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P R O C E E D I N G S

DR. CRAIG: Good morning. We should get started to continue Part II, which is on the guidance document on evaluability criteria.

As was mentioned yesterday, today we are going to be starting to look at the individual indications and going to be at least an initial presentation by someone from the FDA and then also by a member of the committee.

I just will ask one question. If anyone borrowed a pad of paper from my desk yesterday, my overheads were in it, so if anyone has it, please give them -- I had to scribble out something, I will still be okay, but it would have been nice to have the nicer looking ones.

So in case someone by mistake took a pad off of here, please bring it back.

I think we are ready to start. Renata, are you going to have any introductions or shall we just go ahead and start with pneumonia? Let's go ahead and start with pneumonia and the FDA presentation will be presented by Luigi Girardi.

PNEUMONIA

FDA Presentation

DR. GIRARDI: Are we still looking for quarters so that we can have our highly paid consultants park in the

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garage? I knew I took a public service job, but this is getting a little bit ridiculous.

[Laughter.]

DR. GIRARDI: Good morning, Dr. Feigal, members of the committee, my fellow Americans -- I am sorry, that is the wrong speech.

I am very pleased this morning to be able to talk to you about evaluability criteria for pneumonia although I have to say that I am a little overwhelmed. It is a daunting task because this indication has proven to be a very difficult one to try to design trials and to generate evaluability criteria for.

It is a rather explosive topic, and part of is seen in the definition of pneumonia. There have been various definitions. I have taken one recent definition from Dr. John Bartlett, who in the IDCP guidelines suggested that pneumonia is inflammation of the lung caused by a microbial agent usually indicated by infiltrate on x-ray.

I think this definition herein lies the difficulty of making a diagnosis of pneumonia clinically, because one has to gather information from really three realms - the clinical, the microbiological, as well as the radiographic.

The IDSA Guidelines which were published in 1992 categorized pneumonia into six categories which are shown

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here - viral, atypical, acute bacterial, aspiration, ventilator associated, and pneumonia in immuno-compromised or neutropenic hosts.

Since their publication, they have been criticized a number of times. I have taken some of the more recent criticisms. I have not ascribed authorship to these to protect the guilty, but some of the criticisms have included that the clinical criteria are highly subjective, there is an oversimplified classification of clinical categories, and the last one is that they are really a disappointment, they are just a rehash of FDA guidelines.

I am not sure what FDA guidelines they were talking about, maybe the ones from 1977, but in any event, the guidelines have been criticized, so it has really been a daunting task to try to come up with a coherent evaluability criteria in this indication.

Some of the regulatory history. The indication has read in a variety of ways over the past decade including LRTI, or lower respiratory tract infection, either alone or with wording stating "including pneumonia caused by." The indication has also read as just pneumonia.

More recently, the indication has read as "community-acquired pneumonia and nosocomial pneumonia." The last two are really the ones that I will be focusing on.

So what about the CAP and HAP twins, as I affectionately like to refer to them, community-acquired pneumonia and hospital or nosocomial-acquired pneumonia, how do we attempt to look at patients enrolled in these studies?

In general, evidence as was defined by Bartlett is required from clinical, radiographic, as well as laboratory criteria. It really has become a blurred distinction between community-acquired and nosocomial-acquired pneumonia except, of course, for the etiology and the comparator agents used in studying those types of patients, and I will also submit that the diagnostic criteria for a subset of patients, at least in the nosocomial pneumonia group for the mechanically ventilated patients remains very problematic.

Well, how do we handle these patients? Before I go into this any further, I would like to just point out that I am amplifying and going into a little bit more detail than what is in the written document at this point. This is an evolving document, and since its release on the web, I have continued to discuss what the appropriate evaluability criteria might be with a variety of consultants. So this is just an ongoing process here.

Well, I think that many people would like to see stratification of patients before they are randomized into the trials. We are dealing with in many instances a

heterogeneous group of patients, and to stratify them before randomization may ensure an equal distribution into each arm of a study.

So one could stratify according to whether patients had COPD. Certainly, if one includes both community and hospital-acquired pneumonia patients in the same trial, it should be stratified. Stratification as to whether or not patients had antibiotic therapy pre-treatment. Perhaps most importantly is to stratify based on the severity of illness based on established prognostic factors.

A word about the selection of the comparator agent. Of course this should be an approved agent. Local micropatterns do become important, and they are difficult if the sites are geographically varied.

Let's get into some of the diagnostic criteria. For the clinical diagnostic criteria, at least two should be taken from the following list: cough, purulent sputum, auscultatory findings, namely rales, the presence of rales, and the constellation of respiratory findings of dyspnea, tachypnea, and hypoxemia.

And the clinical diagnostic criteria should include one of the following: fever as defined here and total white blood cell count, either a leukocytosis with

bandemia or a leukopenia. Many people would say that all patients should have fever entering the trials.

The radiographic information should be obtained within 48 hours of enrollment. There should be a "new" -- and I put "new" in quotation marks because very often it is difficult to say what is new, and especially when one is looking at ventilated patients who may have ARDS or some congestive heart failure. It is really tough to say what is a new infiltrate, consolidation, cavitation or pleural effusion in these patients.

In general, there should be concordance between what the investigator reports, as well as what the radiologist reports. There have been discrepancies in the past. What we have done is to take the radiologist's report if there is such a discrepancy, and we will even do that even if sometimes you read the radiologist's report, and it just reminds me of the favorite plant of a radiologist which is called a "hedge."

Continuing with the radiographic findings, it should be used in conjunction with the clinical and laboratory findings.

Just briefly mentioned, pediatric patients. The same clinical criteria apply although a fever should probably be present in all of the patients. There perhaps

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is more of a reliance of blood cultures and serologies. Sputum is really difficult to obtain in this patient population.

Let me turn now to the microbiologic criteria. Gram stain and culture of respiratory secretions should be obtained within 24 hours of enrollment, and blood cultures should be obtained in all patients.

For the detection of atypical pathogens, we rely on serology for the atypical pathogens. I am talking about Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae. There should be a fourfold rise in acute and convalescent sera. Antigenuria is useful to detect Legionella pneumophila sera group I.

PCR can also be employed, but we recognize that there are certain amounts of false positives in particular with Chlamydia pneumonia. It is also important to note that atypical pathogens are generally not detected with conventional cultures.

Let me turn a little bit to the Gram stain. I put a quote up here from Van Scoy 1977 because I think it is important to keep in mind how one uses the Gram stain to make or to corroborate a diagnosis of pneumonia. "It is used as a clue to the likely cause rather than as a test to

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determine the presence or absence of pneumonia." So this is really how we use the Gram stain.

The Gram stain criteria that we would look to -- and this differs slightly from what is in the written document at the current time -- we would look for a specimen to have fewer than 10 epithelial cells per low power field, the presence of organisms and white blood cell.

This is taken from a paper by Dr. Reller and colleagues who really looked at endotracheal suction aspirates in mechanically ventilated patients, but I think it is fair to say that the criteria can also apply to community patients since that was what it was based on.

Only appropriate specimens should be cultured. It is ideal to have all three of these characteristics, but I think what we are looking for is to ensure that there is no contamination. I mean in the past, some investigators have tried to equate nasal mucus with sputum, but we know it is not, and all these results should be noted on case report forms, case report form tabulations.

Well, let me go into some of the conundrums we have encountered with sputum. The patients in these trials, up to 30 percent have a nonproductive cough, so it is really tough to get a specimen. Also, 15 to 30 percent of patients are treated with antimicrobials prior to hospitalization, so

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that could easily throw off a Gram stain interpretation. Up to 65 percent of cultures remain negative.

A couple more conundrums. It is known that 50 percent of bacteremic patients with Strep pneumo specifically have negative sputum cultures, and up to 47 percent of patients with proven H. flu pneumonia have negative sputum cultures.

Let me turn now to the exclusion criteria which are listed here. Patients to be excluded include those with known bronchial obstruction, primary or metastatic lung cancer, cystic fibrosis, AIDS, or known TB. Of course, if one is trying to study pneumonia in a specific patient population, then, this only excludes those patients otherwise who would not be studied.

For pre-therapy assessments, there needs to be documentation of pre-therapy evaluation notably a physical exam, x-ray, and laboratory data.

On-therapy assessments will vary really for outpatients. It is determined by the duration of the therapy and should be clearly defined within the protocol, and for hospitalized patients, on-therapy assessments should be carefully noted within the case report forms.

End-of-therapy assessments. Not required. Easy.

For post-therapy assessments, generally, the test-of-cure for clinical efficacy, we will look at seven days post-therapy or at five half-lives of the drug, whichever is longer.

A word about patient withdrawal and how to handle withdrawals in the trial. The criteria should be defined a priori. Reasons for non-evaluability should be clearly stated, and, of course, failures carried forward.

We will talk a little bit about endpoints. As I mentioned, the clinical cure is the primary endpoint, and this is based on resolution of signs and symptoms at a fixed time. Also, for bacteriologic endpoint, which is what we would consider the secondary endpoint, is based on post-therapy sputum cultures, and I would submit that the requirement for sterilization of these cultures needs to be re-examined, and I will go into it a little more in just a few minutes. I think this may serve as part of the discussion afterwards.

For patient compliance and outcome, before we can deem a patient a failure, at least 80 percent of the intended dosing regimen should have been taken for at least 48 to 72 hours. For success, again, at least 80 percent of the intended dosing regimen should be taken for at least

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five days. Of course, this all depends on the half-life of the drug.

Many trials are now employing an i.v. to oral switch, so I thought it would be important to comment on the transition point from i.v. to oral therapy. Optimally, you know, it should be the same drug. This is definitely the case with quinolones.

It is very difficult to define objective criteria for the time of step-down, so one should establish clear clinical criteria, and micro and x-ray data are not needed at the time of the switch. It is really the clinical call.

Now, let me just as we wrap up here, let me get into a little bit about the subclassification of etiologies, and then we will launch into the discussion.

If one is ascribing etiology in these trials to specific organisms, I think one approach may be to create a couple of categories, one, a definitive category in which organisms are obtained either through blood or pleural fluid cultures, or if there is a fourfold rise in antibody titer.

If one just has a microbial etiology based on a sputum culture, perhaps it is more accurate to call everything presumptive, that the etiology is presumptive, and then once one shows cure, that there is presumed eradication of that organism, and I say that because I -- I

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took a quote from Victor Yu, whose paper in Chest in 1989 stated that, "Any organism isolated from sputum may not be the definitive one since specimens may not yield the actual pathogen."

So, I think at this point, I would like to bring up the questions and points of discussion, which Dr. Craig will focus on these three, namely, the first being should sterilization of post-therapy sputum cultures be required.

The second area of discussion is multiple pathogens. I haven't gone into this at all and the guidelines really make no mention of this, but how do we handle patients who may have evidence of multiple pathogens.

Thirdly, what are the diagnostic criteria or how should we use the diagnostic criteria for ventilator-associated pneumonia.

With that, think I will stop and I will turn the discussion over to the committee and Dr. Craig.

Thank you.

DR. CRAIG: Thank you. Any specific questions for Dr. Girardi on his presentation?

[No response.]

Committee Presentation

DR. CRAIG: In terms of the indication for pneumonia, the debate that is currently going on this area

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is a lot between the American Thoracic Society, which tends to look at pneumonia more as a disease-specific, looking more at community-acquired versus nosocomial-acquired infections, while the Infectious Disease Society is taking more of trying to get an organism approach.

I would say, though, if you look right now at the weight of the pendulum, it is clearly right now in terms of acceptance out to the community, right now it is much more in terms of the American Thoracic Society's approach of looking at community versus nosocomial pneumonia.

I think the IDSA is in the process of getting their guidelines published, and I think we will have to see how things evolve whether this approach would be a good and also very appropriate for designing studies.

But clearly, I think one area which many of the people that I have talked to, many of them members of the Infectious Disease Society feel very strongly about is that ventilator-associated pneumonia is clearly different than other nosocomial pneumonia and that if one is going to stratify, this would clearly be one of the areas to stratify, and I think the other major area that many people feel very strongly about is the severity of illness.

What one really wants to know all the time is does this antibiotic really work in very sick pneumonia patients,

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so that stratifying it into severity of illness is also I think an important aspect to consider in these clinical trials.

I think the IDSA realizes in their guidelines that really about only three stratifications, three groups can you really do. If you start to stratify it more and more, you start getting to too small a group to actually come up then with significant findings.

Now, in terms of the diagnostic criteria that was mentioned in terms of inclusion criteria, it was two out of five for many of the clinicals, and I think from most of the people that I have talked to, they felt that this is quite reasonable and that it is hard to think of a pneumonia patient that is not going to have at least two out of the five of those situations.

On the other hand, though, when it comes to fever and increased white count, the IDSA's approach has been with that was a plus or minus, could be or wouldn't necessarily have to be. I think where that problem comes up of fever and elevated white count is when one starts looking at elderly patients, because a requirement to have at least one of those is going to reduce some of the number of patients that are elderly, which tend to oftentimes not have as much

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fever and also frequently will not show as much of an elevation of white count.

So, possibly in this group, one might have some change and also some atypical pneumonia, but where I feel very strongly, and other people feel very strongly that these are important and maybe even both need to be present is when one is talking about ventilator-associated pneumonia because there are so many other causes that can produce an infiltrate on the chest x-ray in these patients, you would like to have as many good science that you have, that what you are really dealing with is an infection, and looking at both fever elevation and white count, you are not going to have a cough, purulent sputum you will have.

Many of these patients, very few of them actually have positive blood cultures. Auscultatory findings, well, if you can hear the lungs through all the sounds of the respirator, you might be able to pick something up, so it is primarily your decreased oxygenation, your cough that you are having there, so you would really like to have some other signs and symptoms that really point to that the patient is having infection.

So, for ventilator pneumonia, the question is should both of these actually be required to try and increase the chance that what you really dealing with is

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pneumonia, not an infiltrate due to some other cause, and the patient has simply just a tracheal bronchitis.

In terms of the microbiologic criteria, one of the concerns that was mentioned by Dr. Girardi is the multiple pathogens on sputum culture. That does clearly occur in a percentage of cases, especially with expectorated sputum, where one always has the chance of contaminating the specimen by upper secretions.

Now, what they clearly state in their criteria for evaluation is that for the case to be evaluable from a microbiologic point of view, there has to be concordance between the Gram stain and the culture.

Now, that may be clearly one of the ways to take around these multiple pathogens where one sees a pneumococcus on the Gram stain, but what one grows out of the culture is both, let's say, a pneumococcus and one also gets an E. coli.

The other scenario also comes in this situation where, as was mentioned, the pneumococcus may not grow out, and what one ends up with, then, is E. coli coming out of the sputum when the Gram stain actually shows, let's say, very characteristic of what one would see with pneumococcus. The question, is that a microbiologic evaluable case, and according to what they have listed in their criteria right

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now, the FDA would say that is not, and I think most of us would also tend to agree with that.

Now, the question on evaluation visits actually comes up to some of the repeat cultures that were mentioned as are these needed. The Infectious Disease Society has tended to suggest that one get a culture 48 to 72 hours after starting therapy.

It is realizing that at least in most community-acquired pneumonias, where the patient is going to see clinical improvement, the cough is going to disappear, this may be the only chance of getting a bacteriologic assessment by getting a sputum relatively early into the course of therapy in order to be able to try and look at bacteriologic response.

If the patient is still presenting material at the end of therapy, emergence of resistance is clearly one of the things that I think we still need to include in clinical trials, and if one essentially said no follow-up cultures were required, it was just being used for diagnosis, we would sort of lose our chance to try and see if emergence of resistance is a problem, and I think clearly we have been able to define that in nosocomial pneumonia, pseudomonas being the classic example, that the emergence of resistance is a significant and major problem with monotherapy in those

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situations, and so I still think it is very important to try and continue to get cultures, not only to look at bacteriologic assessment, but also at the end of therapy, primarily looking more for the emergence of resistance.

The problem, though, comes up is do you need the sterilization for bacteriologic response, and I point out that there clearly are some drug differences. For example, beta-lactams tend to be relatively slow killers of organisms, and there have been a variety of studies looking at how long it takes for the sputum to be cleared with beta-lactams and oftentimes it takes a mean of about six days, so some patients it even takes longer.

On the other hand, quinolones get very high concentration into the respiratory secretions and are rapid killers, can sterilize the sputum relatively quickly.

Now, there has been some data done looking at modeling of pneumonia using a whole variety of different parameters to see if the response by rapid elimination is better than what one sees with slow elimination, and if you look at the disappearance of symptoms in the patients in the studies that have been done, there is really no difference whether you get rid of the organisms relatively rapidly or whether you get rid of the organisms relatively slowly, suggesting that what we are seeing is the response to the

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inflammation, and that getting rid of the organisms, how fast we do is not as important in defining the overall response to therapy.

But you can see the scenario then if one was comparing the quinolone with the beta-lactam and looking at 48 to 72 hours, what one might end up with if one was requiring sterilization is very good results with the quinolone, and much less results with the beta-lactam antibiotic.

So, the question is do we need sterilization, can we look at reduction in the number of organisms present, somewhat similar to what is done with urinary tract infections.

Obviously, it is much easier there to get a specimen, but would we be able to use the Gram stain as a way of trying to at least quantitate the number of bacteria to be able to show that there still is bacteriologic response to the drug, but without really requiring complete sterilization which, as I say, may give some advantage to one drug or another, which may not actually reflect the overall clinical response and the overall treatment to the disease.

So, with that as some of the comments, what I would like to do then is sort of address by the committee

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some of the questions that I have raised to get their thoughts and again we would appreciate any thoughts from members in the audience on some of the various aspects that I brought up.

