion criteria would certainly have to be looked at rigorously, and obviously in kids, getting a clean-catch urine is really not what we do, especially in the younger ones. These are cath specimens. But I think it's something that certainly has to be put on the table to be addressed and looked at once again.

CHAIRMAN CRAIG: Okay. But in general, people are

fairly happy with the breakdown into two groups as was presented?

DR. HENRY: I support that, as far as putting men into the area of uncomplicated and acute pyelonephritis. That's fine. So those two major categories, certainly, I don't have a problem.

CHAIRMAN CRAIG: I guess I would agree, too, but I would think that I would want to make sure that there are men in the study. I would not be happy with a complicated urinary tract study that only involved females and then this was giving the drug approval for using in males, because I do believe that there's differences and I think you have to have the males in there.

DR. HENRY: Well, earlier we heard that it would be looked upon how men and women might deal with the, again, pharmacodynamics of the drug, so I think that it has to be a requirement. I don't know how many men you'd have to have in a study to have some kind of--enough men included in order to have sufficient information to know about the drug and what it does.

CHAIRMAN CRAIG: Dr. Parker, do you want to comment?

DR. PARKER: On her question about how many, it's always the tough one but we'd have to set our guidelines to

how close you wanted to estimate your efficacy and some things like that. It's certainly a solvable problem and workable.

But I had a question that I'd like to address to Barth and ask if you would change or make sterner your criterion for success or differentiate between the short-term therapy applications and the long-term therapy applications. I'd like to have your comments on how you feel this may or may not, the short-term therapies, impact the development, possibly, of resistant organisms.

DR. RELLER: The principal advantages, I think, of short-term therapy are there are fewer side effects from the drug and, presumably, less alteration of--I mean, the alteration of flora depends on which drug is used, but in general, less pressure on the microbial flora. So I think there are many benefits.

I don't think that the criteria need to be nor should be changed for what constitutes success, whether the therapy is short-term or long-term.

DR. ALTAIE: It looks like I did my homework well and I didn't get much discussion opposing my proposal--

CHAIRMAN CRAIG: Well, we haven't gotten there yet. We're only on categories.

[Laughter.]

DR. ALTAIE: All right. Now, before you go into it, then, I want to add a small twist to the situation. That is the saprophyticus issue. I like to have a lower count with the saprophyticus of ten-to-the-four. That's a special case.

CHAIRMAN CRAIG: Okay. Did you have something you wanted to comment on category?

DR. SORETH: Just along the lines of the discussion of men and women and trials of complicated UTI. That's what we have had. We didn't talk about complicated UTI today, but for drugs that we have approved under the indication of UTI, with or without pyelo, men have been well represented. If they were not, it would have been so restricted in the label that only women were studied or very few men were studied, but that's not been the case.

CHAIRMAN CRAIG: What are the practicalities of recommendation from this group as regards numbers, proportion, or requirement for inclusion of children?

DR. SORETH: I think so far, what we have tended to see in the development of new molecular entities is that studies in children with UTIs are usually not done in the earliest development of the drug and the original NDA package to us. What we tend to see is something submitted to us as a supplement after the drug has been approved or in

the purview of single investigators, and it's not that we have any restriction against it. It's just that that's what we're seeing.

CHAIRMAN CRAIG: How many of the agents that are used for urinary tract are actually approved for urinary tract in children?

DR. SORETH: In children? Well, certainly none of the quinolones. That's a safe answer.

CHAIRMAN CRAIG: But that's for a different reason.

DR. SORETH: Right.

CHAIRMAN CRAIG: But I mean ones that are used in kids but were never officially approved.

DR. SORETH: Trimethopreme sulfamethoxazol [ph.], I believe, has an indication in children. I'm scratching my head. I'm thinking.

CHAIRMAN CRAIG: So it's probably a small number?

DR. SORETH: It's small. It's small. There may be--

DR. ALBRECHT: One or two of the early cephalosporins.

DR. SORETH: Cephalosporins specifically done in kids, and that's--

CHAIRMAN CRAIG: So I'm sure for the industry,

there's not much of a push or incentive to do those kind of trials.

DR. SORETH: Right. I think what we've seen recently is some single investigator INDs with single investigators coming forward to study children.

CHAIRMAN CRAIG: Dr. Feigal?

DR. FEIGAL: One of the interesting changes in the approaches to pediatric drugs has been the new approach to pediatric approvals that was suggested a couple of years ago, that said that where you can assume that the pathophysiology is the same and that the drug should work the same in adults and children, that you should then be able to base pediatric dosing on pharmacokinetic studies.

And actually, we've had some preliminary internal discussions about which infections would we feel were similar enough in adults and children that if we thought we got the same blood levels or same urine level, that that's more relevant, would we extend the indication.

You know, that may be another topic that we should bring back to the Committee. I think one of the concerns about that recommendation was that it was a two-edged sword. It would encourage more pharmacokinetic studies in children but it also might short-circuit doing clinical studies in children where clinical studies are already possible.

Yesterday, we heard an infection, otitis media, that you for all practical purposes can't study in adults, so we know children will be studied in that kind of a setting.

CHAIRMAN CRAIG: Yes.

DR. FEIGAL: But for urinary tract infections, there are so many more adults, that you can get your answer so much more quickly. I think whether or not we allow the pediatric rule to establish ages based on pharmacokinetics in some areas will probably kill off the few studies that are done and that's something we should probably bring back to the Committee at another time for your input.

CHAIRMAN CRAIG: I thought when it was talked about with using pharmacokinetics to look at other things, part of that would also, then, be a small trial to sort of document that what you were extending at least looked to be correct.

DR. FEIGAL: Not in terms of a randomized trial.

CHAIRMAN CRAIG: Yes.

DR. FEIGAL: I think there is a requirement to provide some type of safety information about the product in children, but it doesn't even have to be for the same indication, for example. You'd want to know about the adverse reaction.

DR. MELISH: Well, given that we'll talk about this at some time in the future, I would really like to point out that this is a common infection in children, and since we rely on catheterization, we probably could provide better data. The problem is that the pharmacologic data isn't done early enough for the children to be included in the trials that lead to the indication and I don't really see why that should be.

Children could be part of these trials. They would increase the power. It's easy to get children with urinary tract infections and they should be easy to study.

DR. FEIGAL: One issue that--I mean, we put our strongest priority in terms of encouraging pediatric therapies where there aren't satisfactory therapies already and one of the issues, and I actually don't know if the draft statement actually made it into the policy of one of the pediatric groups, it may have been the American Academy of Pediatrics, but they actually in one of their statements on drug development said it was unethical to study children until efficacy had been established in adults for drugs where there were already effective therapies.

I think this is one of the debates that goes on. Some of the companies actually also state that they feel that way, that it's unethical to study higher-risk

populations until they know what the benefit side of it will be. I think it's a continuum and it's all relative, but I think these are the kinds of issues we should certainly come back to.

I think we would agree with you that this is a common and studiable infection in children and that we would encourage companies to do it as early in drug development as they can.

DR. MELISH: I'd like to know what body said that. I certainly think there should be a lot of rethinking of that kind of an attitude because we've actually seen, for example, in the HIV area where drugs were not available, possibly brought to children for years after they were used in adults. If anything, it's not a vulnerable population. It's a population that's hardy and well--

DR. FEIGAL: No, but this is in the area where there are acceptable therapies. In an HIV, I think even if you take all the current therapies, we still don't have perfect therapy, so I think in HIV, it's never been the policy to exclude children. There's been an attempt to do them early.

But the issue, and it's a philosophical issue, if you had very good agents, because there is no requirement to develop a drug that it be needed. Someone can bring out the

5,000th cephalosporin in the year 2010 if they want to and it can be more toxic and less effective than existing agents if it's still acceptable.

The question would be, if you already had good agents, should you study those agents early in children, and I think that this is a debate that goes back a long time and the issue of the whole history of informed consent in terms of who is a--do vulnerable patients, particularly patients who cannot usually consent for themselves, is there a different standard of the risk/benefit for them in the setting where there's already good therapy, and I think that's kind of the--that's the issue there.

CHAIRMAN CRAIG: Can we move on, then, to talking about the entry criteria that were presented? Specifically, we've heard the recommendation or at least the concurrence by Dr. Reller of the Points to Consider document of using ten-to-the-fifth criteria for entry. We just heard, though, that somebody's talking about ten-to-the-fourth criteria for *Staphylococcus saprophyticus*. What is your feeling on that, Dr. Reller?

DR. RELER: It's true that, in general, the colony counts are a little lower with Gram-positives, but the problems of specificity are also greater with Gram-positives. So I, frankly, don't think it's worth

having two criteria for--

CHAIRMAN CRAIG: Let me ask, or maybe some of the people from the industry would be able to respond to this, too. If you look at what cases they are submitting for this indication under uncomplicated, are you getting around ten percent of them being Staph saprophyticus or are we essentially, because we have a limit up as high as ten-to-the-fifth, essentially excluding those cases from being in the group that is submitted? Does anybody want to comment? I mean, are you able to get Staphylococcus saprophyticus cases with a ten-to-the-fifth cutoff?

[No response.]

CHAIRMAN CRAIG: No response. Dead audience. What's the experience from the FDA?

DR. ALBRECHT: The experience is that the organism isn't frequently isolated, so that's my strongest impression, not whether it's ten-to-the-five or ten-to-the-four, whether it's identified.

CHAIRMAN CRAIG: So does that mean you don't see many of them, or--

DR. ALBRECHT: We see very few of them, I mean, from the number of clinical studies that I'm reflecting on.

CHAIRMAN CRAIG: Most studies looking at incidence out in the community would say that you're probably running

about ten percent in uncomplicated infections in females.

DR. ALBRECHT: When we think about the organism distribution, there's an overwhelming representation of E. coli and then everything after that, whether it's clepceloproteous [ph.] or staph, the numbers seem to be lower. That's just a perception.

DR. SORETH: And I think we may even have taken the cutoff at ten-to-the-fourth for Staph saprophyticus generally in review of applications for UTI. But we still don't get as much as ten percent. That's my best recollection.

CHAIRMAN CRAIG: I mean, personally, I would think it would be good to have some of those cases clearly in the group so that if that requires using a slightly lower cutoff, I personally would not have that problem.

DR. RELLER: On the other hand, the consequences of Staph saprophyticus are entirely different from the enterobacteriaceae. I mean, one doesn't get--I mean, in all of these acute uncomplicated, there is a small percentage who really have silent upper-track disease but it's not with Staph saprophyticus.