I guess we can start off right in the beginning on the current indications as far as using community-acquired versus nosocomial-acquired pneumonia and specifically whether stratification of the cases specifically looking at ventilator-assisted pneumonia is something separate, and then also the severity of illness are things that should be stratified in clinical trials of this disease.

Any disagreement, comments? Do you want to say something, Barth?

DR. RELLER: Not yet.

Questions and Comments

DR. CRAIG: Any comments from the FDA on this, Dr. Girardi, in terms of stratifying for those two? Why don't you stay up there, so that you are available all the time, or you can sit here.

DR. GIRARDI: I prefer to be a moving target.

I think in my discussions with a lot of the people that have helped design these trials, I think stratification by severity of illness is probably the more important. I am just talking about community-acquired pneumonia right now.

Severity of illness is definitely something that one should do because, as I mentioned, we want to ensure that an equal number and type of patients are randomized into each arm.

In looking over a few of these trials in the short time that I have been at the FDA, I can see how there is a disproportionate number of severely ill patients that may be randomized into one arm versus another arm, so I think severity of illness for community-acquired pneumonia.

DR. CRAIG: Okay. How about ventilator-assisted pneumonia, what have you tended to do with nosocomial, have you looked at those separately?

DR. GIRARDI: Yes. We have tended to look at those separately. I think I would probably defer to someone who has had more experience in reviewing those applications, if anybody else wants to make a comment about that. Renata.

DR. ALBRECHT: I only recall one or two applications that had those patients, and we looked at them as a subset of the entire population, but the numbers were not such that we could get statistical analyses on them. It was an ad-hoc post.

DR. CRAIG: The next question then was on diagnostic criteria where the IDSA had tended in their recommendations not to necessarily require fever and leukocytosis, essentially had that as with or without, but

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as we see here, the FDA is encouraging having at least one of those two present in all patients.

The argument for it is probably, obviously, it enhances it. My argument against it would be at least for elderly patients, it makes it more difficult to obtain those patients because, you know, seeing a lot of patients, I would say about 30 percent of ours would not meet one of those criteria when we look at pneumonia in the elderly.

So you can require it, and it will make it probably a stronger argument that that is what is going on, but it does make it more difficult to try and obtain the patients.

DR. RELLER: Bill, would it be possible to have your questions put up again, so we can be sure we have finished, I mean if we are going down your list.

DR. CRAIG: Yes. Put up the first one. That is the one that we talked about specifically on stratification.

DR. RELLER: I realize there are constraints of time, but I take it the silence was a consensus that there should be stratification in both community, as well as in hospital pneumonias.

Do you want any discussion about what criteria would go into the stratification? I mean one could split and split and split, but there may be some elements that are

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critical arbiters of putting people into perhaps two different categories in community-acquired pneumonia.

DR. CRAIG: I think there are well-established criteria in the literature for looking at severity of illness that clearly tend to show an increased mortality and requiring hospitalization for the illness, so I think those criteria are out there that clearly have been confirmed at multiple centers and could easily be used in making that stratification.

DR. RELLER: For example, community-acquired pneumonia, which criteria?

DR. CRAIG: The variety of criteria that you can look at there are numbered things - mental status, the presence of tachypnea, the type of organism that one eventually gets out, the presence of underlying disease, the -- I am trying to think -- the O₂ saturation. There are a variety of those kind of things that have been looked at and given a score, and have been used to identify the severity of the infection. Obviously, a positive blood culture is another one of those.

DR. RELLER: S o you want multiple criteria ending up with a scoring system, and if the score is this or that, then, that would categorize them as opposed to some of those elements perhaps being, you know, more important arbiters of

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admission to hospital or not, for example, that would be simpler break points.

DR. CRAIG: If you look, it is really the studies by Fine from Pittsburgh is the one that has really done the most in identifying the various parameters that justify hospitalization and are implying a more severe pneumonia.

As I say, I would use his criteria because they have been studied, they have been evaluated prospectively, and appear to be good at divining patients that are at a higher of having a worse outcome.

DR. RELLER: So the specific recommendation for community-acquired pneumonia is to use those for comparable criteria.

DR. CRAIG: Right, and as I say, we may find that somebody else comes along with something new, but at least what is available right now, it would be the criteria as put forth by Michael Fine from Pittsburgh.

DR. RELLER: And for nosocomial pneumonia?

DR. CRAIG: Nosocomial pneumonia, in terms of severity, I think, first of all, right away these patients are clearly sicker, and makes it not to me as critical to break them out by severity there. It is more of trying to get the ventilator-associated group to be looked at separately, because as I said before, the diagnosis may not

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be as strong in those, and so you may find different results in those kind of pneumonias than what you see in other nosocomial pneumonias.

DR. RELLER: How do you handle the patients who develop pneumonia in the hospital, but then is intubated, at what point do they enter the trial?

DR. CRAIG: I think we are talking about those that acquire it while on a ventilator-assisted, is ventilator-assisted. Those that, as you mention, require ventilation because of deterioration, would not be ventilator-associated pneumonia.

DR. RELLER: It seems to me that would be very important to delineate as far as entry criteria into a trial, because one of the most vexing problems I think are the you might say recurrent episodes of pneumonia in a hospitalized patient who is on a ventilator, and what is a new infiltrate, what is a change, and at what point might someone in, not necessarily desperation, but because of availability of new compound study, and so on, enlists a patient that the situation is not so murky from the outset that any reasonable assessment becomes nearly impossible as far as evaluating efficacy of new versus old agent.

DR. CRAIG: Any comments from the audience on any of this discussion? Yes, go ahead. Please identify yourself.

MS. TEPLER: I am Hedy Tepler and I work at Merck. I am curious if you are going to stratify based on these criteria. Do you feel that these groups should be independently powered, as well, in determining sample size of a study?

DR. CRAIG: It's a good question. If you are asking for an infectious disease person, what they would like to see, obviously, yes, they would like to see this drug work in a lot of severe pneumonias.

In the real world of trying to get all of those and trying to get large numbers, I think it would be much more difficult to try and obtain those, but I think what one would like to have depends on what you are going to say in the label in terms of describing the population that you are dealing with.

I think many infectious disease people, as long as it works in a certain percentage of people, are going to feel comfortable that in a certain percentage of severe pneumonias, that the drug is effective, but if one has very few severe pneumonias and they are in the comparator arm, but not in your own arm, that is where I think you get a lot

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of questions from people as to how valid the study is then in making people feel like it is a useful drug in those situations.

Yes, David.

DR. FEIGAL: The other question is, at what point do these things break down and become mentioned in the indication per se, and so far today I think, you know, as you saw in Dr. Girardi's lists of the indications -- we haven't broken down pneumonias further by severity the way that we have some infections.

I think if we were going to do that, then, the issues of power and prospectively stratifying would be more important. I think the other option is to consider stratification in the analysis, after the studies are over, as an analytic tool to assess balance.

In that setting with multiple factors that you could stratify for, it is probably not as appropriate to test hypotheses and develop indications. So I think it depends a little bit where someone wants to go, and I think if a drug developer felt they had a product that had a particular superiority, a particular niche for severe infections compared to all comers, then, you ought to design such a study, and I think your comments about what type of criteria from the literature or from past experience could

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be used would be helpful, and it should be done prospectively in that kind of a setting.

DR. GIRARDI: Dr. Craig.

DR. CRAIG: Yes.

DR. GIRARDI: We have also recently handled this in another way, and that is to put information in the Clinical Study Section of a label to speak to the severity of illness of some patients in the trial even though the studies may not have been powered and the indication would still read community-acquired pneumonia, but describe a subset of those patients within the Clinical Study Section to give the practicing clinician a sense as to how the drug works in that subgroup.

DR. CRAIG: But our concerns would be, let's say, a drug that doesn't provide very high serum concentrations, and the concern then in patients with bacteremic pneumonia, you would like to be sure that you are dealing with a severe enough group of patients with pneumonia that you are going to get a good evaluation of the efficacy of that drug in that situation.

So I think it comes up with certain drugs. If one is looking at a new quinolone, for example, that has been very effective, and old quinolones have been very effective, the need for specifically making sure you have a good number

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of severely ill or patients with a worse prognosis, becomes not as critical at least in my mind, as it does when you are looking at a compound where you think its pharmacokinetics are different, its mode of action is different, and we are really not as confident that we are likely to see the same results that we have seen in the past.

So I think that is where, at least the feeling that I get from many of the people that I have talked to, become concerned about the trials in pneumonia is with those kind of situations.

MR. LEROY: Excuse me.

DR. CRAIG: Yes.

MR. LEROY: Regarding the severity score, I would like to point out that --

DR. CRAIG: Identify yourself, please.

MR. LEROY: Bruno Leroy. I would like to insist a little bit on what was said by Dr. Feigal, because stratifying is not so easy, and these score, should be easy to recruit at the entry of the patient if we want to stratify a priori, and the only score available for that is the defined score, and sometime if you want to address the problem of mild to moderate diseases, this score is not suitable, because this score, there are some items that are for very severe pneumonia. Then, the score is no more

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suitable, and the tendency to use only some items of the score leads to some pitfall, because then the sum of those items have not been validated. Okay?

And it is very important to understand that it is the score that should have been validated, not only the items. Otherwise, the risk is to build the score and to balance something which is not the severity. Okay.

So the items are pleasant to see, but if you use only 3 out of 10 items of score, you build something that is yours, but it is not the severity.

DR. CRAIG: Right. I think what he is pointing out is that one has to use all the parameters if you are going to use them. If you are only going to pick a few of them out of there, they may not be independently associated and can be used that way, and theoretically, one should have to use the scoring system.

MR. LEROY: The whole score that is validated.

DR. GIRARDI: Dr. Craig.

DR. CRAIG: Yes.

DR. GIRARDI: I just want to make a comment that it is very instructive to listen to all these comments, and it underscores how difficult this area is to study and to evaluate these trials.

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So I would just emphasize to send it written comments, so that we can peruse them very carefully, and so that we can come up with a very comprehensive document.

DR. CRAIG: Now, in terms of exclusion criteria, the question comes up, and the question I am raising, is that the idea, say, in their guidelines we are not requiring fever and white cells. Specifically, it reads clinical findings and then plus or minus fever and elevated white count.

I think that was primarily to be able to incorporate more elderly patients and then also the patients that may have some of the atypical pneumonias, where they may not get as significant fever and get atypical pneumonia.

I think what the FDA has done is to feel more comfortable that they are dealing with is pneumonia, you wanted to have one of those two present.

DR. GIRARDI: That is correct.

DR. CRAIG: What values? I mean I can see where you have got leukopenia, I could see a viral pneumonia fitting that criteria, where you would get a leukopenia with a virus and you might not necessarily get the fever, and we would include a viral pneumonia in that group.

So the leukopenia, to me, is much more when you are talking about gram-negative pneumonia and overwhelming

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sepsis that you are going to see that, much more so than what you would be looking at in community-acquired pneumonia, so the IDSA also does not have the leukopenia, it only talks about an increased white count.

Yes.

DR. MOLEDINA: Nasim Moledina, FDA.

I have reviewed lots of protocols with community-acquired pneumonia, and I do not think that we will be able to see fever or increased WBC count in those patients who are treated as outpatients.

So that criteria would be okay for ventilator-associated pneumonias or nosocomial pneumonias because those patients will be in the hospital and monitored. So I do agree with -- I mean we can put those criteria, but we should not require it.

DR. CRAIG: So, as I said, to me they should be more optional especially for community-acquired pneumonia and I guess, you know, they are one of the criterias that can be looked at for severity of illness, but clearly for ventilator-associated pneumonia, the question I almost have is you almost want to have both of them to try and be sure that what you are dealing with stands a good chance of being pneumonia if one is going to use those patients for study.

DR. BANKS-BRIGHT: I am thinking about elderly patients, too, but there is another group of patients, HIV patients who also get community-acquired pneumonias, too, who may not have those other criteria, and that would leave out another group of patients who may not mount a fever, may not even mount an elevated white blood cell count depending on where they are in the disease.

DR. GIRARDI: In general, those patients would be excluded from the trials unless we had a protocol specifically designed to look at pneumonia patients who are also HIV positive, then the parameters would change.

DR. CRAIG: Any further suggestions? Anyone from the audience want to comment?

So what do I get the gist of the committee?

DR. GIRARDI: I think everybody really likes what we are saying so far.

[Laughter.]

DR. CRAIG: You hear one thing, I hear something else.

DR. RELLER: I would like to see both criteria required for the ventilator-assisted pneumonias to increase the specificity of the diagnosis, and I would like to see that information on the community-acquired ones, but it

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would seem not necessary to require it to be included in the analysis, but I think that information should be available.

DR. CRAIG: Nancy, what do you think? What is the story in kids?

DR. HENRY: Before I answer that question, I guess we have talked about ventilator-assisted patients who get pneumonia, and I agree that fever and white count is important, and that would hold true for kids, as well as adults. Community-acquired, I also fever and white count changes may not be very helpful, but there was that third group, you know, nosocomial pneumonias, would fever and elevated white count be required there. Obviously, I think that would be a criteria that you would need for that group of patients. Again, I think that would hold true for adults, as well as pediatric patients.

DR. CRAIG: I think the FDA would argue that -- not the FDA -- but the IDSA would argue that when you take out ventilator-associated, take out some of those gram-negatives and start looking at the other pneumonias, that they start looking a little bit more like community-acquired, it is just that they happen to be in the hospital.

So you could see the scenarios where we are going to see -- I mean pneumococcus I think is number 10, something like that, on the list, if you looked at the

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missed data, if you believe that, for nosocomial pneumonia. It is one of the organisms that occurs there, and the question is, is that pneumonia in the hospitalized patient, acquiring it there, going to be that markedly different from what we see in somebody acquiring it in the community.

So you could also see in the situation with nosocomial pneumonias, if you shift out some of those major gram-negatives, whether you are also going to have a situation where it may be difficult to get those.

I think I would still probably argue that they would be nice to have, but I don't think I need them for specificity in order to be sure that what I am dealing with is pneumonia. On the other hand, in ventilator-assisted, I think I do need those to try and have a better idea that what I am dealing with is truly pneumonia.

DR. RELLER: Bill, don't you think the probability of having a confounding cause of infiltrate in a hospitalized patient who develops nosocomial pneumonia is, if not as high as the ventilator-associated, is higher than those patients presenting from community with fresh onset of respiratory symptoms, signs, and radiographic changes?

DR. CRAIG: No.

DR. RELLER: You don't think so.

DR. CRAIG: No.

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DR. RELLER: I wonder about that. I mean with, you know, drugs and bleeds and underlying disease, et cetera.

DR. CRAIG: Not with purulent sputum. I mean I think what you would have to -- you know, if we start looking at some of the other signs and symptoms being there and having a good sputum specimen, I think that is much less likely, but I think in ventilator patients there is clearly tracheal bronchitises that occur with these patients that are not pneumonias, and there can be a whole variety of causes that can lead to an infiltrate, so it really starts to be gray there.

Simple tracheal bronchitis in the hospital in somebody without a ventilator, with an infiltrate, is much less likely to occur and much more likely to be pneumonia. So that would be my argument.

Yes. Dr. Melish.

DR. MELISH: There might actually be compelling reasons to have different criteria for children and adults. We have already mentioned some of those situations. One would be that you will not find sputum production in a child, period, so that you will be able to use that criteria.

Another is that hospitalized children, nosocomial pneumonias very likely have been postoperative or have had asthma, and may well have a confounding condition. So, if they have a confounding condition, you are more likely to need the elevated white count and fever, and they will virtually always I think have fever, they have got the fever-producing mechanism.

So I think they are going to part company, maybe not, you know, the same criteria would be appropriate for ventilator-associated pneumonias, but others they probably will need to be different.

DR. CRAIG: Yes.

DR. SCHWARTZ: I don't hear anything, I hear something about white count, which is fine, but what about other acute-phase reactant and specifically a quantitative, well-performed C-reactive protein? We need a whole spectrum of things in order to try to make a global picture because it's so difficult to make.

I can give you plenty of asthmatics with platelike atelectasis just from plugging, where they do produce what you might call sputum or mucus. It is sometimes difficult to tell, and the fact that they have polys in there doesn't differentiate very often, at least with the nose and often with the trachea, between virus and bacteria.

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I think there should be as many easily accessible criteria that you can have to really narrow and become much more precise who has the pneumonia and who has the confounding look-alikes.

DR. CRAIG: At least from my understanding of the literature, when those things have been looked at, it has been much more helpful in pediatrics than it has been in adult medicine to separate viral from bacterial by using C-reactive protein, things like that.

It is just harder to do, and I think that is why, since the great majority of the trials initially start in adults and then eventually get over to children, I think we have been primarily concentrating and looking at it from the adult point of view, but I would agree with you, if there is a test that can help differentiate, so that you really increase your specificity, especially since in kids, at least as I understand, it is difficult to get sputum, so you don't have purulent sputum to look at in many of these situations. Trying to find some other test that increases the specificity, I think is right on, is what would need to be done.

DR. GIRARDI: It is tough to get it when you want the sputum from the kids. When you don't want it, they will give it to you.

DR. RELLER: The reason for not requiring elevated white count and temperature as absolute entry criteria for community-acquired pneumonia was owing to the aberrant presentations in elderly patients and those with atypical pneumonia.

The atypical group are inconsequential issues in nosocomial-acquired pneumonia.

DR. CRAIG: Yes.