CHAIRMAN CRAIG: Yes. But I would bet in your patients with uncomplicated urinary tract infection, if they got upper-track disease, it's exceedingly mild with the very

high success rates that one can obtain with a single dose.

DR. RELLER: But they're not with saprophyticus. And in a way, it's like the low-colony coliforms. I mean, whatever is going to work for ten-to-the-five is going to be, for the Staph saprophyticus, is a piece of cake. They are very sensitive organisms and anything that one uses gets rid of them.

CHAIRMAN CRAIG: But for some drugs, they're less susceptible than the Gram-negatives, so that for some, you'll find more activity, but for some, you'll find less activity. I think clearly with fluoroquinolones, you'll find less activity.

DR. RELLER: In vitro, but what about clinical response with concentrations?

CHAIRMAN CRAIG: Well, if they're not in the clinical trials, how do we know? Is it important? I mean, if we're trying to reflect what the drug's going to be used out for the community, as I say, I would think it would be good to have some of those in the clinical trials.

DR. SORETH: In a recently approved application for single-dose treatment for uncomplicated cystitis in women in which the in vitro data told us that Staph saprophyticus wasn't very susceptible to the test agent, we found a very good clinical correlation that those women were

clinical failures, to answer your point.

CHAIRMAN CRAIG: Yes?

DR. PARKER: I'm not responding to that. Parker. Switching hats a little to becoming a consumer advocate and on the idea of including males as a subgroup, one of the things that I understand is done now in the subgroup is necessary to show that the efficacy is not different from the total group and one way to achieve that is to make sure that the sample size is small enough in that subgroup.

I think if we include males, that we have to add some extra criterion and seeing if that stratum has a certain amount of efficacy or something, an additional such as the confidence interval of 20 percent or some such added thing to make sure that the sample size is sufficient that we're seeing it is effective, not just doesn't differ from the other one, because if I keep my sample size small enough in the males, it's not going to differ from the group.

So I think we need pretty careful consideration on that and I think it applies also to the idea if you're going to throw in a substrata for children. I'm sort of recommending very careful substrata analysis across these subgroups if we're going to include them and allow that in the labeling.

CHAIRMAN CRAIG: A very important point. So does

everybody feel comfortable with the ten-to-the-fifth or do people feel the idea, say, recommendation of a lower count is justified? Yes, we have one from the audience.

MR. WYSICK: Right. Charlie Wysick from Pharmacy and Upjohn. I figured since no one else is going to say so, I might as well.

First of all, I support a lower count for Staph saprophyticus. I'd even go so low as ten-to-the-third, possibly, in the symptomatic or asymptomatic women. As far as some of the other organisms, I think that we are covering up some of the other organisms that--some of the other Gram-positives may well have lower counts as far as symptomatic disease, specifically, some of the Gram-positives, other Gram-positives.

Most of the data that was presented as well as some of the other papers have indicated that Gram-negative rods at ten-to-the-fifth and clean-catch urines are indicative of true lower or upper-track disease, whereas some of the Gram-positives, the enterococcus, the other Staphs may well have lower counts and that's probably a function of the urine itself acting as a sterilizer on the Gram-positives as opposed to the Gram-negatives.

Secondly, I'd like to have some comment regarding the other methods of obtaining urine from people aside from

supra-pubic, a straight cath or from indwelling catheters, and if we can come up with counts for those.

CHAIRMAN CRAIG: This would be more for your complicated urinary tract infections, right? Or are you talking about doing--

MR. WYSICK: Well, as far as you were talking about children before. Obviously, you're not going to be able to get a clean catch from children. Is ten-to-the-fifth acceptable from a child with a straight cath urine? How long do you want to wait between voidings? Should you wait ten minutes after a voiding, four hours after a voiding to determine which could would be proper, and is an indwelling catheter an acceptable method of obtaining a urine and how do you obtain that and what time period.

CHAIRMAN CRAIG: Dr. Melish, since you brought up the children, we'll let you--

DR. MELISH: Well, since catheterized urines are less likely to be contaminated and since true urinary tract infections generally have ten-to-the-five or greater organisms, I think the same standards can work very well for clinical trials. I think that's generally how we do it.

We see a few people talking about lower colony counts in the clinical treatment situation, but I think for

clinical trials, it's much better to have clear endpoints. You might have to throw out some patients who have true urinary tract infections but they'll get treated and they won't have the chance to make it difficult to interpret whether they belonged in the trial or whether they were truly cured.

DR. HENRY: So you'd want ten-to-the-five?

DR. MELISH: I think ten-to-the-five would be fine if you collected by catheterization. You would probably lose some people who had true urinary tract infections but you would still be able to identify the people who had undeniable infections.

DR. HENRY: Part of me says, well, you could probably accept counts that are lower, but then you're adding in more confusion. I think the more simple the inclusion criteria, probably the easier it is to do a study. So I could be convinced.

CHAIRMAN CRAIG: But as was mentioned, Gram-positives tend to grow lower. Would you go a little lower for some of those organisms?

DR. MELISH: They're uncommon in children.

DR. HENRY: Yes. Again, I think you should keep it more simple. I'd stay with a greater than ten-to-the-five.

CHAIRMAN CRAIG: Okay.

FLOOR COMMENT: On the flip side to that, with regards to measuring response in children, one thing we might want to consider would be accepting at the follow-up culture a bagged urine if it's negative, so that if it was positive, either it has to be repeated or then you get the child back to do the cath urine. At least spare them the procedure for that sake.

FLOOR COMMENT: I have just a comment. Regarding children, wouldn't it be possible to treat it reciprocally, because there are a lot of issues regarding UTI in children, namely the problem of scars, of physical reflex, of needle prophylaxis as to the treatment of pyelonephritis, et cetera, et cetera, and it's very difficult to consider a clinical trial pooling with adults knowing that, bearing that in mind.

CHAIRMAN CRAIG: Well, I think what was clearly brought up by Dr. Parker, too, in terms of any type of analysis, one would need to make sure that one had a sufficient sample size, so if one was going to include them in with complicated. So it may be that the best approach is to do them separately and not combine them. So I think this was a way of trying to see if you could get data on children earlier in clinical trials, but if that is not going to be

done, then I would agree with you. Probably doing them separately would be the way to do it.

How about teste of cure? In fact, I guess we go back to uncomplicated urinary tract infections where catheters might be used to obtain specimens. Still stay the same numbers?

DR. RELLER: I don't think the method of collection alters the colony count whatever. I mean, it is what it is.

CHAIRMAN CRAIG: Yes, unless you hydrate people or--I mean, with bladder puncture, there's no question that what you tend to do is you want a full bladder and so you may hydrate people more so which could dilute the urine. But that's the--true, you could let it sit there a while, too, and multiply. They are doubling every 15 minutes, although I realize maybe not unrestrained in the human urine, though in the dilute urine, where you're diluting out the defenses.

DR. RELLER: I believe in simplicity.

CHAIRMAN CRAIG: Okay. Fine. Dr. Melish?

DR. MELISH: However, the question about indwelling catheters, that's an entirely different issue and I don't know if they're showing up in your complicated urinary tract infection trials. Is that--

CHAIRMAN CRAIG: I know--

DR. MELISH: It probably should be an exclusion because they are very different issues involved there.

CHAIRMAN CRAIG: Or stratified.

DR. ALBRECHT: Actually, often, they're one of the complicating factors complicating UTI.

CHAIRMAN CRAIG: Right, so they--

DR. ALBRECHT: That's sort of my recollection of where we tend to see them most often.

DR. SORETH: We tend to define complicated as an infection in the setting of a catheter or a functional or anatomic abnormality of the urinary tract in concert with the IDSA guidelines.

CHAIRMAN CRAIG: Yes. So let's move on, test of cure. What was the issue specifically again, or the number at the end? You're happy to stay at ten-to-the-four or go down to three times ten-to-the-three?

DR. RELER: Well, the IDSA guidelines had less than ten-to-the-three, which is negative, and then a positive was one colony or more, ten-to-the-three or greater.

CHAIRMAN CRAIG: But they were starting at ten-to-the-three, or greater than ten-to-the-three to lesser than ten-to-the-three.

DR. RELLER: I understand, and I don't think that's a reasonable separation.

CHAIRMAN CRAIG: Right.

DR. RELLER: I applaud their lower limits, but I think the upper limits are inappropriate. But to be accurate for persistence, I think one needs more than a single colony at the test of cure.

CHAIRMAN CRAIG: Okay.

DR. RELLER: Now, whether one has ten colonies or more than ten colonies that would put failure at more than ten-to-the-four or more or whether one has more than three colonies that would give you a sufficient number of colonies to tell whether it was the same organism with reasonable certainty of the uropathogen present before, and yet stretch out the differences that one would like to see with effective therapy is what the issue under discussion is.

Is a tenfold reduction in organisms acceptable or would you like to have, given that the natural state is sterility in 95 percent or more of the target population and that that is not too difficult to achieve with an interpretable collection of urine, easy with a straight cath in the children and possible, and one can separate out a little bit of noise with the three or four organisms if they're all different.

I mean, if one got a test of cure that had two or three organisms, you know, a Gram-positive, a dipthroid [ph.], et cetera, I mean, you call that a negative urine culture. I mean, what we're talking about is less than ten-to-the-three or less than three colonies times ten-to-the-three of the uropathogen that was present earlier and I think that's quite a reasonable and it's a sharp lower hurdle that is achievable with effective therapy.

CHAIRMAN CRAIG: Any discussion or disagreement with that? Yes?

DR. ALTAIE: I just wanted to make sure that we are talking about less than ten-to-the-four, not ten-to-the-four as a test of cure.

CHAIRMAN CRAIG: Yes.

DR. ALTAIE: We're saying less than ten-to-the-four.

DR. SORETH: There's one regulatory point that I think I should make in the interest of having a level playing field and it concerns labels which we recently gave to both superfloxicin and phosphomycin [ph.] in the treatment of uncomplicated UTIs in which we included clinical study sections that gave eradication rates, microbiologic success rates based on a definition of eradication of less than ten-to-the-fourth, and in those two

labels, Ciparov and phosphomycin [ph.], we specifically gave the success rates microbiologically for the test agent versus comparators.

So that I think if we wiggle a lot with the definition of eradication, we'll need to go back and rethink those labels because it will be a comparison in the future, then, of apples and oranges, or tangerines and oranges, maybe, because Norby has shown very well in a paper that if you look at bacteriologic outcome and move the bar from ten-to-the-five to ten-to-the-four to ten-to-the-three, you can move bacteriologic failure rates from one percent for a given drug in a given study to about 60 percent with that manipulation alone.