DR. RELLER: And yet one could have -- and you have emphasize purulent sputum -- I agree that is very important, but the two out of five, one could have a patient in the hospital with a cough and altered oxygen saturation or a cough and auscultatory findings who would slip in as a nosocomial pneumonia, and I am very uncomfortable about that.

As Dr. Henry had pointed out earlier, I mean are we going to lose that many patients because of more stringent criteria that make it worthwhile in what is I think more frequently fuzzy for nosocomial-acquired pneumonia than it is patients with abrupt or I recognize in some kinds of pneumonia a more intimate onset, but for the most part, an abrupt change in their community health status.

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DR. CRAIG: I understand your argument. I could easily be talked into one of the two for nosocomial, but another way of getting around it is to say that they are encouraged to enter patients that fever, elevated white counts, but that, you know, their presence is not required or mandatory for admission, so that you are trying to at least encourage them to get those kind of patients, but not making it a strict requirement that they have to have it for entry.

DR. RELLER: For the analysis after that fact that is so terribly difficult, a wonderful editorial in the Archives of Internal Medicine by LeForest that referred to defined criteria for gradation, severity, et cetera, stated, "Few diseases are so characterized by disputes about diagnostic evaluations or therapeutic decisions, little progress has been made on the first problem, namely, the diagnostic end of things, more with the severity criteria and allocating people to appropriate treatment."

For the purposes of an objective, rigorous assessment, it seems to me that the quality of the data on fewer patients is much more important than large numbers that are virtually -- it may be difficult to tell whether they really have the disease or they don't.

DR. CRAIG: Ms. Cohen.

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MS. COHEN: I am curious. Are you going to use emphysema patients who have frequent pneumonias?

DR. CRAIG: Those patients, one of the suggestions I think that you had is that you do look at those in terms of stratification whether they have underlying COPD to make sure that there is not a marked difference, but frequently those patients are included in clinical trials.

MS. COHEN: I know that they are doing lung projections at Women-Brigham, and it might be a place to find some people.

DR. RELLER: Actually, Ms. Cohen's comment is actually very timely, and I hadn't thought of it before, and that is, I think a substantial proportion of patients who develop nosocomial pneumonia owing to age and the frequency of underlying pulmonary disease in persons with chronic obstructive bronchitis and sputum production, they may well, because of their underlying disease, it puts them at risk of pneumonia in the first place be it community- or hospital-acquired. They may ever have a sputum in there that confuses things, Bill. I like more stringent criteria for nosocomial pneumonia.

DR. CRAIG: Do you want both of them or just one out of two?

DR. RELLER: Should I be greedy? I will go for both of them. I think both of them would make it much easier to interpret what is an inherently difficult problem, and then we don't get into subsets of subsets.

I mean we have already said that ventilator-associated and nosocomial pneumonia are entities that need to be looked at differently. In this way, we would at least have similar criteria for all of the hospital-acquired pneumonias with one breakout rather than the possibility of four categorizations in those patients, and then one has the community-acquired pneumonia where the data are available, but owing to atypical pneumonias in elderly patients, it is not an absolute criterion for inclusion in the analysis.

DR. CRAIG: Okay. Let's move on. You have some suggestions and I think there are some good arguments for including one or two of those. As Barth said, he wants to be greedy and take both for nosocomial, as well as for ventilator-associated pneumonia, but not making them a requirement for community-acquired.

Let's go on and deal with multiple pathogens, which is one of the items that Dr. Girardi brought up, and this is always a sticky issue. Some of the examples that I brought were you may grow both a pneumococcus and E. coli out of there, should we make sure that as they state that in

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order for it to be microbiologically valuable, there has to be concordance between the Gram stain and the culture, so if you don't see the E. coli on Gram stain, it would not be classified as the pathogen, but you would deal with the pneumococcus as being the pathogen. That would become essentially not a dual infection, but a single infection.

I personally think that is one of the ways, the best way probably, to try and handle. I think we will find situations where we will get hemophilus and pneumococci out of the same patient. I think that is a well-documented phenomenon. There may be occasions where we may even get the others, but, generally speaking, pneumonia outside of aspiration is primarily a single-pathogen infection and that most of the time one should be able to reduce those down, so that one is looking at one primary organism.

I think where we get into problems is if we call that also an E. coli as being treated, that we then later get into when one starts trying to make break point determinations and start including in an organism that probably really wasn't the cause of pneumonia at all, and can sort of interfere, cloud the picture when one is looking break point determinations.

DR. BANKS-BRIGHT: I would like to make a comment.

DR. CRAIG: Dr. Banks-Bright.

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DR. BANKS-BRIGHT: How many times -- and I totally agree with you, but I am thinking about would you say, then, a predominance of that organism on Gram stain as opposed to just a Gram stain, let's say, if you have just a Gram stain with pure gram-positive diplococci as opposed to a predominance of gram-positive diplococci and a few gram-negative organisms, what are you going to do with that kind of situation which so often happens, because if you are coughing up sputum, quite naturally, your sputum is going to be contaminated on your Gram stain by organisms that are going to be part of the mouth flora?

So, would you say then a predominance of that organism as opposed to --

DR. CRAIG: Well, that is what you would like, but you may not get that in a lot of specimens, and I think that you were trying to bring out, but it seems it is more a problem of not growing out of the culture than it is of not being seen on the Gram stain, so that if you were looking at the concordance or the loss of concordance, I think what you would find with the common pathogens that we see, like pneumococci and hemophilus, it would be a situation where you see the organism Gram-stained, but you don't culture it on the culture.

On the other hand, with some of the gram-negatives, especially in community-acquired pneumonia, the scenario is more the reverse, where you may get the organism out of culture, but you don't see the organism or it is just rare organisms on the Gram stained.

Dr. Reller.

DR. RELLER: In addition to its utility for assessing quality of specimen for all ones, whether expectorated from community or suctioned in hospital, whether adults or children for those intubated patients that have been referred to, to me, the culture cannot, and to reinforce your comments, I do not believe that the culture can be interpreted in the absence of a Gram stain correlation.

It is in a way logical why we get into the difficulties. As the Bartlett article in The New England Journal pointed out, in a superb review of this, the commonest -- and there have been other papers -- the commonest cause of negative cultures for pneumococci and Hemophilus influenzae prior to antimicrobial therapy, and they are often not there, but the Gram stain may show them, in some mixtures are logical and expected, and others are not.

So, a pneumococcus-E. coli is not a known complementary associated polymicrobial finding that has ever, to my knowledge, been validated and makes no sense of a pathophysiologic basis, in contrast to one may have a flora depositive Gram stain, a piddly culture, and have a necrotizing pneumonitis with accompany pleural effusion that is expected with mixed organism that always remains mixed with viridans streptococci, Fusobacterium, et cetera, so that some of the mixtures are hokey mixtures based on colonization in a sick patient of the oropharynx and some contamination of the sputum, and death of the organism that is the real culprit.

The other thing is that presumably other than the relatively unusual bacteremic septic emboli pneumonias, the pathophysiology, if we accept that virtually all pneumonias are aspiration in the start, one is not selectively aspirating pneumococci. It is just that those things with intrinsic virulence only to capsules, et cetera, come to the fore, and it may explain some of the unusual findings like of cavitation with pneumococcal pneumonia where one aspirated mixture of things, the anaerobes are gone, and pneumococcus is there, but you have the residual of what was the mixed picture at the outset.

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So I think, in summary, the Gram stain is absolutely essential. There are reasonable ways to require it, and we use, for example, the Gram stain to dictate how far we work up the culture, what we report, what we do susceptibility testing on, and go for a search, so that if pneumococci are seen on the Gram stain smear and the plates grow out a mixture of organisms, we will go to the extra effort to fish out some of the buried pneumococci, because they are on the Gram stain smear, and ditto for Hemophilus influenzae, whereas, if they are not seen and there is one pneumococcus buried in amongst a sea of mixed mouth flora, it is ignored totally because there is not the Gram stain support.

So I think what drives this entire process and why some have advocated that if you would only do one thing, get the Gram stain, I mean that is the best source of reliability in terms of the Van Scoy "earlier" of using these laboratory results to attempt to delineate objectively the etiology of what one has confirmed a priori to increase the pre-test probability of getting the etiologic answer confirming the diagnosis in the first place because if we try to interpret the sputum cultures when they don't have pneumonia in the first place, forget it, it's complete chaos.

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DR. CRAIG: Right, and I think the guidelines that you are proposing here for evaluability clearly do reflect talking about a concordance between what one sees in the culture and what one sees on the Gram stain in order for it to be microbiologically evaluable, and I think that really does take care of most of the problems that one would have with multiple pathogens.

Let's move on to the next one. I think we had one other thing there that I wanted to bring up. There is another question that comes up, the number of cultures.

This is the question of what is required. You know, it is sort of like what we do for respiratory infections, sinusitis, otitis media, you know, you sort of get what the organism is and then you treat, and everything is presumed eradicated.

Should the same thing be done with pneumonia? Well, my own feeling and from what I talk a variety of infectious disease people, is they feel that we should still continue to get cultures when we can, but realizing that especially in community-acquired pneumonia, that they may be difficult to obtain especially at end of therapy.

The concern though comes is that if one does require the culture, how does one interpret it, and the way that things have been interpreted in general by the FDA is

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that if you started off with loads of organisms and you end up with marked reduction in those organisms, and clinical improvement, that still gets classified as persistence.

There is nothing like for reduction in the number of organisms that is current in the guidelines, and that would be fine if persistence at the end really meant that there was a decreased response to pneumonia, but as I tried to bring out, I think there are differences in the speed at which antibiotics can eliminate organisms from the site that may be unrelated to the disappearance of symptoms and the overall response to the disease.

So, by requiring sterilization, what one in theory does is potentially give some particular advantage to a certain class of agents and put other classes of agents at a disadvantage.

So the question is, is can there be some way, do we need to require sterilization, complete elimination of the organism, or is there a way that we can also somehow incorporate reduction of the organism in order to look at the microbiologic response.

Yes, Dr. Schwartz.

DR. SCHWARTZ: I don't know that you will ever get to consensus on that. I don't have a problem with the significant reduction, but I have the caveat as long as I

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reduce sensitivities on the second specimen because if the reduction means I have killed off susceptible strains and I have resistant strains there, then, I have a potential problem. So, if you redo the susceptibilities, then, I will be happy as long as it is still susceptible.

DR. CRAIG: Right, and I would agree 100 percent that one does need to look at the susceptibility of those organisms later on. If all we are going to do in respiratory infection is make the diagnosis by culture at the beginning, and never getting any cultures later on, we are not going to be able to look at these drugs in terms of finding out differences in terms of the emergence of resistance, so I think it is clearly mandatory that cultures be obtained providing, of course, the patient can produce them towards the end of therapy.

I would, in community-acquired, where in fact most of pneumonias, since the longer you go, the less chance you have of getting the sputum, I would even try and look at it and try and get some bacteriologic response, as I said, around 48 to 72 hours, and that is the recommendation, as I say, that the IDSA has had for getting repeat cultures.

The question comes do you need them at the end of therapy or do you need them at the test-of-cure, because the

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test-of-cure is usually about a week or five half-lives of the drug later in terms of evaluation.

Dr. Henry.

DR. HENRY: I have just a comment, I guess. To me it is confusing especially in community-acquired pneumonias to get sputum cultures at 48 or 72 hours in the adult population, because I am not certain how to interpret them. Number one, if you can get a sputum from a patient, you may not have organisms that grow, so if you are talking about quantitation, then, where do you draw the line as far as quantitating organisms on the Gram stain, and just the distribution phenomenon of organisms, I mean maybe there are organisms in that particular specimen, but what the lab is looking at under the microscope, you know, the numbers are low, and even just the fact that some patients may be able to give a sputum specimen and others not, I mean are you going to require patients to have some chest physiotherapy in order to try and augment sputum production.

Because there is such variability in getting a specimen, in getting an optimal specimen, that the lab is looking at an optimal part of that specimen, it is difficult to interpret it, and that is just among community-acquired patients. You can run into some problems through an

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interpretation with nosocomial and ventilator-assisted patients.

I agree that maybe 72 hours is probably the best time that you might have contact with the patient in order to get it, and they might still have some sputum production as compared to looking at it later, at five days or five half-lives or a week, you know, test-of-cure type of thing, but I am not really sure how to interpret it, because it really is going to depend on those patients -- if a patient is lucky enough to have coughed up a big plug of sputum, I mean great, then, you may even have a culture, but to make that a strict criteria I think would be difficult.

DR. CRAIG: Oh, it is not a strict criteria, it is when the patient can produce it. I mean obviously, if the patient can't produce it, what it gets classified as is presumed eradication.

DR. HENRY: But that is if you label it as persistence. Maybe it is just because that patient was able to bring it up, and some other patient, maybe they coughed up before they came in, and how do you label that one as a cure and the other one as persistence.

DR. CRAIG: My point is exactly that. If one is going to get a sputum at 48 to 72 hours, one has to have some way of not penalizing the drug that is a slow

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eradicator unless that is somehow tied to the overall response to the disease.

I think where we stand right now with our knowledge on that, there doesn't appear to be a concordance with the speed at which the organism is eliminated and the speed at which the patient's symptoms respond.

Now, that has been mostly looked at primarily, as I say, in nosocomial pneumonia, but without that knowledge to know it, what you are doing by looking relatively early and requiring complete eradication is you are essentially giving an advantage to drugs that get very high concentrations of respiratory secretions, and giving them some advantage which may not really reflect, as I say, the overall response that you are going to see.

So if you are going to get them early, I think we have to have some way of not requiring eradication, but even being able to look at it in terms of elimination.

But later on, I think it is important in anyone that is producing sputum to try and get one at the end of therapy or, as you say, it may be at the test-of-cure, but to try and get one later on primarily to look for the emergence of resistance, because clearly, we have been able to see, especially in nosocomial pneumonia, that that is a significant problem that can occur in those patients, for

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example, 50 percent emergence of resistance with imipenem for Pseudomonas, 33 percent emergence of resistance with ciprofloxacin.

So those are significant resistant problems that I think in this era of increasing resistance, we need to collect data not all of a sudden decide that we are not going to look at it and just let it occur out there without any information.

DR. MOLEDINA: The only time that we have really required repeat cultures during 48 to 72 hours is in evaluation point is when the patient is not doing well. In community-acquired pneumonia patients, since they are outpatients and you are giving them oral therapy, you really do not require them to come back for a repeat culture unless they call in and say that, you know, I still have the fever or I still feel lousy, then, we require those culture and we can interpret those as failures. That is the only time that you can use it as a bacterial assessment. But if the patient is doing well, and if he gives you a sputum, and if it comes back positive, how are you going to interpret those results?

Maybe it's a slow killer, you know, and maybe he is doing well, so you are going to continue the antibiotics,

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you are going to keep him on the study, you don't know how to interpret those results.

So I would say that if you want to repeat cultures at 48 to 72 hours, then, you will have to put a little sort of -- say that if the patient is not doing well symptomatically or something like that, or clinically not doing well, and that is what we have written in protocols before, that those cultures should be repeated if the patient is not doing well clinically.

DR. CRAIG: Dr. Albrecht.

DR. ALBRECHT: Just a couple more words to what Dr. Moledina said. When we have had protocols where patients did have the cultures at 48 to 72 hours, and perhaps the culture did come back with -- well, the Gram stain and culture -- with organisms, but with a reduced number, and clinically, the patient was showing improvement, and the investigator didn't discontinue the patient from the study, didn't alter therapy, but simply felt that the patient was showing response albeit perhaps slower than in other drugs, those patients have continued in the study without alterations in the drug that is being tested, and then at the end of treatment or subsequent visits in fact clinically show the patients to have been cured, then, in the context of all that, that 48 to 72 hour culture was

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presumed to be showing a slow response, and not interpreted as a negative kind of response to treatment.

DR. CRAIG: I think it is a slow response in the sputum, it is not necessarily a slow response in the patient, I mean in the clinical development as a clinical response.

So the question that I think that you are raising is whether we even need it.

DR. GIRARDI: I think it is clear that if patients are able to give a sputum sample, it is paramount to obtain it to look at patterns of emerging resistance, but to require sterilization in a patient whose diagnosis may be presumed, microbiological diagnosis may be presumed at best, I think we should not require sterilization.

DR. SCHWARTZ: As one more practical point, giving sputum on command is very difficult even if you are sick. You have a finite amount of time that the person is going to be in the office and for follow-ups that is a very short finite amount of time, you are in and out on their wishes and the investigator's wishes, but who is to say you couldn't get sputum at home in the 48 to 72 hours, because giving them something saran wrap or something they could use, even a simple home Gram stain with a Q-tip and a slide, or anything like that, or a little holding media, I think

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would be a very, very nice, simple, practical, and maybe useful thing to do.

DR. CRAIG: I think, generally speaking, we want to try and get sputums, continue to get them during the course of therapy. Is that correct?

DR. SCHWARTZ: At least the first one.

DR. CRAIG: At least that is the general hint that I was getting. Well, I think if you don't get one at the end of therapy, then, you have lost your chance to look for emergence of resistance. I think it is unlikely to occur as fast as three days. So if you really want to look for emergence of resistance, that is something that you have got to do either at end of therapy or at the test-of-cure.

Usually, the farther you go out, the less chance you are going to have of getting a specimen, so that is why I think the IDSA suggests it at 48 to 72 hours and again at the end of therapy.

DR. RELLER: Perhaps unrealistically, but I had always -- one of my great interests in these guidelines is that the highest standards of clinical practice and those of investigative studies, I don't see why they should be necessarily very different, and because resistance even with the worst combinations, that is, those organisms that are most apt to become resistant with those agents that are most

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apt to lose their efficacy, 48 to 72 hours is early to find it.

I really have questions whether it is worth the effort to get a sputum specimen when many won't be producing it if they are responding well or are we really getting enough information with what is tantamount to an on-therapy culture in someone who is doing well, and I think that also applies to the recommendations that currently stands for getting blood cultures after 48 to 72 hours.

If we have got at best 10, maybe 20 percent in selected organisms positivity, in the first place, with using a drug that is presumed to be active as an ethical basis for starting out, the likelihood of getting a positive blood culture I think is remote in someone who is doing well, and consequently, I think we should be very careful about requiring information that is not apt to provide any useful interpretive information.

In contrast, at the end of therapy, if someone is able to produce a sputum or they are a failure or they are ambiguous or there has been an inadequate response, one of the reasons for that inadequate response may be the emergence of resistance, and I think that we need to look for it.

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I don't think we ought to go to extraordinary lengths to get a specimen to document, and I don't think that someone who has responded by all other criteria should be required to eliminate the organism to be successfully treated, but I am far more interested in the compulsive acquisition of information after therapy for those who have not had a complete response and cessation of sputum than I am getting information that adds a considerable cost and effort during therapy that is unlikely to be interpretable.

DR. LEISSA: Brad Leissa, Medical Team Leader,
Division of Anti-Infective Drug Products.

I have kind of a general comment, and I think that it helps with the discussion of evaluability criteria of a meeting of minds between clinical practice, academia, the sponsors, and the division, which is I think the issue that Dr. Reller is talking about, is that of what do we need to know versus what do we want to know.

The idea, whenever we are talking about these criteria, and there is the implication that we need to have this information, I know the sponsors I am sure out here are thinking, you know, the enrollment has just gone up another 5 or 10 percent, so I think that is very helpful in terms of getting that kind of feedback from you about what is a requirement with regards to data that are collected versus

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we would like to see that, and if we saw that in 80 percent of the patients who are evaluable, or 50 percent, that would be helpful in the discussion.

DR. CRAIG: Yes.

DR. ALTAIE: Sousan Altaie, FDA.

To add to comments of Dr. Reller, in general, is we are trying to get that 48-hour culture to follow up resistance, as a rule of thumb, you don't check susceptibility patterns on a gram-negative until five days later, so within 48 hours, you really would not be able to detect resistance patterns. Five days is the minimum when somebody repeats susceptibility testing on a gram-negative.

DR. CRAIG: I fully understand Barth's position is what are we learning with that specimen at that period of time. Sure, if the patient isn't doing well, one gets clearly in that situation, I would think Barth wouldn't argue it would be good to look at the sputum again to be sure that we may not see any response, the organism is there, or there is something else there that we didn't anticipate, so that that would be a very appropriate one to do.

But in somebody that is clinically doing well, the question is, is what is the value of getting that specimen. As I said, it may be the only sample of getting a true

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bacteriologic response, but is it as good an indicator as the clinical response that the organism is doing well, and should presumed eradication be really all that we need.

I think you can argue that and especially if you still are held by the requirement that if there is any organisms there, that is called persistence, I think you can give a false sense of what is really happening there.

So I can clearly see that 48 to 72 hours that only in those patients that aren't doing well would a sputum culture be needed, but I clearly agree that at the end of therapy, in those patients that are still producing the specimen, we have to in some way try in this era of look for emergence of resistance, so doing it at a later time I think is clearly an important thing to do.

Now, the investigators, you know, they may want to decide that they want to still keep a 48 to 72-hour specimen there, and in the comments, discussions that the FDA has with the sponsor, they may decide they want to do that, but in terms of I think what I would require to be able to evaluate it, it is not a necessary thing, I would agree with Barth.

DR. RELLER: The timing of repeat susceptibilities, I think most of these or all of the guidelines recommend following NCCLS criteria. They have,

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just as an information point, addressed these issues, and with quinolones and all organisms with Pseudomonas aeruginosa and all antibiotics, and with Enterobacter, Serratia, Citrobacter and third-generation cephalosporins, the recommendation is to repeat susceptibility testing beyond 72 hours, so four days or more, and it is what most laboratories in the country do because most follow NCCLS criteria.

DR. CRAIG: Any other comments?

Okay. Let's take our break. It looks like we are just a little bit behind schedule, but I think we will get back on when we do the next one.

We will see you back here in 20 minutes, which will be 20 minutes to 11:00.

[Recess.]

DR. CRAIG: The next topic is going to be bronchitis, which is broken down as acute exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis.

The FDA presentation will be by Susan Thompson.

BRONCHITIS

FDA Presentation

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DR. THOMPSON: Good morning. I have been asked today to present to you the Division's proposed evaluability criteria for the category of bronchitis.

As Dr. Craig mentioned, I am going to approach this by describing for you two clinical entities to be encompassed within our description of bronchitis, and specifically, that is acute exacerbation of chronic bronchitis which for the sake of brevity I am going to be referring to as AEGB, in addition to secondary bacterial infection of acute bronchitis or SBIAB.

Just a couple words on the regulatory history of which you have already heard some background relevant to bronchitis. In previous years, the category of lower respiratory tract infection actually included not only pneumonia as one might predict, but also bronchitis.

If you look in Points to Consider, there is actually a combined indication for these two entities, for SBIAB and AEGB, and in the IDSA Guidelines there is a completely separate indication for AEGB, and actually guidelines are not included for secondary bacterial infection of acute bronchitis.

What I would like to very briefly do is hit on some salient background features of both of these disease

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entities in order to help your considerations of evaluation of the guidelines.

First of all, just very briefly some background of SBIAB. As most of you are probably aware, by far the most common etiology of acute bronchitis is viral. *Mycoplasma pneumoniae* has certainly been described to cause the syndrome in addition, and rare causes of this entity include *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Bordetella pertussis*.

Very often one finds preceding signs and symptoms of the URI which reflects its viral etiology. Having heard then just this brief outline, you can see that the role of antibiotics becomes somewhat problematic in this clinical disease.

To just present briefly some background information on the acute exacerbation of chronic bronchitis that is relevant to our discussion today, chronic bronchitis has been fairly well and consistently defined in the literature as cough and sputum production for more than two consecutive years and for most days in a consecutive three-month period.

The acute exacerbation of chronic bronchitis then is defined in terms of its clinical presentation.

Specifically, what we would expect to see is increased

cough, increased sputum volume, purulence of the sputum or change in character of the sputum, in addition, dyspnea and fever may be present.

Looking at the etiology of acute exacerbations of chronic bronchitis, again, a fairly large number of these exacerbations are caused by viruses of various types. Specifically, the literature gives us figures of 25 to 50 percent.

Bacterial etiologies, there are, of course, three major causes of AECB. That includes Strep pneumoniae, H. flu, and Moraxella catarrhalis. Other causes that have been described, although by no means are they common, include Mycoplasma pneumoniae, Hemophilus parainfluenzae, Chlamydia pneumoniae, and rarely, Legionella.

I would like to briefly just mention some diagnostic issues that play into some of the problems that come up in terms of considering evaluability criteria for bronchitis. In discussing the acute exacerbation of chronic bronchitis, it is important to realize that Hemophilus influenzae and Strep pneumoniae are present in the sputum in 30 to 50 percent of patients with chronic bronchitis, and this is true whether or not those patients are undergoing an acute episode at the time.

In addition, it has been clearly shown in the literature that there is no specific correlation with the development of AECSB in terms of development of purulence of the sputum.

Again, briefly, referred to already this morning is isolation of other organisms from the sputum of these patients -- viridans Streptococci, Staph aureus, gram-negative enteric bacilli. All of these can be isolated occasionally from the sputum of patients who are undergoing an acute exacerbation of chronic bronchitis, and the question of course is whether these represent simply oropharyngeal contamination or whether they may occasionally be playing a pathogenic role.

Lastly, and probably most importantly, the failure to eradicate putative pathogens including, of course, the major three organisms that I have already mentioned in the fact of clinical improvement is very common.

Having presented those items for consideration I would like to move on to the inclusion criteria that we would propose for the acute exacerbation of chronic bronchitis. Clinical criteria would include, of course, the presence of chronic bronchitis together with an increase in cough and sputum production, a change in the sputum character, which may consist of changes in consistency or

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changes in color, in addition as I have already mentioned, dyspnea or fever may be present although we would not, of course, require those.

Radiographic criteria really just consists a chest x-ray in order to exclude pneumonia. Microbiologic criteria, we would suggest that a Gram stain of sputum should show less than 10 epithelial cells per lower power field with polymorphonuclear cells and microorganisms being present. I would also point out that this is slightly different from what is in your draft document.

In addition, we would suggest that the culture of the sputum or of the respiratory specimen should grow a predominant respiratory tract pathogen and that antimicrobial susceptibility testing be performed on the relevant isolates.

Moving then very briefly to secondary bacterial infection of acute bronchitis, inclusion criteria for this entity are similar with the obvious exception I hope of the fact that we would suggest that this population have no underlying chronic pulmonary disease given, of course, since this disease is typically an illness of otherwise healthy people.

We would suggest then that these clinical criteria include a recent history of respiratory infection including cough, sputum production, and possibly fever.

These are identical to the previous slide that you saw. The chest x-ray should be obtained in order to rule out pneumonia, and we would suggest a Gram stain of sputum showing absence of epithelial cells and presence of polys and microorganisms.

For both of these clinical entities, exclusion criteria I think are fairly straightforward, and I include cystic fibrosis, the presence of active tuberculosis, bronchiectasis, pulmonary malignancy, and also excluded would be patients who are taking systemic steroids in the equivalent of 10 milligrams of prednisone a day or more.

In terms of suggestions regarding study drugs and the dosing regimen, fairly standard I think is that the patient should receive 80 to 120 percent of the prescribed dose with their compliance documented either by diary or urine testing depending on the appropriateness with respect to the drug.

The comparator agent should be chosen with consideration given to known resistance patterns in the patient population to be studied or given geographic area,

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for example, considering beta-lactamase production, and we would suggest it be FDA approved.

I would like to briefly just run through the evaluation visits that would be suggested for the category of bronchitis, the first being the entry or pre-therapy visit which we would require in order to be evaluable.

Recorded would be of course the date of visit, the signs and symptoms of the acute exacerbation episode including the presence of cough, the volume of sputum, and the character at that point in time.

In addition, of course documented should be that the patient does indeed have a history of chronic bronchitis.

Concurrent medications of course should be recorded, as should the results of physical exam and the chest x-ray showing that no pneumonia is present. I have already described what we would like to see in the sputum, and these results, including both the Gram stain and the culture results, should be reported, and of course whether the patient is an inpatient or the outpatient at the time of enrollment.

One category of information that we think that could be very helpful in terms of evaluating improvement of these patients would be information regarding the patient's

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illness before they underwent their acute exacerbation - baseline cough frequency, volume of sputum and its characteristics, whether or not the patient requires baseline supplemental oxygen use, whether or not they have been on antibiotics recently including some patients who receive prophylactic antibiotics and a history of environmental allergies.

The next visit that we would mention is the on-therapy visit which typically occurs at day three to five. It is recommended according to our suggestions, but not required in order to be evaluable, and can in fact take place either by phone or with the patient in the office.

If the patient is not improving at this time, the study drug can be discontinued and the patient classified as a clinical failure. Obtaining a sputum, Gram stain, and a culture at that time would be suggested.

The end-of-therapy visit in this clinical entity is also optional. If it is done, the results of the physical examination in addition to the sputum, Gram stain, and culture should be reported. We would point out also that we don't feel that this is a legitimate substitution for test-of-cure visit.

The test -of-cure visit then we would suggest should occur in the time period of one to two weeks after

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completion of therapy. This of course would be required for evaluability and would encompass recording of the status of presenting signs and symptoms at that time in addition to recording the onset of any new symptoms that occurred since the previous visit.

Critical of course would be the sputum description if the patient is producing sputum at that time, in addition to a Gram stain and culture and susceptibility testing should also be performed if isolates are obtained.

Moving then to our proposed evaluation of clinical outcome. The categorization first that we would describe would be clinical cure, and this would be a patient who meets the evaluability criteria that have been decided on, received no additional antibiotics, and whose acute signs and symptoms have returned to baseline.

Patients who would be categorized as clinical failures would be patients who have persistence or worsening in their signs and symptoms of the acute episode. Of course, patients who required either hospitalization re-hospitalization for acute exacerbation of chronic bronchitis and, of course, patients who receive additional antimicrobials.

Just three sort of pertinent points that I would like to mention in terms of clinical outcome or proposed for

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possible consideration. The first is that we would suggest that clinical outcome is the primary determinant of efficacy for the indication of bronchitis.

Secondly, we would suggest if the patient is classified as a clinical failure prior to the test-of-cure visit, this evaluation should be carried forward into the final visit outcome, and this topic was covered also yesterday.

Lastly, we would hope that the use of the improved classification could be avoided, and patients should have every attempt made to classify them into either the cure or the failure classification.

Moving then to microbiological outcome, self-evident I think is that in order for a patient to be evaluable in the microbiological category, a pathogen must be identified in the sputum which had been obtained at the time of entry.

The definitions then that we would suggest included presumed eradication. This would differ slightly in the two entities that I am discussing, and specifically, an AECB, we would suggest that patients receive this categorization when they have an absence of a repeat sputum specimen in a patient who meets the definition of clinical cure.

In patients with SBIAB, because these patients are assumed to be health individuals at baseline, we would expect that they would have no further sputum production at the test-of-cure visit.

Eradication would refer to patients who had had absence of the pathogen which was grown at entry, and the repeat sputum culture which is obtained at one to two weeks post-therapy. Persistence would define those patients who have continued presence of the entry pathogen in a sputum culture which is obtained again at the one- to two-week test-of-cure visit, and presumed persistence are those patients who are classified as clinical failures, but in whom no repeat culture was obtained.

A few more that I think are fairly straightforward. Patients who are superinfection would have isolation of a new pathogen during therapy in patients who are symptomatic. Patients who become reinfected would have a new pathogen isolated in their post-treatment sputum culture, and in addition, those patients would be folks who have signs and symptoms of acute infection still present.

Patients who are colonized, have isolation of an organism from a patient who has no signs or symptoms of infection.

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For interest, I have picked out a few differences in terms of our new draft guideline document and contrasted it with some of the information that is found in the IDSA Guidelines.

I have already mentioned that the guidelines give us information on both AECB -- excuse me -- here we have information on both AECB and SBIAB. In addition, we have suggested that concomitant steroid therapy not be acceptable, whereas, IDSA suggests that patients may be appropriately stratified for the use of steroids.

Here, we have suggested that no improved classification be used in terms of clinical outcome evaluation.

Again, in comparison with IDSA Guidelines, we have the new classifications for microbiological outcome of presumed persistence and presumed eradication, which refer back to the patient's clinical outcome status. In addition, the category of relapse has been omitted.

Another difference is that clinical evaluation at day three to five after initiation of therapy is suggested in the IDSA Guidelines with subsequently weekly follow-up until completion of study.

Lastly, in terms of comparison with IDSA follow-up dates, in terms of both clinical and microbiologic

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assessment, IDSA Guidelines suggest 48 hours, 7 to 14 days, and 21 to 28 days after completion of therapy. This is, just to reiterate, versus our proposed follow-up on day 3 to 5, at the end of therapy, and 1 to 2 weeks after therapy.

Baseline studies suggested by the IDSA Guidelines including hematologic, hepatic, renal, pulmonary function, and arterial blood gases were actually suggested for this clinical entity to be repeated several times during the study, and we have not included these in our current guidelines.

I have just brought these points with me, if you will, from Points to Consider. The suggestion for bronchitis is that one well-controlled trial in which patients should be both clinically and microbiologically evaluable be performed, and then a second trial in which the clinical effectiveness is the only primary endpoint with a U.S. site preferred.

Having said those, then, the questions that I would submit for discussion include the following. I have tried to outline for you some differences in the clinical presentation and differences in our suggestions for evaluability criteria for these two entities, and I think a question for which discussion might be reasonable include is

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it appropriate to include patients both with AECSB and with SBIAB together in a single study.

In addition, I think some discussion of which organisms would be entertained as suitable for inclusion in these studies, would also be appropriate, and specifically I think we would all agree that these three organisms - Strep pneumo, Hemophilus influenzae, and Moraxella catarrhalis, should be included, but what other organisms should be included, and should we suggest that this be based on evidence from the accumulated literature of their pathogenicity.

I think lastly, in terms of which organisms we are considering, we might also look at the antibiotic-resistant organisms and what sort of evaluability criteria might be considered in terms of drug development for these organisms.

Then, just lastly, I would ask whether the inclusion and exclusion criteria as given previously define a patient population which is appropriate for study in support of the indication of bronchitis.

I will be happy to answer any questions on what I have presented.

DR. CRAIG: Any specific questions on what she has presented so far?

[No response.]

Committee Presentation

DR. CRAIG: This is an area that is exceedingly difficult to get a handle on as to what one is doing with antimicrobials. As was mentioned, the IDSA has only provided guidelines for acute exacerbations of chronic bronchitis, and as you are probably well aware, there are many studies in the literature, some of the placebo-controlled, that question the value of antibiotics, but I think if you do a meta-analysis, look at all the data that is present there, one could come up with an argument that there is some benefit, at least in certain patients, tends to preventing them from going on to respiratory failure of antibiotics in this entity.

So I think it was appropriate for the Infectious Disease Society to write guidelines. However, when it comes to secondary bacterial infection of acute bronchitis, I did another search. I was unable to find any data in the literature that would suggest that there is antimicrobial benefit of treatment. In fact, there are several placebo-controlled trials in this entity that show no difference in the reduction in symptoms and no benefit at with antimicrobial therapy.