So I think we have to be careful insofar as we've been explicit in some recent labels what the bacteriologic success rate is and that goes on to be what is promoted, that which is legitimately advertised.

CHAIRMAN CRAIG: And, as I say, you've used ten-to-the-fourth in the past, or less than ten-to-the-fourth.

DR. SORETH: Less than ten-to-the-fourth, so we're really talking about a difference between three colonies and nine colonies.

CHAIRMAN CRAIG: Yes. Okay. Lastly on the

follow-up, the question of

DR. MELISH: Are we agreed, then, less than ten-to-the-fourth?

CHAIRMAN CRAIG: Or did you want less than ten-to-the-fourth or did you want all the way down to three times ten-to-the-three?

DR. RELLER: The IDSA guidelines, I think, were aimed at the premise that the usual state of the patient is that the urine culture is negative, and what one wants to have is sufficient certainty that you're not calling a positive at ten-to-the-three a positive when it really is just a bit of rubbish.

Therefore, I think one needs enough colonies to ascertain whether you've got--what those colonies are, in that one colony to nine colonies, I think, is important and the failures would be represented by persistence of the original urine pathogen, and whether that persistence is three or nine, I don't think makes any difference. That's for the persistence.

But for the ones that have been eradicated, it's hard to convince me that you have eradication anywhere between three and nine. Do you see what I mean? So that what convinces me that there's eradication, that there aren't any of them and the only reason for making it not

less than three, a flat out negative plate, is that one could have a few more colonies and you have to have enough colonies to know whether you really got something or whether you've got something that floated in from the air or somebody coughed and the reality of the periurethral flora.

So I think the real end point for an effective cure with these agents is that you return to the natural state and the natural state is less than ten-to-the-three.

CHAIRMAN CRAIG: So, I don't know, what's done is--

DR. RELLER: The kind of data that's missing for me and I don't think has been done is looking at specimens after somebody has been treated and doing supra-pubic and comparing with urine to make sure that when you get back something below ten-to-the-four, there's not bacteria in the bladder, so that one knows that if you were somewhere less than ten-to-the-four, you were picking up organisms that were part of the colonies in the urethra or in the vaginal tissues and not definitely in the bladder, and I'm not aware that that study has been done at the end.

So I'm still a little concerned because when I look at drugs which should be perfectly effective in treating urinary tract infections like betalactams and I look at their efficacy compared to quinolones or, let's say,

maybe to trimetheprine sulfa, a drug which I know also gets in secretions, tends to eliminate the organism from other foci, as well, tends to give higher success rates than what you see with betalactams makes me believe that why betalactams aren't working as well is because there are still some organisms present in the urethra, on the vaginal tissues, because it doesn't get into secretions well, and so we haven't eliminated that area yet and then the urine becomes contaminated with those organisms and can actually occur, depending on where you put your breakpoint at the end as to whether you call it eradicated or not.

So you would like to have the kind of data that I mentioned at the end, where you look at patients after treatment, see what kind of urine numbers you get back on voided specimens, but also do supra-pubics to see if you do get organisms back. Those organisms are in the bladder, because otherwise, you're really not calling them true eradication.

CHAIRMAN CRAIG: To come to the heart of the matter, I mean, we have those data in normal individuals and there's nothing there in the bladder. What is important to me is on the one to nine colonies is what we're really talking about. If those nine colonies or the one to nine, whatever's there, whether it's three, four, five, or six, I

think we both would agree that if those organisms are the same and the same as the one that was there before, you would want to call that a persistence of the organism and a microbiological failure.

If there are nine colonies there and there are a mixture of things, you would not want to call that, and therein lies the problem of whether the bar is tantamount to ten-to-the-three or ten-to-the-four. It makes a difference what they are.

If it was on the one hand, it would be success because there really is not a persistence of the original uropathogen. On the other hand, it's a failure.

DR. RELLER: No. I mean, I would look at it as saying in the mixture, it's definitely contamination. On the other, I don't know for sure. There's a much higher chance that it's a failure if it comes back at, let's say, two or three times ten-to-the-fourth, but I don't know for sure unless I had done a supra-pubic to know that those percentages are relatively high. But I agree, it does increase the chance that it's a failure.

So I am happy with using the cutoff of going down to ten-to-the-four. I'm not sure--I mean, the farther down you push it, the more I think you have the chance of, as was mentioned, all of a sudden increasing your failure rates now

and that shouldn't be, that by dropping it down, that your failure rates should markedly go up unless--I mean, it doesn't make sense to me unless you're starting to pick up organisms that are somewhere around the area, not specifically in the bladder, because if it's in the bladder, why aren't they back up to ten-to-the-fifth? Why should they be down at the lower numbers? If the organism seems to grow well in the urine in the patient, why shouldn't it be all the way up to ten-to-the-fifth?

CHAIRMAN CRAIG: Well, it may be at four to six weeks.

DR. ALTAIE: My comment, also, maybe at four to six weeks. So since we are proposing, do we need to get them back at four to six weeks? Maybe only we need to get those ones back that had less than ten-to-the-four, somewhere between three and nine colonies. Those are the ones we need to see back in four to six weeks.

CHAIRMAN CRAIG: And that may be the case to know if they eventually get back up there, because having been a fellow with Cal Kunin, we did a lot of studies in women in the area where we were doing urocults on a regular basis, every day in women over periods over time, and it was not uncommon to get ten-to-the-three, ten-to-the-four bacteria on supposedly clean-voided specimens at various times in

these people when they were asymptomatic. As I say, I think you can get those at times and I think what we need to be sure, if we're going to call it a failure, that it's a true failure and not just a colonization.

So I'm a little bit more for keeping it where it is at ten-to-the-fourth than going all the way down to three times ten-to-the-three until I had better information to know that the lower count was clearly still useful in separating it. The other potential it had of going down was to give an advantage to drugs which also get into secretions as compared to drugs that don't, but that may be still equally effective in treating the urinary tract infection.

DR. RELLER: If the lower hurdle or the test of cure is less than ten-to-the-four, I think it would be important to delineate for the reviewers whether those were a mixture of organisms or a single organism--

CHAIRMAN CRAIG: Yes. Yes.

DR. RELLER: --and I like the idea of looking at four to six weeks in those patients that have success at less than ten-to-the-four but don't have a flat-out negative urine culture, because I think those are the ones that, in fairness, are in the ambiguous zone. I mean, if the drug is really successful and this is a transitional--later on, I mean, they ought to have a reasonable likelihood, if this is

just random noise, they ought to have a pretty good chance of being what 95 percent of the population is with a properly collected specimen, that is, no organisms.

The reality is 95 percent with a supra-pubic, but the practical reality is at least 50 or 60 percent of them have zip on the plate with a well-collected specimen. I mean, it's not an unrealistic endpoint to have a negative plate, and those are the ones that are easy to process. You look at them and get on with it.

So maybe that is the best encompassing way to deal with it, is those that fall into the one to nine colonies would be--that every effort should be made to get the follow-up specimen at the four- to six-week time point.

CHAIRMAN CRAIG: Okay. Fine. So do people feel comfortable with some of those thoughts? Any other questions that you--

DR. SORETH: Maybe if we could just briefly summarize, so we understand.

CHAIRMAN CRAIG: Okay. I think what we thought for the categories, we thought the two were fine, that the two that you have proposed, but we felt that we wanted to make sure that there were men in the complicated infections--

DR. SORETH: We'll get them.

CHAIRMAN CRAIG: --and there was some groundswell at least for trying to include children relatively early, if possible, but again with the caution as presented by Dr. Parker about subset analysis.

In terms of entry criteria, we felt that the ten-to-the-fifth was the ideal, but I think the Committee was willing to consider something like ten-to-the-fourth for Staph saprophyticus to try and enhance getting some of those in the clinical trials, especially since it might be that their response to drugs might be different.

In terms of the test of cure, we, I think, hopefully ended up, but maybe not, but I thought that keep it where we are, at less than ten-to-the-fourth, but for those that are in the range between ten-to-the-three and ten-to-the-four, those are the ones, at least in follow-up should have a look at four to six weeks to see if that's just random noise or if that is truly a relapse in infection.

Does that sort of summarize it as far as the group is concerned?

DR. SORETH: Thank you very much.

CHAIRMAN CRAIG: Okay. Let's take a break and we'll start again in about 15 minutes.

[Recess.]

CHAIRMAN CRAIG: Could people take their seats?
We need to get started again so we can not be too late at
finishing.

The next topic is going to be skin and skin
structure, uncomplicated and complicated, and Alexander
Rakowsky is going to do the FDA presentation.

SKIN AND SKIN STRUCTURE

UNCOMPLICATED AND COMPLICATED

FDA PRESENTATION

DR. RAKOWSKY: Actually, on baseball teams, the guy who can barely hit the ball out of the infield bats ninth, so I wonder what it means being the 16th speaker in the last two days.

My name is Alex Rakowsky. I'm a medical officer in Anti-Infective and I'll be your cruise director through our mutual journey through skin and skin structure infection guidelines.

I'd like to have several acknowledgements first. Dr. Albrecht listed the list of the core Committee members earlier on Wednesday and I'd like to thank them for their positive criticisms and critiques of the multiple drafts that we went through of this indication. In addition, several coauthors, Mr. David Bostwick, who was a coauthor for the initial drafts, Dr. Sousan Altaie, who wrote the micro section, and my team leader, Dr. Roberts, who I tortured with about nine drafts of this before it finally came through.

Several points before we get started. One of the purposes of this three-day session was to essentially get an interaction between us, the Committee, and industry. I know

it's been fairly difficult to comment when you have a moving target, where you have the guidelines on the Net and then you have a presentation on evolving indications then presented to you.

So when Dr. Tuazon, who was a Committee member of the advisory, and I spoke about this, we decided to basically present what was on the Web two weeks ago. So if there are any comments, please feel free to comment about them. These are evolving guidelines, but for the purpose of discussion, we kept them as is.

A second point is that this is the largest organ system in the body and, therefore, it encompasses a large scale of infections and what is to be covered here is every infection that is on the skin and skin structure, so this may be a little bit of a bulky talk.

The nice thing, which is the third point, as many points as a mortgage would have and probably just as painful, the third point is that most of these points tend to be fairly logical and agreed upon, and I think the key to all of this is to be meticulous and methodical about data collection.

What better way to start the last talk than with the difficulties with the disease definition. As mentioned, there is a vast array of skin and skin structure infections.