In this era of resistance to antibiotics, I think it is exceedingly important, if we are going to give an

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indication, it needs to be an indication in which it is clearly documented that antibiotics are beneficial.

So my overall approach is, as is said there, is to eliminate secondary bacterial infection of acute bronchitis as an indication or if one was going to study it, to do it in terms of a placebo-controlled trial, so that one could try and show that there was clearly a clinical benefit of using antimicrobials if one was going to give that indication.

On the other hand, I do not have that problem, the people I have talked to having that problem with acute exacerbations of chronic bronchitis.

So, again, they were talking about combining this into one indication. What I am essentially saying is do away with one of the indications, and so I think we need to discuss that a little bit more.

The question is on evaluation visits, if you look at what the IDSA did, they wanted you to essentially get a sputum about every week or two out for a month following the therapy. Again, I find it difficult, looking at the literature, to try and find out what was the justification for getting all of those sputums as if they were implying something about the overall efficacy of the drug.

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We know that from a bacteriologic point of view that many of these patients stay colonized, that this is a viral infection and that it then, because organisms are already there, it is not a new organism coming in. Oftentimes an organism that is already present, then, becomes complicating the infection, and when that infection dies down, one may not have completely eliminated it, and then frequently the organism comes back.

So, does look at it at three or four weeks give you a higher chance of having it come back than what you would see at one or two weeks? Yeah, there is a little greater chance, but to me, I don't know what that means overall in the overall evaluation of the antimicrobial, and I think I would agree primarily with the FDA, is that the clinical endpoint is primarily the major one, and I find it very difficult in order to determine the value.

Now, the question of end of therapy. If one is deciding that, well, you know, not everybody is going to benefit from the antibiotic. Some patients do, so it may be difficult of using clinical data. Maybe we can at least get some bacteriologic data out of this in terms of being able to eliminate the organism.

Again, my comments from what we talked about before, fall with this when you start looking at

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elimination. You may find a situation where the organism is reduced, but not eliminated, and then if you are requiring elimination, one gets that confusion as to what really persistent means.

So, again, I am not sure that that is really a requirement, but clearly again, for emergence of resistance, this is one of the reasons that I think sputum cultures are required in order to try and look at that, and the question I had was, is it better to look at emergence of resistance at end of therapy or is it better to look at it at one to two weeks down the line.

Well, in pneumonia, the reason that we said that probably looking at it at the end of therapy was important or was maybe more important is because the longer you go out, the less chance you are going to have for the patient producing sputum.

So, by looking at it at the end of the therapy, you had a greater chance of getting data, having the patient still producing the sputum in order to be able to do that.

In this situation where we have patients that "have chronic bronchitis," have a persistent source of being able to provide sputum. Looking at that at one or two weeks or looking at it at the end of therapy, I was really not able from the literature to be able to say that there would

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be a difference in terms of finding the emergence of resistance if one looked right at the end of therapy or one looked one to two weeks later.

Now, the primary reason the FDA indicates looking at one to two weeks for elimination of pathogen instead of looking at the end of therapy is on the fact that there still may be persistent antibiotic at the site of infection at the end of therapy, and so one needs to have that antibiotic disappear in order to look and see if there is true bacterial persistence.

Well, that is true. It is important from the point of view if you believe that elimination or eradication of the organism was important for overall evaluation in this parameter. If you are putting your primary emphasis on the clinical, and that the bacteriologic is primarily more for diagnosis, and not for specific evaluation, then, getting cultures at a later time, of getting them one to two weeks is probably perfectly fine. You could get them at the end of therapy.

But I have really no strong preference one or the other, and if the FDA feels that they want to be sure the drug is gone, then, looking at it one to two weeks is probably the better time to do that kind of evaluation.

Can I have that last slide.

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The other question that I have specifically about acute exacerbations of chronic bronchitis is should the data be used to support break point determinations. I think here we have a disease in which clinically it is relatively weak that everybody is benefiting from the therapy. I think the studies, as I say, would tend to suggest some.

Bacteriologic elimination evaluation is difficult because these organisms tend to persist, and the fact that they can occasionally be colonized with gram-negative organisms which then "come out to say" that they are effective against Pseudomonas when the MICs are very borderline for that organism, and thereby we get data that starts to conflict or starts to confuse looking at break points.

My own feeling is that this kind of data, I have no trouble with pneumonia being used for a break point determinations, but I really have great difficulty in using the data from acute exacerbations of chronic bronchitis for supporting break point determinations.

So my answer to this would be no, but I would be interested in hearing what the rest of the committee thinks.

Questions and Comments

DR. CRAIG: So I guess the first question comes up about inclusion of secondary bacterial infection in acute

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bronchitis, whether that is something that should be looked at, and if so, is it appropriate to combine it with acute exacerbations of chronic bronchitis in clinical trials.

Dr. Melish.

DR. MELISH: I thought that was a very good question. I think it probably should be looked at in a placebo-controlled way because there is no question that there is a lot of antibiotics prescribed for this sort of thing, but even in the trial design that was mentioned here, I found that it was absent any evidence that there was a biphasic illness.

If you are to have a secondary bacterial infection of an acute bronchitis, I should think that you would probably have to show evidence that you got worse, not just that you had a preexisting illness, but that there was something biphasic about it, and more evidence that there was bacterial infection than just a sputum, such as an elevated white count or C-reactive protein or something like that.

Then, a placebo-controlled trial would be a very important scientific advance to either constrain people from giving antibiotics to patients who have negative chest x-rays and lingering cough or illness, or to demonstrate that

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it can do some good and return them to work faster or do something favorable.

So I thought that was a very good question that you posed, and a placebo-controlled trial, which would then not be able to be combined with an acute exacerbation of chronic bronchitis, then, there are two different populations. You are talking about elderly people with chronic bronchitis or people with impaired lung function. Otherwise, you are talking about people who are probably just coughing too long, want to go back to work, don't feel well, but who are probably of a completely different age group and in general, so I would favor the placebo-controlled trial.

A second question I have is I have a lot of trouble with the category of presumed persistence. If you don't demonstrate persistence, how do you know you have persistence? You may have continued illness, but the illness itself may not have been due to the organism that you were monitoring, so I think you should do away with the category of presumed persistence. You either demonstrate persistence or you have no idea whether you have persistence or not.

DR. CRAIG: But the situation comes with the patient's failing clinically.

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DR. MELISH: He is failing clinically. He is a clinical failure.

DR. CRAIG: And you have gotten your initial culture. So you would just do a clinical evaluation and not do a bacteriologic.

DR. MELISH: That's right, clinical evaluation. You can't do a bacteriologic evaluation if you don't have the second one, and in this case, we don't even know that the organism that you isolated the first time around was really an important organism or just a fellow traveler.

DR. CRAIG: But I mean that to me is the problem, is that then you give all the advantage to the presumed eradication, because you make everything now if you are giving presumed eradication, you are giving everything of benefit to that, and I think if the patient has failed, even though we don't know, the simplest thing to sort of keep it at an even keel in terms of balance would be to call it presumed persistence.

DR. MELISH: But he may have failed because he had a viral illness to begin with, and then he stripped off his cilia and --

DR. CRAIG: I agree with you. I agree with you that that may be the case. It is just like the patient may not have completely eliminated the organism, but we assume

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when we call it presumed, because they can't produce a specimen.

How about other comments on the first topic? Again, what does the committee sort of feel on secondary bacterial infection of acute bronchitis? As I said, I know of at least three, possibly four, placebo-controlled studies that have not shown any benefit. Yes.

DR. MOLEDINA: This diagnosis of secondary bacterial infection in patients who have bronchitis, FDA was battling with this diagnosis for a long time because we had applications for actually chronic bronchitis patients, and when you look at the baseline of those patients, they did not fit in the criteria for chronic bronchitis, so we did not know what to do with those patients because they did not have like cough for consecutive three months or they were not sick for two years. They really did not fit in that picture.

So we tried to sort of stratify those patients in a different category and realized that they were younger patients. They really did not have diagnosis of chronic bronchitis. So we created a diagnosis of secondary bacterial infection in these patients, and I did that for one of my applications for dirithromycin where this study was done actually in Europe, not in U.S., but the patient

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population was totally different from chronic bronchitis patients, and because they did not fit in that category, we gave them an indication, and when you read the label for dirithromycin, you will see that such an indication exists.

So I don't feel comfortable scrapping it out like you said, that you don't want -- I mean I am just giving you my opinion as to --

DR. CRAIG: I have no trouble with keep something if the antibiotic is doing something that is beneficial to the patient. If the only thing the antibiotic is doing is setting up the patient for side effects and the emergence of resistant organisms, we haven't done society or that patient any benefit, and if one looks at the data that is in the literature, specifically at this entity as best as you can describe it from the literature, you can't find data that supports it.

You can for acute exacerbations in chronic bronchitis, but not for secondary bacterial infection. So I think we might have been --

DR. MOLEDINA: I know, I understand you, but everything that is in the literature that you are trying to tell me about maybe some things are not written up in literature, and some of the things, the data that we see at FDA, some of those data are never written up by anybody, and

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what I am trying to say is when the data comes in, and a sponsor is asking for an indication for acute exacerbation of chronic bronchitis, and when you look at the baseline symptom of those patients, they don't fit into the criteria of chronic bronchitis, then, you have to find a way of trying to make those patients unevaluable to fit them into a category. They are younger patients, they are not as sick, and they have a bacterial infection because you have cultured bacteria from them.

You know what you are dealing with, and then they get cured. That is the category that I am trying to say that you just have to put those patients in. That all depends upon what sort of patients were entered into the study and what sort of data you get.

What you are trying to say is if you don' have such a category, that means we should not enroll those patients at all, because they don't benefit from antibiotics, and maybe placebo-controlled studies should be done, and I agree with that, too. Maybe it needs to be done.

DR. CRAIG: I would agree with you that the standard of practice, if you look at the standard of practice throughout the United States, is that many of these patients that "have secondary infection of acute

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bronchitis," do receive antibiotics by their physician, so that it is not difficult to be able to get these patients entered in clinical trials, but the point I am trying to bring is that the IDSA did not feel that this was an entity that antibiotics had any documented benefit, and so did not want to encourage it as an indication for approval by the drug.

I think especially in this era of increasing resistance, we really have to look very closely to make sure that when we are giving the indications, they are for indications in which there is clear benefit for the patient.

DR. SORETH: Janice Soreth, FDA.

I think one practical point that we might take from this is that we have any number of drugs either under development as NMEs or seeking line extensions that have protocols ongoing for secondary bacterial infections of acute bronchitis, and I think in all of them, they have active controls.

So what we might consider taking away from this is discussions with the various sponsors to ask them if they would consider changing the trial to a placebo-controlled trial, so we might generate data to answer this question more conclusively.

DR. CRAIG: Dr. Schwartz.

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DR. SCHWARTZ: Dr. Craig, you had showed a slide some time ago with a seesaw, and the seesaw had two sides. One side was the Infectious Disease Society of America, and the other side was the American Thoracic Society.

DR. CRAIG: Yes.

DR. SCHWARTZ: Well, if you took away the American Thoracic Society and put in its place emergency physicians, primary care physicians, people who are actually seeing these patients in various settings, I think you could show the same slide.

Now, the fact that the IDSA and infectious disease people don't believe this is a treatable entity, I don't disagree necessarily with the philosophy, but the truth is that they are being treated with tons and tons and tons of antibiotics, so we have to do trials, and we have to do them, not so much with the highest level of antibiotics, but the comparator should be something like amoxicillin or something where at least if you are going to treat, treat it with the lowest level of antibiotic rather than third or fourth or fifth or sixth generation newcomer on the block.

I think the trials are necessary because what is being done is not what is being proved.

DR. CRAIG: Brad.

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DR. LEISSA: Brad Leissa, Division of Anti-Infective Drug Products.

I guess the one thing that intrigues me, I find the placebo-controlled arm very interesting. I guess the question I would have, though, presumably, the patients that have the most severe disease, that are like being toxic, high fever, would be the ones that will be most likely to benefit from therapy.

Is it ethical to put somebody on placebo who is most likely to benefit, and therefore aren't your studies only looking at mild to moderate disease if using placebo-controlled?

DR. CRAIG: If you would go back and look at those studies, fever was in a percentage of patients, but it wasn't something where somebody was looking specifically at high fever, and I would bet that in most of the trials that are entered, again, they are not necessarily looking at patients that have temps of 103, 104, which you would tend to have those criteria.

DR. LEISSA: I am not isolating those to temperature, but at some point, somebody who is toxic, and that is obviously a myriad of signs and symptoms, but is there a point where it is not ethical to put somebody on a

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placebo-controlled trial when you are trying to then extrapolate that over to an indication?

DR. CRAIG: It is a good question. There may be obviously a situation where you are talking about somebody that is looking relatively toxic that may be difficult, at least initially. I think what you do is you look first at mild to moderate disease and if you don't see any benefit there, then, one could start to look at more severe illness to see if that is also the case there, as well.

I mean I think you would like to have data to enable you to move up instead of all of a sudden, right from the beginning, going ahead and saying we should start a placebo trial in everybody.

Dr. Feigal.

DR. FEIGAL: One of the difficulties as you move into severe diseases, I think the patients would probably begin to meet your definition of pneumonia.

DR. CRAIG: Yes, right.

DR. FEIGAL: So that is another difficulty.

DR. CRAIG: Very true.

Dr. Reller.

DR. RELLER: I think it was a giant step forward to separate lower respiratory tract infections into acute exacerbations of chronic bronchitis, community-acquired,

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hospital-acquired, and now ventilator-associated pneumonia, and a major step forward would I think be to delineate these two entities and treat them entirely differently in every way as follows.

The patient populations are fundamentally different. By definition, the entity, as it is commonly recognized and treated, whether appropriately or not, one starts out as Dr. Melish emphasized, with someone who is well before they get sick.

They have a negative chest radiograph. They do not have pneumonia. As you have emphasized, there are no compelling data that antimicrobials are required for this, but yet they are used extensively, so I would translate this into that in the public interest and for truth in promotion of antimicrobials and their use in the package insert, it is absolutely necessary to extract SBIAB from studies that are of acute exacerbations of chronic bronchitis, and therefore it to me then follow that we not only have an opportunity in those with negative chest radiographs and previous wellness, and no fundamental underlying lung disease, that we have an obligation to do placebo-controlled trials, and in addition have the obligation to document the associated microbiological findings at the beginning, during, and after therapy for those who still produce sputum.

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So some of the issues about persistence and documentation, Dr. Melish, you have emphasized, would go by the wayside if that is there. I have considerably assessments when we get to this discussion of acute exacerbations of chronic bronchitis.

So I think that the should be separated, that we need microbiological data, because we don't know if antimicrobials are of any use, and moreover, may be of considerable detriment to the public's health given the tonnage that is used for an indication that may not be appropriate at all, and I think we would only perpetuate the problem by allowing trials that had a comparative agent that may be contributing to the problem including resistant *Streptococcus pneumoniae*, a real pathogen in serious disease in children and adults.

Ms. Cohen.

MS. COHEN: I served on another board. I am kind of a wanderer. They were talking about a medication, and the pharmaceutical company said, well, only 12 people died. I don't want to be one of the 12.

I think it would be unconscionable to have a program including the placebo unless the individual consumer understood exactly what is going to happen. I cannot see in a case like this, that you have already defined an illness,

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and then to have a placebo, I can't understand the rationale of it.

I am a consumer, everybody is a consumer, and I think it is a little cavalier to want to do that, and I can't see how you could use a placebo in someone that has a definitive illness.

DR. CRAIG: But it is a viral illness. It is a definitive viral illness, it is not a definitive bacterial illness.

MS. COHEN: I understand that.

DR. CRAIG: It is a viral illness and antibiotics do not affect a virus.

MS. COHEN: I understand that, but just the same, I think consumers should be part of this, they should understand in plain language what is going on, because they are the recipient of all of us sitting here.

My husband was a scientist, so it isn't as though I am unfamiliar with it. I just think it is just cavalier, and we have got to think of the end product all the time, and that is the consumer.

DR. RELLER: Bill.

DR. CRAIG: Yes.

DR. RELLER: To address Ms. Cohen's concerns, I mean they are right on target. I think that what we are

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trying to emphasize is that the bulk of the scientific community, I believe, feel that there may well be both for the individual, as well as for the community, more harm being done by prescribing antimicrobials for this precise entity.

We are not talking about persons with marginal pulmonary function damaged by years of chronic bronchitis and emphysema who may be on the brink of breathing, continuing breathing with pushing over the edge with a bacterial infection where we don't think we could have a placebo-controlled trial for acute exacerbations of chronic bronchitis.

These are people who are well, who are bringing up purulent sputum, who in the individual patient in terms of reactions to the drug, with selection of resistant organisms that may then in their otitis give them a resistant organism or, you know, colonization with a resistant pneumococcus that then gives them meningitis. I mean for the individual as well as society, that there may well be more harm being done by giving them as is currently practiced than denying them with full disclosure before enrolling of the patients.

DR. SCHWARTZ: Dr. Craig, do you honestly think that you are supposing now that that holds sway, that

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philosophy, no more trials for bacterial or presumed bacterial superinfection?

DR. CRAIG: No, I am not saying. I gave an option there, and I think the option is what Barth says, is that we should look at this from a scientific point of view to try and again to see if there is a demonstrated beneficial effect and to also look at it enough, so that we can say look, there is no beneficial effect, there is actually a detrimental effect, and that kind of information then --

DR. SCHWARTZ: Well, that is presumptive also. I mean let's look at it neutral. I don't care what comes out, but let's find out what comes out, and secondly, perhaps we ought to look at it in economical terms and return to work and feeling better rather than just the traditional ways because this is how people today are beginning to think about it.

DR. CRAIG: The traditional ways, I mean if you look in the studies where they have looked at symptoms and looked at the disappearance of symptoms, not just looking at time A and looking at time B, they are superimposed when one look at placebo, that what one is seeing is the natural response of the inflammation from the viral infection, and that giving the antibiotic doesn't speed that up at all.

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DR. SCHWARTZ: Then, why don't people listen to that on the outside?

DR. CRAIG: There are many other reasons for why people give antibiotics.

DR. SCHWARTZ: You might be 100 percent right, but yet that is not what is being done.

DR. CRAIG: But I mean the thought I think is that what everyone says is well, I am not doing any harm, they might have something a little bit more severe, so I will go ahead and use the antibiotic. That is a very common scenario to use.

What studying it well would provide was the potential of telling them look, you do have the potential of doing harm if that can be documented, and then one has a much stronger argument to come to people, not only with the fact that it doesn't benefit, but you can actually then say that it potentially does harm.

People respond to that better than, well, it doesn't benefit. Their thought is, well, maybe still it might benefit a little bit, and I think that is what tends to foster that use.

Yes, Dr. Banks-Bright.

DR. BANKS-BRIGHT: I think Dr. Reller and I had the same point at the same time. The comment that I was

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going to make in response to Dr. Schwartz, too, is that a lot of this is driven by the consumers themselves. They expect antibiotics, they expect drugs, and so it's not a lot of time always because the physician is giving antibiotics when, in fact, they know probably in their heart they are not really treating the patient, they are treating what the patient expects.

I think we were discussing the issue of more education and that the consumers are certainly we think capable of understanding this were they to be presented with all this information that we are talking about here today, but it is more consumer driven I think than it is physicians. Patients expect an antibiotic when they walk out of the office.

DR. SCHWARTZ: It is a two-step process. Those that get better whether because they get better because of time and the virus wears itself out. That is not a problem. The problem is those that don't get better, because then you come to a decision point, are they in fact not getting better because the professors were right and this is viral and therefore non-responsive, or are they not getting better because they need yet a more powerful or more broad a spectrum antibiotic, which is likely what is going to really happen in the real world, and that could be another point of

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a study, what happens in the failures of acute bronchitis in otherwise healthy people, does another antibiotic actually help them. Lots of questions.

DR. CRAIG: Yes. Dr. Feigal.

DR. FEIGAL: One of the things I think that is difficult with many self-limiting diseases is how small the benefits are even from active therapies.

If you look acyclovir for zoster or herpes infections, the difference even when the drug is given properly is a matter of hours of the effect of the drug. Although it has been a while since I have looked at the studies, as I recall, there is relatively little impact on symptoms in strep pharyngitis from treatment, that there is other benefits from treating strep pharyngitis, but I think the patient feels --

DR. CRAIG: Although more recent studies I think have clearly documented that you can shorten the illness with antibiotics therapy.

DR. FEIGAL: But often in self-limiting diseases as opposed to more chronic conditions, it is a matter of hours to days, and I think that makes the design and the patient selection, all of those factors, often require very large trials to show a small benefit.

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One of things that there hasn't been as much of a tradition of with antibiotics is actually quantifying to the patient exactly what the benefit of the treatment is or that component of the treatment.

With some of the infections that are severe infections, I think it is self-evident, it speaks for itself, but I think that is a more daunting task, and that gets to some of the issues around quality of life.

Many of those things are actually being asked for by the decisionmakers who purchase drugs of all kinds is to quantify what the benefits are, and I think it is something else that, as we look at these evaluability criteria we may think of is where do we need some quantification of benefit beyond time to resolution of symptoms and eradication and change in culture results.

DR. CRAIG: Dr. Melish.

DR. MELISH: We had a meeting about antibiotic resistance within six months in this group, and we had a talk by a Finnish pediatrician who talked about the actual incredible change in the consumers' minds when antibiotic resistance became overwhelmingly a fact of life in Finland, and the practice changed within a short period of time, from when parents were asking for antibiotics every time their child had a fever or were ill, to the point where they said

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I hope you are not going to give my child antibiotics, Doctor, because I just brought him in to find out if he was seriously ill or not.

I think these kinds of education are possible when we have data, and I am really excited about the possibility that we could do a placebo-controlled trial and make a scientific advance. If people who have bronchitis without pneumonia, who are otherwise well, are going to take 14 days before they can get better whether they take antibiotics or not, I think it is important for them to know that.

DR. CRAIG: Dr. Reller.

DR. RELLER: I have confidence. I mean there have been tremendous changes in public attitudes over time, I mean regarding the environment, across all sides of the political spectrum of how important this is.

I think the time has come to be more forthright in a collegial way with the patients, that this is a major issue, and if we are going to preserve the utility of these drugs, they cannot be used because of all of the pressures of the past including it is easier to get the patient out if you give them something, satisfying patient demands, and I think the public are capable of understanding the implications of unnecessary antimicrobial use.

At a minimum it seems to me that there should be no reference to the utility of an agent for acute exacerbations or secondary bacterial infections of acute bronchitis in any descriptive material regarding an antimicrobial agent unless there is evidence presented for that claim from a placebo-controlled trial of same agent. You can't slip in that, you know, acute exacerbations, you know, and by inference acute secondary bacterial bronchitis. You understand what I am saying.

DR. CRAIG: Yes. Ms. Cohen.

MS. COHEN: Since most HMOs probably require physicians to see four patients an hour, and there are 40 million Americans without any health insurance, who use emergency rooms, who is going to share this information with them? Because we haven't done enough education. I am just repeating what needs to be done, and I expect, and I think it behooves a physician to say you have a viral infection, not a bacterial infection, therefore, one, two, three.

But what is going to happen now with the kind of medicine that is going to be delivered in this country? And the FDA has been working very hard to encourage pharmaceutical companies to use plain language. That is part of the problem, too. The mystique should be taken out of medicine.

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DR. CRAIG: Sure, but there are attempts already. The CDC has been working with the Infectious Disease Foundation on a big educational campaign for otitis media. So, I mean I think there are attempts that are starting to do this, but you are right, it is going to take time and a lot of education in order to get that changed around.

Yes, Dr. Albrecht.

DR. ALBRECHT: I wanted to ask since we have heard the suggestion made that perhaps these SBIAB studies could be designed as placebo-controlled studies, and since as previous folks have mentioned, this category kind of came about because these patients didn't fit into chronic bronchitis, but we nevertheless felt they were patients that had an infection and should be in active controlled studies, and with the caveat raised by Dr. Leissa, what do you do if you have got somebody who is really sick, that doesn't have the criteria for AECB, and you think it is SBIAB, but you are feeling uncomfortable not giving them an active control, my question is, could I encourage the committee to give us some ideas on what inclusion criteria would be useful for us to consider if we are going to be discussing placebo-controlled studies as has been proposed.

DR. CRAIG: I would think that what you would be looking at would be patients that would tend to be young, no

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previous history, that were essentially well, that developed an illness that probably had some viral components, that then all of a sudden developed purulent sputum, and with that purulent sputum, they could have -- I mean then you start looking at it.

If you look at the ones that have high fever and high white count, things like that, you would probably exclude those people, so that you don't, at least in the trial, have patients that are toxic or might be early pneumonia, but try and look at those patients that had low grade fever as one of the possibilities, slight elevation, but not to the point where they were toxic would be the inclusion criteria.

And I think you would like to have people that have white count elevations and/or fever, so that you would have at least a representation of something besides just the fact that you were culturing the organisms out of sputum that suggested that there might be a bacterial infection.

DR. SCHWARTZ: And the telephone call within the first 36 to 48 hours, project assistant making a call to each and every patient.

Yes.

DR. HENRY: Just for the record, I would like to say that I agree that there needs to be a lot more

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information to help better define SBIAB, and actually the data that has come into the FDA in these other studies, that doesn't fit into the category of acute exacerbation of chronic bronchitis, what information has already been compiled, that might help better define some of the inclusion and exclusion criteria. There must already be some data if these patients fall out of the other category.

DR. ALBRECHT: We would have to go back and look at what the data are. I think that the reason I brought up the question is because in those studies we hadn't been concerned about patient safety since the chance was randomization to one of two active arms.

I think the reason I raised this is because of the concern of the patient who may actually be sort of on that borderline of is this just an SBIAB, are we bordering on something more toxic, are we facing an early pneumonia that, you know, in three days the patient will have an infiltrate or something.

So I am raising the question very specifically, talking about patients previously where we have enrolled them in active control studies, and therefore we are certain that regardless of what criteria they met or didn't, they had a chance of being on an active regimen and now sort of reformulating that scenario when we are talking about

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possibly enrolling them in a placebo-controlled study, and how to be comfortable that we are not overlooking a bacterial infection that needs treatment from the first day.

DR. SCHWARTZ: I am doing a similar study with nasal purulent secretions that had to have been at least three days, and we are close to 50. It has taken over two years because they have to have very rigid criteria and while cell counts of their nasal pus and quantitative cultures.

Only a couple of times -- and we have a project nurse making such a phone call -- only a couple of times have we had to -- in fact, I think it was only once -- that we had to switch a person within the first 36 to 48 hours. So it is not something that is likely to gobble up a person who otherwise is immunocompetent and young, it is unlikely, and by having a visit in day three to five and a phone call in the first 36 to 48 hours, I think you can cover your bases.

DR. CRAIG: I think we need to get on to acute exacerbations, and Barth was going to give us his version on that entity.

DR. RELLER: Starting out pathophysiologically, by definition, I think all the studies that have been done, that these people, one, they have sputum, and secondly, they

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do not have a sterile tracheobronchial tree. They have the same organisms below the cricothyroid membrane as they have above it, and consequently, if they are producing sputum at anytime along the line, one would expect with the organisms that have been associated, bacterial organisms that have been associated with it, I fail to see how one is going to legitimately, objectively separate out pre-, during and post-cultures to make any assessment as to efficacy of therapy, eradication, et cetera, and my own belief is that persons with acute exacerbation of chronic bronchitis, by definition, do not have pulmonary infiltrates, do not have pneumonia, and I think at most one would do a Gram stain to show that they have got purulence, white cells, and bacterial organisms present, but I don't think cultures are necessary at all, pre-, during, or after in the management of patient with acute exacerbations of chronic bronchitis.

DR. CRAIG: How about for emergence of resistance?

DR. RELLER: What emergence of resistance is one looking for? For the individual patient, are there data whether they haemophilus influenzae that is beta-lactamase producer not when they are treated with doxycycline, amoxicillin, or sulfamethoxazole/trimethoprim make any difference?

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DR. CRAIG: Quinolone pneumococci, where you could have clearly resistance because of mutation.

DR. RELLER: Precisely. So that if one want to assess the impact of quinolones on the emergence of resistance or any other antimicrobial in this patient population, and that is why you getting a culture at the beginning and at the end, and you are going to use that information, then, I would delineate it as the reason in the trial that you are getting the sputum, but it has nothing to do with the diagnosis or the assessment of response to therapy. That is the point I want to make, because in ordinary practice, unless there is a clinical reason why one would want to know that the patient's normal respiratory flora, expected respiratory flora has an isolate of one agent or one organism or another that has become resistant to antimicrobial X, then, in usual practice, there is no benefit to getting these cultures.

In the document as it exists now, under acute exacerbations of chronic bronchitis, it says should be submitted for Gram stain culture and susceptibility or in the case of Mycoplasma and Legionella for nucleic acid probe tests, I am sure that that is the way to best diagnose those entities currently, but moreover, I didn't think either of

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those was documented association as causing acute exacerbations of chronic bronchitis.

I think the guidelines need being cleaned up to be specific about what the known pathophysiology and the known likely response to antimicrobial agents is in this now more defined entity that is excluding the secondary bacterial infections of acute bronchitis and getting a more homogeneous group of patients who start out with underlying pulmonary disease, who have persistent production of sputum, and who do not have a sterile tracheobronchial tree below the cricothyroid membrane, and I think the knowledge of those things, you know, alters quite dramatically the microbiological approach and what role it does not play in the assessment of response to therapy compared with the recognized useful agents.

DR. CRAIG: I guess I wasn't reading where they talked about Mycoplasma here with that. You are talking about the IDSA Guidelines?

DR. RELLER: Yes.

DR. CRAIG: I think the IDSA Guidelines from what I remember, in terms of this etiology, said that more information was needed to really understand the potential role of Chlamydia or Mycoplasma infection in these patients,

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but I think, looking at the FDA guidelines, they don't talk about that. They talk about just the bacterial causes.

DR. RELLER: I think that is good, but the guidelines here say "should," and it implies that for clinical trials, that looking for these organisms should be done at the outset, et cetera, and the follow-up, and I am not sure. I think that clinical assessment of a homogeneous group of patients at entry should be the principal, if not the only, criteria, I mean with several components, the clinical assessment, assessment of efficacy of these agents.

DR. CRAIG: So at least I am hearing at least from some is that the only reason for primarily using those to evaluate bacteriologic response is not a very valid assumption.

DR. RELLER: Well, I don't think it makes pathophysiologic sense and I think it is better to delineate why you are doing something than simply -- the easy way out is, you know, you get the laboratory, you send it for culture and susceptibility at the beginning, sometime during, and at the end, and I think that is an easy way out that is not consonant with what we know about the pathophysiology and the pre-existing condition, the pace of the illness, and the useful information, and is not a necessary part or not a logical part of good practice, and

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if we want them, we ought to delineate why we want them and why that is a rational thing to do.

DR. CRAIG: Yes.

DR. MOLEDINA: Dr. Reller, my next question to you would be in our division, we write the indication section of our label as acute exacerbation of chronic bronchitis caused by susceptible organisms, and we list the organisms.

What you are telling us, that now we have to write the labels in a different way because if you are not going to do any cultures for susceptibility or only looking for resistance, and not doing follow-up cultures, and we don't know what organisms we are dealing with, then, we will have to give like a blanket indication without listing any organisms, so that is a big jump for our division because the way that we practice by writing labels, unless I am missing the point and I don't understand what you are saying, if you can maybe clarify that, because --

DR. CRAIG: Let me try and interpret it. It is always fun to try to interpret what Barth has said.

I think what Barth has said is that it may be exacerbations of chronic bronchitis associated with these organisms, but I don't think he is trying to get away from saying that it is due to these organisms, and that since they are already there, they are probably going to increase

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in number and that to essentially say that everything is due to the organism is difficult to evaluate.

Now, I will let him tell you exactly what he said.

DR. RELLER: Well, the point is that the patient's lower respiratory tract reflects what is in their mouth. Now, if they have got a dry mouth, they are not eating, not brushing their teeth, et cetera, I mean they could have gram-negative rods, they could have Staph epi.

What I am very concerned about is that in a person with acute exacerbation of chronic bronchitis, who gets one of the recognized agents or would get a new drug that would be compared to one of those recognized agents, no placebo trial involved here, that one would have purulent sputum. These patients virtually always have mixed organisms on culture, and which ones do you want to look at?

I mean if they happen to be colonized with E. coli, I have seen patients with acute exacerbation of chronic bronchitis, and I think some of them have come into the agency, acute exacerbations of chronic bronchitis owing to Staph epidermidis or owing to E. coli or owing to whatever, and I just think that is rubbish.

So it seems to me that one might do like in sinusitis, where you have got some target organisms that are known to be associated with infection like the hemophilus

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and the pneumococcus and moraxella that are commonly present in these patients, and I think most people think that the real acute exacerbation that has a bacterial component that responds to therapy is actually one of these three organisms, and that it is not the E. coli or the Staph epi. or whatever that is thrown in there, and that if that is what we really want to do is see what is the effect of this massive use of antimicrobials, appropriately to some degree, for acute exacerbations of chronic bronchitis and their target organisms, that because of other implications, we are looking at the influence of therapy on resistance, that we should select out those organisms that we want to see at the beginning and after therapy to see what the effect of resistance is if that is what our objective is.

But where I think we are making a mistake is to try to put a response to treatment in something that has got organisms in the beginning, it has got organisms in the end, and it has got organisms at the end of therapy, that may have nothing to do with the clinical response to the antimicrobial given.

Is that clear enough?

DR. MOLEDINA: Yes, but that is what we do. I mean when the application comes to FDA and a certain indication is being sought, the sponsor puts like a list of

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20 organisms, and we don't give them all those organisms, because we know they are contaminants, we know that they come from the mouth, and whatever causes the illness, and we are aware by whatever you are saying, which is atypical organism causing the disease, we only give indication for those organisms.

So, you know, that kind of strategy is already being used by FDA.

DR. RELLER: Well, I think it would be a matter of delineating what it is one wants to get out of the culture at the beginning and at the end, and the purpose for getting that, and we do this with -- I mean one of the exclusions for this is patients with cystic fibrosis who, in fact, have acute exacerbations of chronic bronchitis when they have intervention of escalation or change of antimicrobial therapy, and there clearly is a precedent in the guidelines for the microbiological management of those patients, of looking for certain target organisms as opposed to looking for anything that is in their sputum, and we might get more useful information having to do with the emergence of resistance, the implications of emergence of resistance, to look for targeted organisms rather than being less precise.

DR. CRAIG: Michael.