Because they are so well seen, they have a lot of historical names and a lot of different commissions will call the same exact entity by different names, depending on when they trained and that complicates the matter, as well.

In addition, it is difficult to categorize clinical presentations. That's one reason why a lot of dermatologists will give you both an anti-fungal and a steroid at the same time. Just the sheer fact that such an entity exists shows the difficulty when the specialist can't decide.

The next two points go together. There is a large list of potential pathogens, especially when it comes to complicated skin and skin structure infections, and unfortunately, the most common pathogens are also the most common colonizers, therefore, the most common contaminants, as well. It makes life even more difficult to interpret these things.

To give a historical perspective, due to the various presentations, the labels have traditionally and in a general sense tried to be rather specific as far as indication is concerned. For example, some of the earlier indications would read, skin and skin structure infections: impetigo due to Group A Strep and Staph aureus.

In addition, there are situations where a small

number of patients would have a relevant pathogen, and due to the smaller studies in the past, there would be less than ten pathogens found in actual clinical trials and what we used to have was an asterisk which would mention, not studied in more than ten patients to warn the clinician. But due to the fact that this was still a relevant pathogen, it was still included.

In 1992, the IDSA guidelines came out with four general categories of study, and if you really think about it, they tend to be logically divided based upon the complicating factors that you see along with them.

The first is your basic spontaneous infection, limited to the skin subcu fat and lymphaticus, and these are essentially infections of an intact skin system, so you don't have to worry about damage to the skin system per se. It's just a spontaneous infection, usually of little medical history involved with it.

Secondly is wound infection, where you have a break in the actual ability of the skin to protect you from infections and then the wound actually gets infected.

It gets further complicated when you get into ischemic ulcers, be it diabetic, be it decubitus ulcers, et cetera, where the medical history starts to play more of a role.

And lastly, infected full-thickness burns, which is really the whole gamut of medical complications.

The same year, the Points to Consider came out and the policy was to divide, just as with the urinary tract infections, into two, uncomplicated and complicated, and I do want to mention that in the actual Points to Consider, it's called skin and soft tissue infections, but we've been calling them uncomplicated and complicated skin and skin structure infections.

The uncomplicated in the Points to Consider listed things such as a simple abscess, impetiginous lesion, furuncles, and cellulitis. The complicated included such entities as infected ulcers, burns, major abscesses, and infections of deeper soft tissues. And then the broad category, other infections requiring significant surgical intervention in addition to the antimicrobial.

So what's our current proposal? Essentially, to continue the use of the two broad categories of complicated and uncomplicated, and the reasons for division are multiple but these are probably the four biggest ones.

Most uncomplicated are caused by primarily two pathogens, Group A Strep and Staph aureus, while complicated has a whole gamut.

Number two is depth of involvement.

Number three is the need for concomitant surgical intervention, as has been mentioned with the Points to Consider document.

And lastly, the underlying medical condition which can complicate a "uncomplicated" infection and make it more difficult to treat.

Several caveats about this, though. Infections that can be treated by surgical incision, namely an IND, or vigorous scrubbing alone, and two examples here are isolated furuncles or isolated folliculitis, should not be included in the clinical trials due to the uncertainty that antimicrobials are even needed in such situations.

And secondly, even though it is important to get information about the rare entity, it is difficult then analyzing properly any controlled clinical trial. So on the whole, rare entities such as, for example, necrotizing fasciitis, have not been enrolled and have been discouraged to be enrolled unless specifically looked for.

More caveats. Complicating factors, and there are multiple, such as immune deficient states, involvement of prosthetic materials, or underlying conditions that may impair the evaluation of the actual drug effect, should be either accounted for and stratified for or randomized for, et cetera, or more easily not enrolled, depending on what is

being studied. And as mentioned before, a lot of these clinical situations, you can't pigeonhole and you're stuck with a situation where you cannot categorize.

Let's talk about the disease breakdown. But uncomplicated and complicated should be studied separately and efforts should be made to include a wide array of disease entities involved in both of these. At the present time, we're starting to look at burns separately. Even though Points to Consider had mentioned it as part of complicated, we're starting to look at them separately now. This will be an issue that will be brought up a little later. We actually had an Advisory Committee in July of 1996 where we started to discuss some of the protocols of how to look at burns.

What do I mean by an even mix of patients? It's really a comparable number, and comparable is a broad term. We're not recommending certain percentages, but a comparable number of patients with impetiginous lesions, simple abscesses, and cellulitis should be enrolled in uncomplicated trials, and for complicated, really three, infected ulcers, extensive abscesses, and deeper soft tissue infections that usually require surgery.

In all honesty, this really should be a micro-driven indication, where microbiological input is very

important, so all efforts should be made to ensure a high yield on the culture, and we'll discuss this in terms of what should be seen as acceptable micro-specimens.

It should be noted that there are at least two entities and two common entities that have a low yield commonly, and they are cellulitis and erysipelas, that even in the best hands will have about a 20 percent rate of recovery.

As mentioned before, it is difficult to separate pathogens from colonizers, so the proper attainment of a microbiological specimen is paramount.

Getting back to the ten pathogens or ten percent, like had been noted before in the labels, we no longer--I just want to bring up this historical perspective again--we no longer use the asterisk and if the pathogen is a relevant pathogen and the numbers appear to be less, it does depend on the situation, but they will be listed at times without an asterisk.

Inclusion criteria, and here's a guy happy to have the skin structure infection able to be included, you should have a clinical picture consistent with either one of the two skin and skin structure infections. Both males and females should be enrolled. There must be a microbiological specimen obtained prior to initiation of therapy.

And even though the following is not really an inclusion criterion, since we are dealing with evaluability, I want to bring this up and now and stress these several points. The evaluation of the patient really depends on as much information as possible, and again, because these things are hard to categorize as, for example, say middle ear infection or sinus infection and almost prove that, it's kind of hard to call something a cellulitis, compare it to an erysipelas, compare it to what have you. Depending on the situation, that could be complicated. There are situations where it's difficult to tell, so the more information we get, the easier it is for us to evaluate and come to a decision.

So we are proposing that the following information should be included and documented in both the case report forms and case report tabulations, and this is just a list, and again, most of these are usually seen anyway.

The first is the anatomical site of infection, and that does make a difference in uncomplicated if they happen to be in areas of the body where Gram-negatives can play a role.

The next two deal with the dimensions, length, width, and depth. In addition, time is usually noted, which is the fourth dimension. You can mention the fifth

dimension, but they have had no recordings in the last 20 years and these are current guidelines, so you don't have to include those.

Another important issue is a description of the actual site, and I just list a listing here. It really depends on the skin structure that you're looking at, but most commonly, we mention such things as erythema, swelling, tenderness, extension of redness, heat, discharge, et cetera. This actually may play a large role in fasciitis cases if they are studied.

Other things include the actual cause of the infection, and what do I mean by that? Is it trauma induced? Is it a post-op wound infection? Is it a cellulitis that developed in somebody who's bacteremic, et cetera? Again, the more information, the easier it is to make an evaluation about these patients.

The underlying medical conditions, and lastly, previous medical and surgical therapies that have been used for that site infection, and this is more seen in the complicated skin and skin structure infection studies, and there is the optional picture of the infected site that Dr. Tuazon will discuss.

As far as exclusion criteria, presence of infection that has a high cure rate, as had been mentioned

before, really should not be enrolled. No culture obtained prior to therapy, and a medical condition where the response may be altered, as had been mentioned several slides ago.

In addition, a medical condition leading to difficulty in interpreting response, for example, a super-infected eczema, where you're not sure if it's the steroid, if it's the antibiotic, et cetera, leading to the response because of the large inflammatory components. In addition, it's very difficult to interpret cultures in a situation like that. So in situations where the medical condition really leads to a difficulty in interpreting response, in all fairness, it may be better not to enroll such patients.

And prior antimicrobial use, except in situations where a culture prior to therapy, meaning the study drug therapy, shows persistence of a pathogen. In other words, if there is clinical persistence, it may be due to the inflammatory component, not so much the infectious. Therefore, we would require that there at least be a positive culture to show the infection is still present.

Several points about therapy. As far as investigational agent, we've spoken about this with every indication, so I just want to bring up the point that in situations where we do have acidic environments, such as

abscesses, there are certain classes of antibiotics like aminoglycosides, that don't function as well. So if there was a concern about the antibiotic not functioning properly in a certain environmental setting, for example, an abscess, it should be accounted for, be it a more frequent dosing, higher dosing, et cetera.

And again, comparators have been spoken about before, and just one quick point here. One of the most commonly granted indications are skin infections, so there is a large number of potential comparators. Especially in complicated infections, it becomes difficult to interpret data when you have five, six, seven different comparators being used. So the study protocol should really specify one or two appropriate options which are considered to be first-line therapy.

And it's okay to compare agents via different routes of administration, so topical can be compared to an intravenous without any problem as long as the double-blind is maintained.

Duration of therapy is very hard to really come up with anything strict here because it really varies from condition to condition and drug to drug. I guess the best word of advice is to always discuss the protocol prior to initiation with the agency, and it should be based on

pre-clinical data.

Switching therapy, again, is very common, as had been discussed with the pneumonia protocols. There are now situations where the same drug with the same pharmacokinetics is being given in different formulations, which makes life easier. However, in the past, we did have, for example, one IV being switched to a different oral and at such a point, we need some clearly defined criterion which should be established prior to study initiation, and again, discussed with us. Some potential criteria to consider are presence of fever, number of apyrexia days, extent of erythema and pain and formation of granulation tissue.

Adjunctive therapy, this one's fine. Daily standard of care is allowed, especially for complicated skin and skin structure infections. There are some adjunctive therapies that are considered standard of care at this time and it would be unethical not to continue, but these should be clearly defined in the study protocol and there are some that should be seen as therapeutic failures. For example, an abscess drainage several days into therapy, unless you have a situation where that is being done as standard of care, should be considered a failure.

In addition, we have seen amputations of infected

sites called as unevaluable since it was part of the study protocol, not so much as part of protocol but it was considered standard of care to actually amputate the site. Again, these should be discussed with the agency prior to study initiation.

As far as micro-specimens are concerned, the next three or four slides will deal with the cultures and how to obtain them, et cetera. Again, beating this point to death, all patients should have appropriate cultures obtained. A Gram stain--I forgot to attribute it to Dr. Gram--should be performed on the obtained specimen.

The Gram stains aren't as strictly defined in these indications as they are, for example, in sputum samples or, for example, sinus samples, et cetera, but they do give you some help in terms of interpreting what you have back on your culture, and especially when you're dealing with an indication where colonized with contaminants and pathogens may all be one in the same, a Gram stain is important to have.

For superficial skin infections, namely impetigo and superficial wound infections, after vigorous debridement of the area, a swab of the area should be fine and an aerobic culture usually should be adequate unless you have an anatomical site where a Gram-negative should be--excuse

me, an aerobic should be considered.

For cellulitis and erysipelas, again, these tend to have low yield rates. Most people still lean towards a leading edge mutal aspiration, even though the success is fairly low, and the two sets of blood cultures do increase the sensitivity somewhat. And again, aerobic cultures only usually unless there's a clinical situation which accounts for an anaerobe to be done, as well.

For complicated, really two sources or two types of sources, either a deep culture of a contiguous area, especially with infected ulcerations where you don't want to really stick right into the ulcer but in the contiguous area, and in addition, either surgical specimens, including the actual fluid and pus, a needle aspiration or a biopsy of the area all count as perfectly fine micro-specimens. An actual swab of a surgical specimen or fluid, et cetera, would usually not count.

There are four different types of cultures, or five if we count virals, and again, as the clinical picture indicates, that's really what should be sent for, and when in doubt, I guess all four, and two sets of blood cultures, which should include an aerobic, as well, especially when dealing with deeper ulcerations.

On-therapy assessments, the number and time will

really vary depending on the study drug and diagnosis. Again, we're dealing with a vast array of indications here. For uncomplicated, it may be reasonable to just have a phone contact. For a complicated, especially with, for example, a very complicated ulceration, you may need to see them on a daily basis and document that. It should be discussed with the agency prior.

And again, it's important to really paint a complete clinical picture at each assessment. For us, it's hard to interpret when it says "patient improving". It's a lot easier to see where the erythema is, where the swelling is, where the induration is, et cetera.

In the therapy assessments, again, as has been mentioned prior, it may just be a phone contact, but just to give you some points that should be considered when dealing with entire course of therapy. Patients should receive between 80 and 120 percent of the proposed dosing regimens. Prolonged use may be allowed. We have seen situations where a certain drug didn't seem to work within the adequate or the proposed time period to begin with, but if it was continued for several more days, it appeared to have a good efficacy rate.

I can think of one drug where the company actually decided that it was a failure but actually may be indicating

that a longer course should be evaluated, and such data, even though such data is already available and should be considered to just point towards an additional study needing to be done.

Daily care of complicated infections can continue between the end of therapy and the post-therapy assessment, and this study protocol, again, should clearly spell out which therapies are allowed, excluding the daily amputations.

As far as post-therapy assessments, a different twist to the same number. A test of cure should be at least about seven days after the tissue levels of the study drug have gone lower than the MIC of the expected pathogens, so that comes back to the usual seven to 14 days.

A full clinical picture should be presented for our evaluation, as has been mentioned before. And again, because of the fact that just having a line listing to say, "cellulitis improved, cured" for the two evaluations, it really doesn't help us with the evaluation. Lack of such information clearly lead to the patient as being deemed unevaluable.

If appropriate material is available at the post-therapy assessment, it should be sent for culture, and again, presumed eradications that has been discussed

previously are not only allowed but commonly seen.

Evaluability--patients can be either clinical or clinically and microbiologically evaluable and all patients must have had an appropriate pre-therapy micro-specimen.

To be clinically evaluable, no violations of the inclusion and exclusion criteria. Pre-treatment culture, again, seeing this yet again. Adequate length of therapy--for failures, at least two full days of therapy are needed to be called a failure. And, no use of concomitant antimicrobial therapy or an unallowed adjunctive therapy. And adequate time to follow up, meaning at least seven days out, and we've said this multiple times.

To be both clinically and microbiologically evaluable, the patient should be clinically evaluable, as described before. There should be growth of a recognized pathogen on the pre-therapy culture and appropriate susceptibility testing done and a repeat culture and susceptibility testing done, if appropriate material to culture is present.

To discuss efficacy, in this indication, there is both a clinical and microbiological evaluation for each patient. The possible final choices, at least for clinical, are cured, not cured, and unevaluable. I put in the eradicated/not eradicated. What I really mean for

bacteriologic is there is a bacteriological cure or a bacteriological failure and not cured and unevaluable, and we had discussed all the different permutations of that just in the last talk with the relapse, reinfection, et cetera, so I was not going to get into those again. There's also a combined therapeutic response that we're starting to do with these indications, and I'll get to that in a second.

The reason for the therapeutic response is that there really should be correlation between the clinical and the microbiological responses, as will be shown in the next few slides.

Clinical response, to be called cured, and these are just logical definitions, the first is a total resolution of all signs and symptoms, which would be the gold standard. The other one which the clinician will count as a cure is really improvement of the above, meaning the signs and symptoms, to such an extent that no further antimicrobial therapy is warranted.

This gets a little complicated in complicated skin and skin structure infections where there are some patients that need to go back on prophylactic antibiotic creams, smears, et cetera, and again, an issue that needs to be discussed prior to study initiation, but that is recognized.

As far as micro response, a patient should be

considered to have the organism eradicated if there is no growth of either the pretreatment pathogen or a new potential pathogen on the post-therapy culture. Included under this is the pathogen who then develop resistance and that should be monitored for. And the post-therapy culture was not obtained due to lack of culturable material comes up with the presumed eradication. And a therapeutic response is a combination of the two.

If you have a yes/yes situation, then it's overall cure. All other combinations should be seen as either failures or unevaluable, but efforts should be made to explain the discrepancies between the clinical and the micro-responses.

And what are some of the discrepancies? One potential is a clinical cure micro not cure, and there is a potential that what we're calling a pathogen making this patient a micro not cured is really a colonizer or a contaminant. Again, proper microbiological specimen collection should exclude or decrease the number of such situations.

Secondly, it is the reverse, where you have a micro cure and a clinical not cured. Again, with a lot of these disease entities there is a large inflammatory component, so if there appears to be a major improvement and

a micro cured, it may be perfectly reasonable to have a repeat assessment several days later to see if you then have a full resolution of an inflammatory component.

And just several questions raised. Initially, we just had this one and we're going to leave the floor open to further discussion by industry and the Committee, so this is the very specific question. Do these guidelines encompass the basic minimal criterion needed to conduct and review a skin and skin structure study?

Several more, and that was just to get things rolling, several more, more specific questions to think about. One is the whole burns issue, where they're being studied separately at this time. Should that continue to be the case? And if so, what should we do with deep decubiti and diabetic ulcers, where a large number of them are being treated by burn surgeons and treated as though they were burns?

And lastly, a major issue when dealing with antimicrobial agents for uncomplicated infections where they're going to be used empirically and you're dealing with the two big strains, namely Staph aureus and Group A Strep, if you have a large number of patients enrolled who are then found unevaluable because their entrance strain is resistant to the study drug and you then essentially evaluate only the

ones who have a sensitive strain of that organism and you find that agent to be efficacious, what do you do in situations where you have such a large number of such strains available, in other words, when you're running a patient count where 20, 30, 40 percent of the patients are excluded due to resistant strain, and this in light of the fact that these agents will be used empirically.

That should be it.

CHAIRMAN CRAIG: Any questions for Dr. Rakowsky?

[No response.]

CHAIRMAN CRAIG: Our next speaker is going to be Carmelita Tuazon from George Washington University, who is one of our consultants and we're pleased that she's here.

COMMITTEE PRESENTATION

DR. TUAZON: Thank you. I think, if I may just stay here--

CHAIRMAN CRAIG: You may stay there.

DR. TUAZON: Okay. What I'd like to do is give you my comments and suggestions and then respond to the questions raised by Dr. Rakowsky and then that probably would start off the discussion.

I think it's important to emphasize that even in the so-called uncomplicated skin infections, that there is a wide variety of infection, and just for the entrance

criteria that those various entities should have an adequate number of patients for each entity, and I think we are quoting a minimum of about ten patients per group.

CHAIRMAN CRAIG: Can you hear her in the back, or does she need to get closer to the microphone?

DR. TUAZON: That's for the uncomplicated skin infections. Then, secondly, for the complicated skin and skin structure infections, we should also subdivide the various entities, like as emphasized already, the burn ones should be studied separately. The diabetic foot infections should be studied separately, as there are enough patients to be studied in this group to evaluate the specific drugs and they are basically an entirely different population. And the other group that also would fall under that category would be sacral decubiti.

The next point is, in the inclusion criteria, I think instead of making the picture of whatever skin structure site is involved, I would suggest that that be required instead of being optional. Very much similar to the discussion that you had on the examination of the middle ear, I think there's a lot of subjectivity and variability in terms of evaluating the site of the infection.

What better evidence you have to follow to have a clinical picture of the infected site on therapy assessment

and end of therapy assessment with documented by picture, and I think that's probably very doable because what you need is just a Polaroid camera and take those pictures at those various points to correlate with the clinical course of the patient.

In fact, we do that all the time in our clinical practice, that residents, when they present the case, they bring a picture of the infected site and I think the picture is more worth 1,000 words.

CHAIRMAN CRAIG: Yes. You can get them with grids and everything so that you can measure very accurately.

DR. TUAZON: You can measure, right.

In terms of the microbiologic specimens, I just would like to reemphasize the role of the Gram stain, as mentioned by Dr. Rakowsky. I'm from the old school that it's still a very useful, simple diagnostic procedure. It's probably the best tool that you can use to determine whether one is dealing with colonization versus infection.

With regard to the comparator agent, I think that's where we're going to run into problems. For the uncomplicated skin infection, I think it's easier because you're basically dealing with two major pathogens, either Group A Strep or Staph, but I'm familiar with some of the people who have been trained in the Northeast that they

don't feel comfortable using agents that are effective for Staph aureus use to cover for Group A Strep, but I think that's probably a minority. I think most of us can feel that whatever covers Staph should cover Group A Strep.

Although the issue of resistant strains of Staph Aureus has been raised, at least from my clinical experience, we haven't seen that as a major problem in terms of localized skin and skin structure infection. Certainly for bacteremia and newly acquired infections, MRSA has been a major pathogen.

Now, I think it becomes more of an issue for the complicated skin and skin structure infections because I think most clinicians would not feel comfortable just using one agent from the very beginning, just because of the wide variety of organisms that we see in the clinical setting, and I think this will be a major point for discussion.

Regarding discrepancies, again, to reemphasize the distinction between colonizer and contaminant, again, Gram stain would be most helpful in such settings, short of quantitative cultures.