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DR. SCHWARTZ: Could I just see if I understand your proposal. I take your point very well that in the practice, the culture really doesn't have any particular role the way that it is used in these studies, but I think the philosophy has been, and I think part of it, too, has been with the realization that not all of the agents that are being tested are necessarily strong against all three of the usual culprits, is to at least make sure that we have seen patients who have those culprits and to see what the impact of a short course of antibiotics is on that, not that the clinician is going to use responsive sputum to assess the benefit of treatment in that setting, but if you had a product, for example, that didn't have good H. flu coverage or didn't have good Strep pneumo coverage, you would have an opportunity to at least see that in that setting with those patients.

So I guess I am still not understanding -- and that isn't always expressed just in terms of resistance. There may not be new resistance that is developing -- so I guess what I am trying to understand is are you suggesting that to get an indication in this area that patients should primarily not -- well, I guess I don't understand --

DR. CRAIG: Clinical response.

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DR. SCHWARTZ: Just clinical and that we no longer require that patients be identified who have H. flu.

DR. CRAIG: No. I think he is willing to go along with that to make sure that they probably fit the definition better and stand a good chance of having the organisms that are associated with there, but the primary reason for getting subsequent cultures is to look for the emergence of resistance.

DR. SCHWARTZ: If you have two highly educated people in this room --

DR. CRAIG: You think we don't, huh?

[Laughter.]

DR. SCHWARTZ: -- noted for their expertise, and they are having trouble understanding the concept, God help the master physicians on the outside. I mean think about what the implications of what just happened is really saying. You may be 1,000 percent right, but you are going to have a hard time selling it.

DR. CRAIG: But that is what physicians do. I mean most physicians oftentimes don't even bother to get a culture, they just go ahead and start the patients on the antibiotics.

DR. SCHWARTZ: Based on the studies -- I don't say the culture is going to tell them, I know the problems with

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the cultures, but why don't you cull out those cultures where quantitatively you have not just is H. flu present in 10 colonies, but the overwhelming third quadrant, fourth quadrant, why more than the primary streak with a lot of garbage is one of the big three.

Let's say that of the people that you culture that were able to produce sputum, 50 percent have third-quadrant cultures -- and I am just picking a number out of the air, it could be 20 percent, I don't care what it is -- are there any differences between those that have Big 3 and relatively pure, large amounts on third and fourth quadrant versus those that have a lot of garbage including one of the Big 3 in the primary streak.

DR. CRAIG: You mean response in what?

DR. SCHWARTZ: Everything, response to antibiotic, is there a difference between placebo, are they feeling better any faster with the antibiotic even though the test-of-cure, they are both the same.

I am starting from ground zero, but I think it would be to me important to know.

DR. CRAIG: If you actually looked at a lot of the studies, and Chodash [ph] is probably the one that has been involved in a lot of these things, you can find even -- I mean it is crazy results when you look at some of the

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quantitative stuff, but again, a lot of his stuff is relatively small numbers, he doesn't get up to the really large numbers of cases that you would require to tease out some of these factors.

DR. SCHWARTZ: The presence of the Big 3 in such a thing as sputum, which has to go through the mouth, or whatever, you could find it in many, many people especially if I do selective --

DR. CRAIG: You have no problem finding these organisms in the patient.

DR. SCHWARTZ: Large numbers that I think to me, if anybody would make a difference, those people might, and I would like to look at them, at least analyze them differently to see are those the people more likely to respond to the true drug versus placebo compared to the gimmish where you don't get such a heavy, predominant growth of potential pathogens.

DR. CRAIG: I have know of no stu dy that specifically has been able to separate that out.

Yes.

DR. ALEXANDER: John Alexander from the FDA.

I just wanted to make the comment about the sputum cultures. In patients with cystic fibrosis, they are actually looking at quantitative sputum cultures where you

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have a certain amount of sputum that is obtained by gram, that is measured, and then that way they can do quantitative cultures.

In terms of normal sputum cultures that are done in most laboratories on the outside, there really isn't a difference between an organism that is found on the primary streak as opposed to an organism that is there in three or four plus, it is just a matter of how much sputum was in the sample that was streaked out.

DR. SCHWARTZ: When you do quantitative, it means you -- it is an art, you have to balance a globule of sputum on a quantitative loop by 0.01, use a larger one, it takes a lot of skill to do that, and then you streak that out appropriately, and it is possible to do with practice.

DR. CRAIG: Yes.

MR. LEROY: Bruno Leroy, HMR. Coming back to the problem of the primary population to analyze, can we conclude now that the primary population should be the clinically evaluable population in acute exacerbation of chronic bronchitis?

DR. CRAIG: I think that is what the FDA --

MR. LEROY: The primary population, and not the clinically plus microbiologically evaluable.

DR. ALBRECHT: Let me preface that, that we were hoping to focus on evaluability criteria during this meeting, but I guess we can't separate that from approval. The tradition has been that the statistical power has to be in the clinical population.

MR. LEROY: Yes, but in the Points to Consider, it is written clinically plus microbiologically evaluable population, and this is very important, because it doubles the number of subjects to be recruited in the study.

DR. ALBRECHT: I will wait for my colleagues to jump in if I say anything that is false, but we have approved indications of acute exacerbation of chronic bronchitis on statistically powered clinical-only studies with information from the clinical micro studies to allow us to know which organisms have been studied, but not subjecting the individual organisms to statistical tests.

DR. CRAIG: So you are going to have the conclusion remarks, Brad?

DR. LEISSA: Yes, I will wrap it up.

I totally agree that this should be a clinically driven indication. I guess the thing that concerns me a little bit is that our experience is that if we look at the micro subset for here, the main three organisms, we have the time to learn very important information where the efficacy

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is great, let's say for moraxella and hemophilus, but it is not as good for Strep pneumo, and we have tried to communicate that in the label either by not including the organism or making a note of it or putting it in the clinical study section.

Now, someone could say how effectively is that being communicated out to treating physicians. That is an issue unto its own, but we have learned very important things where it looks equal, but it really isn't if you look at the organisms.

DR. CRAIG: Are these primarily, let's say, for drugs that would be borderline in their concentrations for pneumococci?

DR. LEISSA: No, not necessarily.

DR. CRAIG: Or ones that you would expect would be perfectly fine?

DR. LEISSA: Yes, there are some where you would have expected, but obviously more likely where there are in-vitro susceptibility concerns already upfront.

DR. CRAIG: But does it affect the clinical response?

DR. LEISSA: Yes, in this situation where it is clinically driven, where you have -- I mean clinically driven in that you have taken a patient you believe has the

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condition, has a positive culture that you believe is truly a pathogen, and then you follow them clinically, and then all of that in most cases is going to be presumptively determined.

DR. CRAIG: But I mean I am saying does looking 10 days later to see if the organism is gone, correlate with the clinical response, or is it just the fact that you have picked up pneumococcus at the beginning tends to identify a group that tends to respond less frequently and that subsequent cultures are of no discerning value in identifying who is going to respond well for those who do not respond well.

DR. LEISSA: That is a good question, and I would say that what I am looking at from would be from the perspective of really almost ignoring the follow-up culture.

DR. CRAIG: Yes.

DR. LEISSA: Looking at it clinically.

DR. CRAIG: So I think that is what we have been trying to say, that at least for us the follow-up culture is primarily from a question of emergence of resistance, that getting the culture can be important for identifying those organisms that are present.

It is interesting that you find that it also helps to identify those that may respond a little bit less, but

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again not following or requiring cultures subsequently except for emergence of resistance would be I think what we would tend to include.

DR. LEISSA: Yes, and I am just saying that I don't think we want to ignore the imputed micro response.

DR. CRAIG: Okay.

DR. RELLER: May I ask a question of Brad?

DR. CRAIG: Yes.

DR. RELLER: Brad, I understand that some agents in these studies have been less effective at eradicating one or the other of the prime three co-participants. Have those differences been associated with differences in clinical outcome in those whose organism has been eradicated, on the one hand, or not eradicated, however you have assessed less good for that particular pathogen?

DR. LEISSA: I am supposed to wrap this up, right?

[Laughter.]

DR. RELLER: Because to me that is the critical issue, does it make any difference. I mean that it is real, I have no problem with, but does it make any difference. If it does, then, it is important to capture. If it doesn't, there may be reasons to capture it, but not for the purposes of clinical assessment.

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DR. CRAIG: Dr. Rakowsky and then Ms. Cohen has the final say, and then we will go to lunch.

DR. RAKOWSKY: Alexander Rakowsky, FDA.

What was brought up at the resistance meeting is about pooling, and if we are dealing with an indication where the micro is not as clean as, for example, in sinusitis, et cetera, I think we take some credence that if you can eradicate the Big 3 in an indication where you can actually have a pure culture, it gives more credence to accepting all three for something like AECSB even though you might not have the clinical response.

DR. CRAIG: You are talking about, let's say, penicillin-resistant pneumococci and being able to --

DR. RAKOWSKY: Even overall and just I guess more thrown out the idea if you have body systems where you have the same pharmacokinetics, the same levels of drug achieved, et cetera, and we are not sure what to do with micro issues in this indication, and yet you have shown that the Big 3 are eradicated in similar situations, namely, ears, sinus, pneumonia, et cetera, then, I can see having more credence to accepting this indication with those three organisms even though the micro data may be unresponsive.

DR. CRAIG: But I guess the question that we have is does the fact that it persists or that you find the

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organism persists mean that the antibiotic has not been effective, which is what you are trying to imply, and I think we are saying we are not sure that that is the case, that the antibiotic still may be effective even with persistence of the organism.

Yes.

DR. SORETH: I think what we have tended to see is not proven microbiologic persistence. If you take two indications like acute otitis media and acute exacerbation of chronic bronchitis, what we have tended to see is parallel outcomes, successful outcomes in those two indications.

When we look at the subsets within those two indications of microbiologically evaluable patients, we tend to see similar clinical outcomes, successes and failures, with the indication driven by the clinical outcome.

When a child enters with Strep pneumo, acute otitis media, and clinically fails, we usually do not have any follow-up tap for any number of reasons, and the child is a clinical failure and in most cases, this category, which we don't like either but we use it, presumed microbiologic persistence, because we never got any additional information.

Similarly with acute exacerbation, even when patients continue to have purulent sputum and cough and dyspnea, you have a clinical failure. A patient entered with Strep pneumo and moraxella, but you don't get the microbiologic information, it is presumed, but what is interesting is that our experience has been parallel in something clean like acute otitis media and some with multiple microbial etiology in acute exacerbation of chronic bronchitis.

DR. CRAIG: As I say, that is useful information because I think at least for otitis, what we are talking about is an organism that normally doesn't belong there, so it is a new infection, and I think there is data looking at following subsequent cultures that say looking at bacteriologic cure is actually a little bit more sensitive indicator of antimicrobial activity than what one finds with looking at clinical effects, but that requires the repeat puncture.

But that is with an organism that doesn't normally belong there. The overall concern that has been with bronchitis is that this is an organism that is already there, it has got a niche, and it may come back as soon as you stop the antibiotic and that it is difficult to eliminate.

But it is interesting. If you can find that bacteriologic elimination correlates with what you tend to see at other sites, then, I can see getting some useful information from looking at bacteriologic cure.

But as I say, I would want to be sure that there is a good association there because in one situation here, you are talking about an organism that doesn't belong there and once it is gone, it is gone.

Here, you have got an organism that has got a niche there, that may be in crevices around in places, and so once the therapy stops, it is very likely that it could come back, and so that is why many of us have not felt that looking at bacteriologic cure in this particular entity is going to be as predictive as you might be able to look at bacteriologic cure somewhere else.

DR. SORETH: But it speaks to the importance of getting the microbiologic information when the patient enters the trial for acute exacerbation, and not giving an empiric indication for empiric treatment of AECSB, which I think would be a mistake.

DR. CRAIG: Yes. Okay.

DR. ALTAIE: To help Dr. Reller with the amount of resistance and clinical failure, I recently was looking at a sinusitis study where my resistant organisms actually were

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clinical failures, and where the antibiotic was okay for the Hemophilus influenzae and Moraxella catarrhalis.

So, we do need to look at the differential susceptibility of these organisms to make those notes in the labels. In addition to that, Hemophilus influenzae, we need to be looking for the beta-lactamase and negative resistant strains, so we do need to pay attention to those. By saying not culture, not follow-up, I think we are going to face some sort of problems in labeling those.

DR. CRAIG: Last question before lunch.

MS. COHEN: Just a brief one. Are you going to include smokers in your tests, in your trials?

DR. CRAIG: No question, they will be there.

MS. COHEN: Are you going to determine whether they are heavy smokers, light smokers? Of course, then, you have those that don't, so you can compare. Thank you.

DR. CRAIG: Let's go to lunch. We are a little behind, but let's try and see if we can get by 1:15.

[Whereupon, at 12:20 p.m., the proceedings were recessed, to be resumed at 1:20 p.m.]

AFTERNOON SESSION

[1:20 p.m.]

DR. CRAIG: The next topic is Gonorrhea. The FDA presentation will be by John Alexander.

GONORRHEA

FDA Presentation

DR. ALEXANDER: Hello. My name is John Alexander and I am here to talk about the evaluability criteria for uncomplicated gonorrhea, so please hold all your clapping until the end of the session.

[Laughter.]

Uncomplicated gonorrhea is truly a microbiologically-driven indication with really set criteria. Part of what I hope to bring out from this discussion is some of the public health impact of the criteria that have been set forth.

First, I would like to give a brief overview of the scope of the disease. These are the latest data that are available from the CDC web site. These are data from 1995, which show that there were 392,848 cases of gonorrhea that were reported to the CDC through state health departments from most sexually transmitted disease clinics.

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This gives a case rate of 149.5 per 100,000, which was second among sexually transmitted diseases only to Chlamydia.

The other point that was brought out by the CDC data is that although penicillinase-producing organisms had decreased, there has been noted an increase in chromosomally mediated penicillin and tetracycline resistance.

One of the other things that was brought out is that we have also started to recognize decreased susceptibility to some of the quinolones. They reported in 1995, eight isolates that were fully resistant to ciprofloxacin and are expected to be fully resistant to other quinolones as well. While still only 1 percent of isolates have this decreased sensitivity for those that were tested, this is still expected to increase with time.

So now let's talk a little bit about guidelines. Guidelines regarding evaluation for gonorrhea have been present for quite a while in the Division. The 1972 clinical guidelines included instructions for obtaining appropriate cultures in patients. Interestingly, it had a list of some control agents that were recommended at that time including things like ampicillin and spectinomycin, three-day courses of doxycycline, which aren't necessarily used anymore.

The Points to Consider document specifies the number of subjects per study, which is still held - 100 males and 100 females in the treatment arm for cervical and urethral infections, and 20 males and 20 females for rectal or pharyngeal infections.

The IDSA Guidelines also laid out a similar framework and with the evaluability criteria guidelines that we have now, very little has changed.

Inclusion criteria for study. The target population that we have is postpubertal males and females. Consideration should be given to the study of pregnant women and adolescents especially because of the fact that these patients are really noted with a high proportion of gonorrhoea.

The culture of appropriate sites. The evaluability criteria guidelines that we have suggest that the urethra, all males should have urethral culture done, all females should have either urethral or cervical culture and a rectal culture obtained.

It is important in those patients where there is a clinical indication, that in males, rectal cultures should be considered, and in both sexes, pharyngeal cultures should also be considered, but these are the ones that are required for study.

The next point is part of what I had mentioned about the public health topic. This is one of the few indications that is really microbiologically driven, and there are so many patients that are asymptomatic, that patients who are asymptomatic are still acceptable as part of the study. It is more on the basis of clinical suspicion as opposed to symptoms of disease for which we base our treatment.

Exclusion criteria. The patients who actually have gonorrhea that have symptoms are a lot of times the ones that we end up excluding from the study because of the fact that usually the symptoms that we would be talking about in those cases, like pelvic inflammatory disease, arthritis, ophthalmia, or disseminated gonococcal infections, such as gonococcemia, endocarditis, or meningitis, are things that aren't within the scope of the evaluability criteria that we are setting forth.

The other point needs to be made that the guidelines state other symptomatic STDs can be part of the exclusion criteria, but while coinfection with Chlamydia or syphilis should be investigated, it does not require that these patients should be excluded, and it is very important because a lot of patients will have coinfection with Chlamydia especially, and it doesn't necessarily mean that

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patients should be excluded from the trial as long as they are able to receive appropriate therapy at the post-therapy visit for Chlamydia or for syphilis.

The last point resistance is not a reason for exclusion, and this is important because of the fact that our therapy basically begins and ends before we have the cultures available to us, and the concerns about noncompliance with follow-up in patients who had these types of infections is very important.

Right now in terms of drug regimen, we have an emphasis on the use of single-dose regimens in order to treat gonorrhea. The goal is for simple observable treatment. Now, there is a caveat to that, that as we see increasing resistance emerging, then, it may be important for new chemical entities that may require longer periods of treatment to still show that they are effective against gonorrhea in these longer treatment periods.

The next point is regarding the use of a control regimen. There are many FDA-approved regimens that are out there right now, along with those regimens being recommended by the CDC, as well. We would recommend that you use the approved regimens that are recommended by the CDC, but at the doses that were approved by the FDA.

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In terms of using a control, there are both PO, as well as intravenous or intramuscular medications that are available, and we would recommend using antibiotics with a similar route of administration as a control regimen.

The question comes up in this microbiologically driven indication where we have a set endpoint as to why should we use a control drug, and these are some of the reasons that I had come up with, one related to a comparison of clinical response.

While you can show that you have reached a certain threshold endpoint, in order for a sponsor to claim that a particular drug shows equivalence or superiority to another drug, we would need a comparative study.