Those are the comments, and then I'd like to address the questions raised by Dr. Rakowsky. I think the first question is can an agent still be approved for empiric use if a large percent of isolates are resistant, even

though clinical efficacy has been demonstrated against the susceptible strains.

I think the answer there would be yes because I think we are very familiar with settings that there have been mixed infections, where the major pathogen would be Staph aureus, but there are other organisms such as coagulase negative Staph and other organisms that may be resistant to the antibiotic that's being used for there and yet you would recover the organisms that are resistant and yet you have a clinical response to the particular agent.

Now, I think the first question he had was, if the guidelines encompass the basic minimal criteria needed to conduct and review skin and skin structure study. Again, the answer there will be yes except for the specific disease entities that he has mentioned, the necrotizing fasciitis.

I think this is somewhat critical because this is one soft tissue infection where we see a significant morbidity and mortality and yet there is no guideline in terms of what to do with this type of infection. It may not be under the purview of this Committee, but certainly that can be brought up in discussion with the IDSA in the light of some animal studies as well as limited clinical data in terms of the antibiotic usage, as well as immunotherapies that are being currently used or recommended at the present

time.

And the last issue is the number of--the agreement in terms of the clinically and microbiologically evaluable number of patients in order for the agent to be approved, and I think what has been recommended is for the uncomplicated skin infection, that at least 50 percent of the clinically evaluable should be microbiologically evaluable.

I've had some informal discussion with Dr. Albrecht as to how those figures were arrived at. I think if you're dealing with a subset of patients with cellulitis or erysipelas, I think this is probably not a very altruistic percentage to aim for because, as you know, in the very best hands, maybe 20 to 30 percent of those would be positive cultures. We, in fact, learn even by their culture, leading-edge lesion. Maybe the number was arrived by grouping all the various entities and came up with an average.

And the other agreement is between the clinically and microbiologically, the 70 percent of complicated clinically evaluable should be microbiologically evaluable. Again, I don't know how they came up with that number, why not 80 percent, why not 90 percent.

And the last thing is, I think in terms of

evaluating the results of the trial, it should be properly recorded what type of adjunctive therapy is being administered to patients, such as dressing changes, topical solutions, debridement, use of local antiseptic, that those should be uniformly used for all patients to have objective and comparable evaluations.

QUESTIONS AND COMMENTS

CHAIRMAN CRAIG: Okay, thank you.

I guess we can start first with the indications in terms of complicated and uncomplicated. It was your feeling and also what's proposed that the burn wounds should be looked at separately. Does anybody disagree with that?

[No response.]

CHAIRMAN CRAIG: The question, I guess, in looking at diabetic foot infections, for getting the approval of a drug for complicated skin infections, I mean, I agree there are enough diabetic foot infections, but are you suggesting that that should be an entirely different indication than complicated or should there just be some of those included in the clinical trials?

DR. TUAZON: No. I think it would be preferable for certain settings, and I'm familiar with certain drugs that have been studied specifically for diabetic foot infections, because I think when you look at that

population, it's not a simple infection.

CHAIRMAN CRAIG: Yes, but, I mean, is it different than complicated? I think what we're trying to get at is, do we need another indication that's called diabetic foot infections or is complicated skin and skin structure infection sufficient to include that entity, so that you can have some of those mixed with other types of complicated infections to get your total that meets up the number, or is it so different than everything else that it should be a separate indication?

DR. TUAZON: I'm not asking for a separate indication, but I think a separate subgroup of those patients, like a separate subgroup of postoperative wound infection would be analyzed as a separate entity, yes.

CHAIRMAN CRAIG: Do people have any trouble with that?

[No response.]

CHAIRMAN CRAIG: Okay. Yes, Brad?

FLOOR COMMENT: Just a question about it from an indication standpoint. Looking at pediatrics in general, all this is the same with the one exception of buckle cellulitis. I'm wondering if there would be any need or desire to have patient studies in light of the Hemophilus influenza B vaccine making the condition very hard to study.

DR. MELISH: Buckle cellulitis was almost always due to Hemophilus influenza Type B and it basically doesn't exist anymore, so I don't think that's going to come up. I think it's going to be Staph and Strep cellulitis that will overwhelmingly be in the uncomplicated skin structure.

CHAIRMAN CRAIG: And sequelae decubiti, did you feel that that should be--

DR. TUAZON: No, very much similar under the category of diabetic foot infections as a separate subset in that complicated skin and skin structure infections.

CHAIRMAN CRAIG: Okay. But necrotizing fasciitis, where did you sort of--I understand your interest, especially with all the drug regimes that are used that are based primarily on animal studies and not much in the way of human studies. But that would require a sufficient, a large number of patients.

I think it would be hard to get much useful information by including a few of those in the overall complicated skin and structure group, and as I say, since criteria for evaluation might be difficult in those, it just might confuse issues instead of making it easier to look at.

DR. TUAZON: I would prefer to have that under the category very much similar to the burn infections as a separate entity.

CHAIRMAN CRAIG: As a separate entity, okay. And I think that's what the FDA feels, too, in that those patients should be excluded. Any disagreement with that?

[No response.]

CHAIRMAN CRAIG: Okay. I think that sort of summarizes, at least for the indications.

Is there any way, as far as other tests that we can do to try and increase the yield of cases in cellulitis and erysipelas? By that, I mean, I think there are studies to explain why one gets a low yield with aspiration.

There are studies that actually have done skin biopsies and looked at the number of organisms per gram of tissue, and unlike most other infections where you have ten-to-the-fifth or higher number of organisms, in Streptococcal cellulitis, it's frequently that you may be down even as low as ten or 20 organisms and this is using sensitive fluorescent stains to really identify these organisms. So they are there in relatively low concentrations, so it's not surprising that we may be able to miss them by doing an aspirate of the tissue.

I guess the question I would add is, can we use something like ASO titers, anti-DNAs, at least to being able to show a rise and a fall, as that being relatively specific for beta-hemolytic Strep, so at least that would hopefully

increase the yield, being able to bring a few more patients in that you would be feeling confident enough that that was a beta-hemolytic Strep infection and being able to increase the yield, because as I say, with 20 percent, you've got to do a heck of a lot of cellulitis and erysipelas in order to get your numbers up. What do people think about that possibility?

DR. MELISH: Are you excluding microbiologically negative cellulitis?

CHAIRMAN CRAIG: Well, you've got to get a certain number that they want to get that are positive. Is that--

DR. MELISH: Yes.

DR. RAKOWSKY: No, not necessarily. The certain numbers are in actual Paints to Consider and these guidelines would be more in terms of, like, an appropriate microbiological specimen should be obtained. If it comes back negative after it was done properly, just a fact of the micro life that it came back as negative.

With cellulitis and erysipelas, most studies do indicate that almost always you end up having Group A Strep alone. I mean, there are some settings where you--

CHAIRMAN CRAIG: Cellulitis, I would say, could be either, but I would agree with you, erysipelas is almost always--

DR. RAKOWSKY: So at least there aren't many studies unless you're dealing with an anatomical location which warns you to think of other organisms where you're kind of sure of what two organisms you're shooting for. It would be nice to get the micro-specimen, but if it's not obtainable in terms of getting a positive culture, then I'm not sure how to change that.

I guess my one concern about DNase [ph.] and the ASO titers is the timing problem, where, again, you bring these patients in initially, you put them into a study protocol, then you bring them back seven days later and not all people will have a predictive ASO titer going up or DNase going up and that comes into the whole aspect of what titer levels do you need to be positive, et cetera. It kind of complicates it even more.

DR. MELISH: Well, I'm not so sure, because you bring them back seven days after treatment, so you bring them back 14 days later, so you're actually pretty much hitting a good window.

CHAIRMAN CRAIG: Yes.

DR. MELISH: I think that's actually a good suggestion, that you could study some Streptococcal titers. I think the other one that's very important is maybe there should be a requirement for these, as well, for the

photographs. A well-done photograph ought to allow people to distinguish between whether it's categorically erysipelas or whether it's cellulitis.

And finally, in terms of guidance to the people who are trying to make a microbiologic distinction, I'm not certain that leading-edge cultures are appropriate for cellulitis. I think if you were--non-erysipelas cellulitis, if you wanted to get the highest yield, you'd probably biopsy in the middle of the erythema.

What happens if you do leading-edge for cellulitis that's not erysipelas is you're way out where the inflammatory response is just dwindling out and the hottest area is probably closer to the center. It's possible with trisipelas [ph.] that the leading edge should be--leading-edge cultures are almost never positive in erysipelas, but I guess in terms of pathophysiology, we do think that that's where the action is.

But when you take the other types of cellulitis and apply the leading-edge thought to it, I think you're often in the totally wrong area because all that's happening at the leading edge, it's not really a leading edge, it's just sort of a dwindling out of inflammation.

DR. RAKOWSKY: In response to that comment, I tend to agree, there is more and more data saying that a leading

edge may be probably the most insensitive way to actually get the culture positive, again, an evolving document.

In response to the first comment about the Streptococcal tests, it was done in the Division in the past. I'm not sure if anybody wants to add a historical perspective about that, where there were studies actually used on Streptococcal titers, and I'm not sure if anybody from the Division wants to mention what the results were there, if it was predictable or not.

DR. ALBRECHT: Streptococcal titers were used in pharyngitis, but I'm not really familiar with them being used in skin indications.

CHAIRMAN CRAIG: Yes, Dr. Henry?

DR. HENRY: Well, if anti-Streptococcal antibodies are one thing to consider, perhaps another is in someone who has cellulitis, trying to decide if it's Group A Strep or Staph aureus, that maybe nasal cultures to look for Staph aureus, and if they are positive you'd have an organism so that you could do susceptibilities to see if they are MRSA. I know in kids I've seen, the ones that tend to have Staph coming from a bite or a scratch, there's a high number that are nasal carriers for Staph aureus.

CHAIRMAN CRAIG: Dr. Tuazon, you've obviously done a lot of studies in this from your publications.

DR. TUAZON: I'm not sure that if someone is colonized with the Staph aureus in their nasal area that you can implicate that as a cause of cellulitis. I think we've documented that in patients or drug abusers who are carriers who come in with Staph aureus endocarditis, that's the most likely source, but I don't think we have any data to show that in patients with cellulitis who are carriers of Staph aureus, that that's necessarily the organism that's causative.

CHAIRMAN CRAIG: Dr. Reller?

DR. RELLER: It seems to me it would be good to recommend, not necessarily require, the collection of pre-acute and convalescent serum samples. What it could do, and I think it's appropriate to do, is to increase the number of patients that the sponsor could appropriate claim were caused by Group A Streptococci.

An important consideration to me in this issue is the reality, and I think the pictures are a wonderful idea. They're being used more and more frequently. It's objective and I think that for the uncomplicated ones that are presumed owing to Streptococci and Staphylococci, that that--I think it's good for all of them--

CHAIRMAN CRAIG: Sure.

DR. RELLER: --but where the microbiological data

are going to be sparse and may be augmented by serological data, that that, I think, could be a requirement to have the pictures for those kinds of infections that are difficult to document otherwise.

The last point I'd like to make has to do with the reality of the overwhelming preponderance of these pathogenic organisms and much of what we see is toxin-related, not necessarily the organisms, and one of the reasons why the--I mean, the clinical findings are out of proportion to how many organisms one finds.

I would like to put the emphasis on the selection of the comparators and the study drug, I think, should have demonstrable activity to these two organisms because there is the possibility that mixed in with other infections, one could end up with a situation analogous to otitis media, where one had an approved drug that overall was clinically comparable in activity that leaves out a hole, like the penicillin-resistant pneumococci and otitis media and I think that's a mistake that needs to be avoided in the future so that the selection of comparators becomes an important issue and if the working between the agency and the sponsors do not get a high standard, the highest possible standard comparator so that we raise the level of the lake or the ocean as opposed to sinking to the lowest

common denominator with slippage and comparators, that this might be an appropriate thing to utilize Advisory Committee to help deal with the regulatory realities versus what the standards to which we should be aspiring.

CHAIRMAN CRAIG: So let me just raise the question. If you're in an area that has relatively high methicillin-resistant Staph, what kind of comparator are you going to be using?

DR. RELLER: Well, I would go back to Dr. Tuazon's comments. I'm not sure. I mean, these should be predominately community-acquired infections and there may come a time where, like penicillinase-resistant Staphylococci or Staph aureus isolates where there is no important or clinically important difference, no perceptible difference between community-acquired penicillinase producers and hospital-acquired penicillinase producers, I don't think that is true for methicillin resistance.

One might have to change that in the future, but again, this is where the use of the comparators--I mean, if the reality becomes that there's so much methicillin resistance in the community, then I think we'd have to raise the bar. But Streptococci are more important, I think, in this entity overall than--well, maybe I shouldn't say that. I'll retract that.

[Laughter.]

DR. RELLER: There are some geographical differences in emphasis of Strep, Staph. I mean, they're both important and I think that a comparator and the study agent ought to cover these two organisms. Now I'll draw back and be safe.

DR. TUAZON: Let me just second his suggestion in terms, I think this would be a great opportunity to study the relevance of serologic titers for a Group A Strep in the setting of scheme infections because I'm not familiar with any published study using that as a follow-up test except in the setting of Strep pharyngitis.

CHAIRMAN CRAIG: It definitely--I can tell you from experience where we do use it, it does go up, even in elderly patients in VA hospitals, in a percentage of the cases, the ones we assume are Group A Strep. And when we have isolated it, it goes up, too.

So again, as I say, if we can reduce the cost, make them use less patients, then they can go out and buy cameras for all their study sites so we can get the pictures, as well.

A question about mixed infections comes up. Oh, yes, Dr. Roberts?

DR. ROBERTS: Rosemary Roberts, Anti-Infectives.

Just a comment. We have never used, to my knowledge, any kind of serologic parameters for Group A Strep when it comes to skin and skin structure infections. It's just been for Strep pharyngitis. But I think that's a very good idea and certainly these patients, even if the culture, however it's obtained, or the serology did not show anything, these could be captured as clinically evaluable patients.

CHAIRMAN CRAIG: Sure. Sure.

DR. ROBERTS: That doesn't help for your microbiologically evaluable portion, but certainly we would keep them in as clinically evaluable patients.

And then a question for Dr. Tuazon. You made a point that the Gram stain, you think, is helpful in determining whether you're dealing with a contaminant or a colonizer. Could you be a little bit more specific as to how you would use the Gram stain, what you would expect to see on it?

DR. TUAZON: Right, because your culture is a lot more sensitive than Gram stain. Often, your culture may show organisms that you really don't see on Gram stain, and what you look for when you're actually dealing with infection is the inflammatory response to that particular organism. So in addition to seeing organisms, you see white cells, as well.

DR. ROBERTS: So if Gram stains were done on a routine basis and the Gram stain did not show evidence of any white cells, would that indicate to you that it was not really a good specimen for culture, or--

DR. TUAZON: It really depends on the clinical setting. I think if you have someone who has been treated and the patient has responded and you don't see any more inflammatory response, but at the very beginning of the infection, the presence of pus cells, unless you're dealing with a neutropenic patient, would be very helpful.

CHAIRMAN CRAIG: I guess I would say is if you've got a wound and that's where you're getting your material and you don't have white cells and the patient's got white cells, especially if their white count is--and they're not leukopenic, I guess I would wonder if we could really call that an infection.

So I think that the Gram stain is useful and I would go almost like what we said before, of trying to look at concordance when you're talking about microbiologically valuable of having not only the organism grown but being able to see that organism if it's from a specimen where you can get it.

Obviously, if it's a deep aspirate, you may not get much out. With cellulitis, I mean, you're not going to

find much white cells there, so that's not going to be useful at all. But if it's an abscess, you should be able to see polys, and if it's a true wound infection where there's material draining out, one should be able to see polys. But in aspirates of cellulitis, you may not see them at all, so you don't think you can use polys at all in that indication.

Dr. Reller?

DR. RELER: Because of the difficulty in many of these sites with colonizing--I mean, everywhere on the skin there are going to be organisms and it's warm and moist and there are often going to be a mixture of enteric organisms, and why we never culture swab specimens for anaerobes, period.

We very much utilize day to day on the benches in the clinical microbiology laboratory of trying to correlate the Gram stain with the culture on these swab specimens, which we discourage, but for some places, that's the only thing one is going to get, so that if there are Gram-positive cocci in clusters or chains in the Gram stain smear, we'll go after it in the culture. But if it's a mixture of things and those organisms are not seen on the Gram stain smear, it's sent out as mixed flora, presumably contamination, and that's the end of it.

So the presence of clusters of Gram-positive cocci and chains of Streptococci or chains of Gram-positive cocci are utilized to find the Staph and the Strep and the rest of that rubbish is ignored. But the Gram stain is not corroborative, because it's impossible in a superficial wound to interpret all that other stuff.

DR. MELISH: I think as a study monitor, if you have a well-described Gram stain and then you have a culture, and maybe particularly in the complicated skin structure infections, you'll be able to ascertain the organism much more easily, even if it's an odd organism, because you'll be able to tell which was the predominant organism on the Gram stain when you have multiple organisms in the culture. It might not even be Staph and Strep.

So it seems to be just good policy. Some of the time, you probably won't get a Gram stain, but if you aren't getting a Gram stain from places that are real pus and not aspirates, then somebody just hasn't collected a specimen that they really should have collected.

DR. ROBERTS: Well, certainly having reviewed several of these indications now, we have not requested or mandated in the past that Gram stains be done, and they may have been done but it wasn't captured on the case report form. We are beginning to--certainly, we have a trial now

that's in-house where we did state that you have to have a Gram stain and that for the type of infections that we're dealing with, you had to have white cells present on that Gram stain in order for it to be considered an acceptable specimen to be cultured.

But that's only been of recent. In the past, we did not ask for Gram stains and so that's why I wanted to bring this up and--

CHAIRMAN CRAIG: Just from the quality of the specimen, to know that it's potentially from an infected site, I would think Gram stain would be important to do. However, I will put in that qualification that I said before. If you're aspirating cellulitis or a tissue like that, you're not going to get much and to try and do a Gram stain on that can be exceedingly difficult.

It doesn't mean you can't try, but you may not see any polys on such a specimen, and sometimes you get so much little fluid that you decide that the best use of it is to go ahead and use it for culture than to go ahead and use it for a Gram stain.

DR. RELER: Those few situations where it's not possible to do a Gram stain are the very specimens that the nature of their collection, if you get something, it should be interpretable and it will be, if it's interpretable, a

Staphylococcus or a Streptococcus, most of the time. I mean, there can be look-alikes with--I mean, there have been descriptions of, in the past, amophylous influenza Type B, pneumococcal cellulitis, pseudomonas--I mean, there are other odd ones, but they're in pure culture and they're there and they are from an aspirate that is not subject to, done properly, contamination.

I would think that one would want to require, unless there is by the nature of the collection impossibility with the paucity of material of doing a Gram stain, of having it both as the best quality assurance indicator for the specimen as well as, I think, absolutely necessary to interpret what frequently is a mixed picture on the culture plates.

That brings up the question that I had of what do you do with mixed organisms. If they're both present on the Gram stain and it's in sufficient numbers, are they believable?

DR. RELLER: Are you asking me?

CHAIRMAN CRAIG: Yes.

DR. RELLER: Well, I think there are certainly clinical entities where mixed organisms are the rule and real, in necrotizing fasciitis, et cetera. But those are not entities that can be confirmed as to etiology with a swab

specimen of superficial exudate. I mean, those are ones where it's, I think, absolutely obligatory to have aspirates or tissue biopsies, to interpret them, and if the method of collection is beyond repute, not subject to contamination, then the mixture is real and interpretable.

But if the kind of specimen, an open lesion with a swab, is fraught with contamination problems, then I think the mixtures defy interpretation, and sometimes one has purulent material coming forth from what is a deeper problem that truly is mixed, and there it may be true but uninterpretable with a superficial specimen, true and interpretable if one goes to the effort of getting the aspirate or the tissue biopsy.

Dr. Tuazon, what do you think about that?

DR. TUAZON: Well, I think for the most part, when you're talking about complicated skin and skin structure infections, the rule is most of those are mixed infections.

DR. RELLER: But to interpret the mixture, one needs a specimen that's interpretable, the aspirate or the biopsy.

DR. TUAZON: Exactly. I mean, for diabetic foot infections, for decubiti, for necrotizing fasciitis, those, I think, are good examples of that.

DR. RELLER: Right. But a swab would never give

you a believable answer in that situation.

DR. TUAZON: I think it depends where the swab was put in. I think if it's in the deeper cavity and you've got pus, then that's interpretable.

DR. ROBERTS: This is a really very difficult area, because certainly Dr. Rakowsky outlined the types of specimens we wanted and they're key to knowing what the etiology is for the microbiologically evaluable patient. It's just the--especially our patients with ulcers, where what we tend to get, it just says "swab", and--

CHAIRMAN CRAIG: Well, most of it is surface. It's what you do.

DR. ROBERTS: Yes, and you get everything under the sun, and yet even though we're writing the protocols that those are not acceptable specimens, that's what we get and I think that a strong endorsement by the Advisory Committee and, I guess, the strongest language we can put in the guidance document that those patients will just be unacceptable to be considered microbiologically evaluable unless we have some assurance that that specimen means something.

DR. RELLER: I mean, to put this very crisply, I mean, for swabs from decubitus ulcers in our institution, they are cultured on a blood auger plate only. They have,

if possible, a Gram stain smear and the report goes out, no Staph or Strep isolated. Now, we're well aware that that's not necessarily the issue in a decubitus ulcer, but it's telling them that that's the only thing that we can interpret from this swab and if you want something else, you better give us the right specimen because we're not going to do a complete workup on a hokey specimen that defies interpretation.

CHAIRMAN CRAIG: But we're not--we decided that decubitus ulcers are, or sacral decubiti, but other, let's say, more--if there's pus coming out and it's got a good specimen, are you going to turn it down and say a swab isn't reflecting? I mean, you'd like to be able--

DR. RELLER: From a decubitus with pus oozing forth from it?

CHAIRMAN CRAIG: No. No. An infected wound.

DR. RELLER: An infected wound with pus coming out of it, will we culture a swab? Yes, we'll culture it aerobically.

CHAIRMAN CRAIG: And if you saw--

DR. RELLER: And correlate it with a Gram stain smear.

CHAIRMAN CRAIG: And if you saw Gram stain and it had numerous Gram-negative rods on it, how would you report

it?

DR. RELLER: We would report what--the reality is that if that surgical wound is, for example, on a thigh or an abdomen and there are Jackson drains and it looks like railroad tracks, I mean, what that means is very problematic. I mean, you know yourself that in a post-surgical patient who is sick and in the bed, I mean, there is a thin veneer of fecal flora over the entire body. I mean, if the Gram stain smear shows, you know, four-plus Gram negative rods and you grow E. coli on an aerobic plate and the Gram stain and the culture correlate, it's probably an E. coli wound infection.

But a mixture of things, Staph, a little E. coli, a little pseudomonas, I mean, I think you're kidding yourself and I'd want a tissue biopsy.

CHAIRMAN CRAIG: Yes. I mean, I agree with you that tissue biopsy and aspiration are clearly the ideal specimens to get, but I personally could see where a swab, if it was your only source, if the gram stain was characteristic of pus and a single organism of being able to be satisfied with that and not toss out that as an unevaluable case.

DR. RELLER: I think the key is the Gram stain correlation and what numbers one is talking about.

CHAIRMAN CRAIG: Yes.

DR. RELLER: I mean, there are beautiful published reports of somebody diving into Lake Mendota in Madison with a gash in the head pouring forth pus. Four-plus Gram stain smear, Gram-negative rods grow out on the aerobic plate--

CHAIRMAN CRAIG: Sure. Sure.

DR. RELLER: --and everyone would believe that, that it's the Gram stain as well as the plate and not a mixture of stuff on the plate with an out-of-Gram stain that is what really defines interpretation.

CHAIRMAN CRAIG: So, in other words, I think we're encouraging to get good specimens, which would be biopsies, deeper aspirates in complicated infections, but that if someone did have a swab, you would really have to make sure that the Gram stain was really very collaborative, that that was a real infection.

DR. RELLER: I think the Gram stain is so important that it ought to be a requirement, because it gives at least a reasonable chance for interpreting what's often a most murky situation.

DR. FEIGAL: Could I just ask for a clarification? Is it useful to interpret the culture or is it useful standing on its own, because our problem is when we have a Gram stain from a swab and that's all we've got.

CHAIRMAN CRAIG: Say that again, that--

DR. FEIGAL: Well, I understand the point that if you've got a culture, that the gram stain may help you interpret it and the two together are stronger than just the culture, particularly if the culture is--

CHAIRMAN CRAIG: Oh, but you've only got a Gram stain--

DR. FEIGAL: But what if we've only got a Gram stain, and we're told it's a very high quality Gram stain, but--

CHAIRMAN CRAIG: And nothing grows out?

DR. FEIGAL: Or a culture wasn't done or no growth, yes.

DR. RELLER: Well, I don't think one can--

CHAIRMAN CRAIG: I think we need to collaborate--

DR. RELLER: --make any assessment of etiology off of a gram stain smear. I mean, I think they are inextricably linked if one is going to have scientifically valid assessments of therapeutic responses in clinical trials.

DR. FEIGAL: But linked to the culture results? I think I understand you now.

DR. RELLER: The cultures and the Gram stains--

DR. FEIGAL: Are linked.

DR. RELLER: --are a package and one without the other raises grave departures from scientific integrity in clinical trials and clinical practice.

DR. FEIGAL: No. I understand it.

CHAIRMAN CRAIG: Right. And it's sort of like when we come to before, when you've been giving it a cure and giving it both clinical and microbiologic, what we've tended to do with most of the others is to say that there's also a concordance between the Gram stain and the tissue. Now, that wouldn't be possible in all of them, but where that is possible, you'd like to have that concordance, to make sure that it's not some other contaminant that grew out that wasn't seen on the Gram stain and now you're giving credit to an organism that may not have been causing the infection at all. Am I correct on that?

DR. RELLER: [Nodded head up and down.]

CHAIRMAN CRAIG: Okay. I've sort of--other questions that you had, or is that--other questions or comments or anything from--yes, Dr. Parker?

DR. PARKER: One of the things that I think this area is very vulnerable to is something that maybe should seem obvious, but I'm not sure it always is because I see submissions that don't take this into account, and that is that for most of the studies, the thing that is randomized

to the two sides are patients and yet we end up--I see some rates being submitted on a per wound basis or per ulceration basis and we have to treat ten subjects with ten wounds each considerably different from 100 subjects with one wound each.

It doesn't mean that they can't design studies, perhaps, that are using two sites within the same wound, you know, the left side tingles and the right side doesn't or something, but you have to take that into account, and I've seen many of the rates submitted sometimes where they double, triple, quadruple counted the same patient on different sites. I think we have to be very careful about that and make it very clear that it's a per person--in fact, once we decide on what is a positive and what's a negative, make it on a per person basis.

CHAIRMAN CRAIG: Yes. Anything else? I'm sure that--I guess if we're done talking about this, did somebody want to comment about what might be available, or--

DR. FEIGAL: Well, yes. Actually, I did. Actually, I wanted to start by thanking everybody for a very stimulating two and a half days of discussing these documents. This has been a very helpful start.

As Dr. Albrecht mentioned on the first day, you can find these documents, and as they're revised and

improved or we may even wish to attach comments and discussion points to them, you'll be able to find them on the FDA Web site. The easiest way to remember that is just www.fda.gov. That'll take you to the main FDA home page and then you'll be able to navigate down to the CDER home page and then below that you'll find a guidance home page that'll take you to these documents.

I think we need to have a process where we have a period where we can accept written comments, and I hope that industry in particular will take a look at these guidances and provide their comments from their experience with doing trials in these areas, of where they think the documents can be improved or issues that still need to be discussed.

It may well be that it would be useful to actually have another format where we could actually get some additional discussion of some of the documents since there are a large number of indications, I think the total is 28, and some might even spawn other documents. I'm not sure that all of them would warrant a follow-up type meeting. The ones we've started with have been very large, major indications that commonly have studies done.

One option that people may wish to comment on is whether it would be useful to have a workshop-type format as a follow-up sometime in the next four to six months, where

the Division, the Advisory Committee, and industry could sit down and go over, particularly once we have some of the commentary.

We hope that we will get written comments. This is not formal rulemaking, the way that regulations are, and so we have some flexibility in terms of how we respond and incorporate. But I think what we would like to do is identify a process where the major comments and complaints or comments of praise of things that are improvements can be publicized. Probably, we'll try and use the Web site initially to do that, and this Committee will continue to meet as we look at many of the other topics.

I guess I would see it--we'd like to probably finalize some of these topics through this process perhaps over the next four to six months. This may be ambitious, but it would be nice to bring the other topics that need Committee discussion sometime within the next year to the Committee and to be able to have a completed document within a year, as a rough time table.

CHAIRMAN CRAIG: I think that's a very good idea, and especially, I think that once you get more comments back in, somehow trying to get all the groups together so that some further discussion could occur before just incorporating those and finalizing it, I think would be

useful.

How the format for that, whether it's a workshop or what, but I think it would be very important that if we did have it, it was different than what we had here, where it was primarily the Committee talking and without much input from industry. So I would want to make sure that however the format was designed, and we'd probably need to consult industry on that, is how could it be designed in a way that we could hear their side of the story, as well, so that we could incorporate those in the decision process.

DR. FEIGAL: I think we have some experience with designing and having workshops, and I think that we certainly would want the Advisory Committee to be involved and want that to be an open process. When the Advisory Committee gets involved, it actually almost gets announced almost as though it's an Advisory Committee, but I think we would want the format, I think, and change the way that we've organized the presentations so that we do get industry involvement.

We could work perhaps with some of the industry groups, such as Pharma, but I think we would also want to look at other mechanisms, since not all of our NDA and IND holders are Pharma members.

CHAIRMAN CRAIG: Any comments from any of the

other members on that topic? Dr. Reller?

DR. RELLER: When we have had this, we have had FDA Committee precis on these topics. Could we have an industry summary on these? I mean, we had the short presentations--

CHAIRMAN CRAIG: Sure.

DR. RELLER: --of just having three of them for each subject so that we would elicit response, volunteers to which the sponsor was particularly interested in skin or soft tissue or urinary tract or whatever to speak out, recognizing that it wouldn't be speaking for the entire industry necessarily, but it would be a complimentary perspective that could then be debated in the discussion.

DR. FEIGAL: That might work very well. I think we used that format at the meeting that we had discussing resistance issues--

CHAIRMAN CRAIG: Right. Right. And there was much more--

DR. FEIGAL: --that Dr. Rakowsky organized, and that, I think, was much more interactive. So I think we can do that.

CHAIRMAN CRAIG: Anything else anyone has?

[No response.]

CHAIRMAN CRAIG: It is only seven minutes past 12.

mpd

Have a good day and have a safe trip back. Thank you for attending.

[Whereupon, at 12:07 p.m., the proceedings were adjourned.]