The other important reason for it is to compare adverse reactions to the antibiotic, so that any new chemical entity can be compared to a treatment that is already used standardly in order to look at adverse reactions.

The other part is important that the control is available for maintaining an appropriate blind in a study for those studies that are blinded, and that helps to give us some protection against bias and reassurance that the study is conducted in a proper manner.

Going on to evaluation and evaluability, basically, there are two different visits that are part of the evaluability criteria for patients with uncomplicated gonorrhoea. They have an entry visit and then a test-of-cure visit.

At the entry visit, subject must have a positive, confirmed culture for *Neisseria gonorrhoeae* in order to be considered evaluable. Now, that doesn't mean that they need the culture to be done already in order to be entered into the study, and we usually expect to see a proportion of patients who are entered into the study and have negative cultures.

The other important point here is that antimicrobial susceptibility testing should be performed on the isolates that are obtained in the study.

Looking at the test-of-cure visit, the guidelines set forth that the recommended time is three to seven days after entry for the test-of-cure visit, but exceptions for agents with longer half-life should be made in the protocol prior to the study being started for those agents that are known to have a long half-life and where we may be dealing with simply suppression of the organism as opposed to true bacterial eradication.

All sites that were cultured at entry should be cultured at follow-up in order to see whether there is any indication of the organism being present.

In terms of outcome measures, our primary outcome for this indication, as I have stated, microbiologic eradication, and that is by site. We look at the cervical site, the rectal site, and the pharyngeal site separately. Eradication is basically no growth on the test-of-cure culture. Persistence is presence of *Neisseria gonorrhoeae* on the test-of-cure culture, and as I said, culture sites are considered individually.

What we hope to see for a drug for approval is a 95 percent eradication rate at urethral and cervical sites, and then afterwards, if this is met, then, a 90 percent eradication rate for rectal and pharyngeal sites.

There are several secondary endpoints that have been put forth by the sponsors in different applications. We see clinical response by site, so looking at each particular site, the urethral response, whether the patient was asymptomatic, whether the patient was improved, or whether the patient was a failure in terms of their symptoms.

It is recognized that due to coinfection with other organisms, that the clinical response doesn't

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necessarily exactly correlate with the microbiologic eradication that we see, but it is still something helpful for us to be able to correlate the response.

The clinical response by site may also be important for certain antibiotics that have activity against Chlamydia or other organisms that cause bacterial vaginosis, as well as those agents that are active against gonorrhea in order to show a difference in clinical response.

Many sponsors have turned in as secondary endpoints, microbiologic response by patient or clinical response by patient. The microbiologic response by patient doesn't really add a lot of information to what we see by site.

The clinical response by patient also can be confusing where you are talking about a patient who is considered improved, are they improved because of the fact that their pharyngeal symptoms improved, are they improved because of the fact that they no longer have proctitis, but still have some cervical discharge, so I am not sure how much more information that these will necessarily add.

So, in terms of questions for discussion, these are some of the topics that I have thought of that the committee would be able to discuss.

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The first one: what are the benefits of an active concurrent control regimen in studying acute gonorrhoea?

What would be considered the optimal timing for the test-of-cure visit? This is not only considering drugs with a longer half-life, but also considering the natural history and spontaneous remission of the disease.

Which secondary endpoints provide additional information?

Some other topics for discussion are also some geographic variation in susceptibility of *Neisseria gonorrhoeae* is important, and how much do we need to know about that for a protocol that is done at a specific site.

Questions about emerging resistance and concerns that we have with that. Infections at specific anatomic sites and engender specific indications. Typically, now the FDA approves indications specifically by site, and will give specific indications for males or females, but the question has come up. Actually, the comment was specifically made when I was practicing this presentation, is a rectum a rectum a rectum, and that may or may not be so.

Multiple pathogens in patients are also another thing to consider.

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So, for now I think I will just go back to the previous slide with the questions and take any comments or questions from the committee.

DR. CRAIG: Any specific questions, or are you going to start, Roselyn?

Committee Presentation

DR. RICE: Hi. Roselyn Rice. I think I would like to go ahead and maybe lead off the discussion following the very nice presentation that Dr. Alexander has provided for us.

I think one of the first questions we should really look at would be perhaps the benefits of an active concurrent control regimen. Based on the IDSA Guidelines, sponsors are given the option of historical or, for example, an active control regimen. There are pros and cons I think both.

I think that the issue of perhaps emerging drug resistance, as well as the benefits of comparing regimens for adverse reactions or events are pros for an active control, but I would like to entertain I think discussion of that point first, Dr. Craig, from the committee.

DR. CRAIG: Does anybody want to comment specifically on that question?

Questions and Comments

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I guess I can start. I would think it would be appropriate for having a concurrent control especially with the emerging resistance problem, because I guess all we know right now, many of these organisms have decreased susceptibility, but we don't necessarily know whether that is translated into other differences.

Now, the question comes up, if you are using bacteriologic failure as your only criteria, do we need a concurrent control if we are going to cause any presence of the organism still there as a failure.

One could look at that and say that if you have got a significant number of these organisms that are there, and bacteriologic failure is all we are going to look at, you may not need a concurrent control.

On the other hand, if one is tying symptoms in or at least trying to tie those in, as well, and specifically side effects, as he mentioned before, then, I think the need for a control starts to be there.

So in my mind, if you are just look at bacteriologic response, it might not be there, but there are other things you look at in any evaluation. You look at side effects, you look at possible clinical efficacy. In those situations, it would be nice to have a concurrent

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control if you were going to say that it was comparable to another agent.

Barth.

DR. RELLER: There are regimens that are approved and work other than those that are recommended for therapy by CDC Consensus Group, and I think one of the important reasons for an active control is to continue to gather data on the complex of things, compliance, emergence of resistance, side effects, that may go into a decision about what would be the first-line therapy in public health ventures in addition to simply efficacy and safety.

DR. CRAIG: Other comments? Most people sort of agree then that we think it is appropriate? Does that make sense to you, John?

DR. ALEXANDER: That is fine. Then, I would like to put a little bit of a spin on it then. If we are talking about a sponsor that is seeking an indication specifically for a urethral or cervical infection, would we require that they do a control drug, and what your thoughts would be about that.

DR. RICE: If I am may respond first. Having come from a public health culture, back to Dr. Reller's point, I think that the nature of the gonococcus is changing so rapidly and the issues of resistance and sexual practices

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are so dynamic, it should be given strong consideration that the FDA would consider requiring an active control.

I think that should be open to further discussion.

DR. CRAIG: If you have a drug that even with decreased resistance or decreased susceptibility eliminates 100 percent of the cases, I mean it should have to produce a lot of side effects, which I mean you would probably find out anyway with the clinical trial.

Again, I mean I think it puts a lot more restraints on the industry to try and have to get two situations in order to try and look at that. For something like GC, where we are oftentimes talking about a single dose of drug, it is not like there is big side effects, people are going to get a lot of diarrhea and things like that, so if the best we were doing with the drug was it was only getting about, you know, 20 percent failure or something like that, then, I guess I could see doing concomitant control, but the more I think about it, the fact that many of these drugs sort of have virtually 100 percent efficacy in their approval process, and oftentimes the single drug, single dose, there is not big side effects that you are having, I am not sure that you learn a lot by having a concomitant control.

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Now, the situation where with new drugs you might have to do multiple doses and treatment, and things like that, then, I could clearly understand that need to do that because then you would be exposing the patient to a longer course of therapy, more chance for side effects, and things like that, but I personally have a little trouble seeing doing it with a drug that is given as a single dose.

So, I am not sure that I would require people to do it.

Dr. Melish.

DR. MELISH: I just have a question about how good are the comparator drugs over time. I think that maybe one of the reasons why we are developing new drugs is because there are problems with the comparator drugs.

I well remember at another meeting here we talked about how over just a few years, there was a dramatic decrease in the effectiveness of over-the-counter therapy for vaginal candidiasis, where it had been about 90 percent down to about 50 percent, so the historic standards may not be able to be maintained.

It may be that they are tested enough in other forums, but if not, there may be an advantage to always using what you think is the best regimen and comparing it

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with the new treatment. It might not be as good as it used to be.

DR. CRAIG: Dr. Albrecht.

DR. ALBRECHT: To answer Dr. Melish's question, in the studies that we have been reviewing in the recent past, ampicillin doesn't tend to be a control, so that one is out of the picture, but as far as the IM-administered cephalosporins, the orally-administered cephalosporins, and orally-administered quinolones, we are continuing, at least the studies that I am aware of, to see 95 percent-plus eradication in those approved regimens.

DR. RICE: I would have to ask the question, then, Dr. Albrecht, are those studies looking at multiple geographic sites, are we looking at a good representation of geographic locations that have high incidence of chromosomal as well beta-lactamase producing gonococci?

DR. ALBRECHT: We will see occasional isolates with those kind of resistance patterns. I can't recall what percentage, but occasionally, we will see those.

DR. RICE: I feel the compelling question again for the committee and for the agency, has to be one of the points put forth by IDSA that there be at least geographic representation of study sites based on the knowledge from the Public Health Service's surveillance of gonococcal

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isolates over the last decade, that there has been emergence of extremely high levels of both beta-lactamase producing and chromosomal resistance in some selected geographic locations.

Often the study sites selected may not adequately represent the issue of drug resistance.

DR. CRAIG: I agree with you. As these organisms become more common, obviously, you want to make sure that you get some data included on them, because otherwise if you just look at perfectly susceptible organisms, you are not going to gain any information of how they are going to work in the other situations.

So if the resistant organisms are out in the geographic areas in sufficient number that you would acquire a few, you would like to see at least a few of them in the clinical trial, so you can see what happens.

Dr. Schwartz.

DR. SCHWARTZ: I don't know what the major laboratories are doing with cephalosporin susceptibilities, but there is a lot of cephalosporins out there, and there are only a very few disks being used usually, so that if one is going to monitor with a specific cephalosporin or a specific quinolone, I think that it should be not global,

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but that those specific disks be used not only in the study, but at selected monitoring sites throughout the country.

DR. CRAIG: The NCCLS is specifically the fastidious pathogens group has been starting to look at this question and had a presentation last time from the CDC, trying to see if we could get a little bit more information, so that we can start looking at break points for deciding what is susceptible, what is resistant.

For quinolones, as I said, we have organisms that have decreased susceptibility, but you can't translate that into necessarily resistance in terms of failure to eradicate. So it is trying to get additional data, so that you can more clearly fix those things, and obviously, that is what you would especially want for clinical trial with a new compound is to have some of those resistant organisms to help you more closely fix a break point for susceptibility for these organisms.

Dr. Reller.

DR. RELLER: In no area of infectious disease practice of the best recommendations changed more often in such a short period of time because of the moving target, and to me, it is reassuring to know how new and potentially better keeping ahead of the gonococcus regimens act in relation to currently widely recommended and used regimens,

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so that on the one side, the argument that it is unnecessary expense for a sponsor to include something that it not necessary, I look at the benefit side of that, that if, in fact, because of the plasticity of the organism and the social circumstances under which it is acquired, that the trade-off is that you may find something that in this time is actually better than a widely used comparator, and the benefit would come from having that information in hand.

If we knew a priori that -- it is true that one wouldn't need a comparative agent if the new one was 100 percent effective in eradicating the organism -- if we knew that a priori, we wouldn't need a trial at all but even if it is 95 percent, 95 percent would be great if the comparator now is 85 percent. I mean it would be a real boost.

A single dose, and you are not going to see the side effects, well, the trials, it may require large numbers, but I think the numbers of patients are clearly out there, and they are not going away, and they are easier to do when it is short-course therapy trials.

DR. CRAIG: I think what you are saying is you are not necessarily requiring people, you are saying that if somebody thinks they have got a drug that is going to work better than anything that is out there, of doing a

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comparative study, but if somebody just wanted to go ahead and do a study and show that they got 95 percent or high eradication with their compound, do they need to compare that with something else when we are looking at a single case.

Dr. Feigal.

DR. FEIGAL: There is actually a sample size feature of the comparator arm. The 95 percent and above is the point estimate of how effectively the drug works, and then it has to meet our usual confidence interval for equivalence to the other product, which also has a point estimate above 95 percent.

So if you just had an absolute value, you would actually also have to specify the lower confidence bound that you would be willing to accept, so that you wouldn't just take a study that had 19 out of 20 patients and say that is 95 percent.

DR. CRAIG: But you could still make those estimates without necessarily needing to have a comparative group.

DR. FEIGAL: You could do that. It provides some protection. You occasionally get a trial where the efficacy rates are low, if they are also low in the comparator arm, then, you realize there may be something about the study

design, the patient population. You wouldn't unnecessarily abandon a drug because you didn't have it. So I think the comparators serve multiple purposes.

DR. RELLER: Could I ask a statistical question? Does it make any difference -- and I know nothing about these issues -- does it make any difference whether there is a comparator or not in terms of the numbers of patients required to be more confident that the result doesn't have as much wiggle in it? I am following up to Dr. Feigal's comments.

DR. FEIGAL: Well, when you have two arms, you have two things which can vary, you have two things which can wiggle, and if you are willing to accept a single arm, then, you have really only got one source of variability. So, your total size of the study would be smaller.

But if you think of it just in terms of information, if you want to know something with a certain degree of precision, you have to observe that phenomenon a comparable amount of time to have that same level of precision.

The issue often comes up in study designs, well, what if I have more unbalanced randomization, I learn more about the other arm or my p value, well, I get to a p value quicker that way. That is all because you are learning, you

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have a more precise estimate of the other group, and that is not your objective with the new study.

So I think in terms of the adequacy of the data about the new product, it probably doesn't make that much difference whether it is one arm or it is two arm. It is some of the other advantages that you get that were mentioned, about having comparable data about adverse reactions, which are very sensitive to populations and to the way the questions are asked, having comparable information about time to cure, those types of things.

DR. CRAIG: Personally, in terms of adverse reactions, I would think that you would gain that from other indications for the drug, I mean unless this is the only indication that they are going to be doing for the drug, because people would be on the drug for a longer period of time than what they would be for many of these single-dose exposures.

DR. FEIGAL: You know, there are times when the single-dose drugs have longer, but I think the issue for the patient isn't comparing the side effects of how the drug would be like compared to if they had a sore throat. It is how the drug would be compared to another choice for gonorrhoea, whether it is more or less than that. So there are relative advantages.

DR. RICE: Could I add another comment to that also, in the case of comparing drugs for the treatment of gonorrhoea, I think that a sponsor with a new product would be interested in knowing if the new product also had efficacy or activity against coexisting Chlamydia, knowing that in the majority of populations that are studied, we have coinfection rates up to 20 to 40 percent.

So another advantage would be looking at activity against coexisting Chlamydia in these populations.

DR. CRAIG: Dr. Parker.

DR. PARKER: I will see if I can reply. He is always sticking me with some sample size problem.

The thing that I see as the major difference, if you are going to just estimate the proportion of successes in this group, and that is the only sample that you have, you are playing a slightly different game. Now you are talking about setting a confidence interval for your estimate and seeing if it includes testing against that one.

I think we need some new rules because we are playing a different game from what we are playing now for equivalency, which is a confidence interval on the difference of two random samples, whereas, in the case of where you are just going for a particular one, that is a different probability or a different confidence interval.

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I don't think we would still have that 20 percent type, but if it includes less than 20 percent, we would call it equivalent, we would have to set a different statement down there.

The other thing that I think is important to realize, that if we don't have a control group, we may be playing on a different ball field. I like the idea of the control. I am supporting that.

DR. CRAIG: So you are getting different views.

Yes.

DR. HARKINS: Ralph Harkins, Biometrics Division.

When we put in a comparator arm, yes, we increase the number we are going to need to buy our confidence interval on the difference.

The other part of the equation is that when CDC set the 95 out of 100, they used a statistical approach to set that combinatorial statistics, and that is basically, well, we could set a confidence interval on that point estimate, and it would give you a figure as to what the lower bound of that 95 percent might be, but in answer to your question, yes, the sample size goes up in both arms to calculate the confidence interval on the difference between the two.

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DR. CRAIG: So that it almost may be it gets close to the same amount if you split them into two?

DR. HARKINS: You mean have 50 on each arm?

DR. CRAIG: If you just did one arm, would you need to be up to close to 100 instead of having 50 on each arm in order to get the --

DR. HARKINS: You would be closer to 180 per arm to get your confidence interval of 10 percent on the 95 percent success rate.

DR. CRAIG: But if you were only doing one arm?

DR. HARKINS: If you are only doing one arm, the calculation was that they needed -- well, okay. They came up that they needed 96 people in the study to be 95 percent assured of getting the success rate they wanted, which was about 93. They said we don't want to deal with 93 and 96, so they said 95 and 100. That is where it came from.

They are assured of being this better or this good or better with the 100, and that is what they were working on.

DR. RELLER: Does that mean that the 95 percent figure was derived from data that originally came from where there were two arms to a trial?

DR. HARKINS: No.

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DR. RELLER: Or a single arm, or had nothing to do with the trial?

DR. HARKINS: Talking to them six or seven years ago, talking to the lady that had been involved in setting this, it was set based on a single trial, a single drug given to so many people, and they wanted to be 95 percent assured that at least 95 percent of the people would be cured with one shot, one dose of the drug, and that is what they set it with.

DR. RELLER: Not that this is the exact number, but if one needed 100 patients or 200 or 1,000 patients to get that 95 percent determination, if one did a comparative trial and for either compound wanted to have comparable, would you need the same, fewer, or more patients? I mean would it be twice as many patients, three times as many patients, or the total number would be -- if you had 100 patients without a trial, if you had a trial, would you need 150 patients, 200 patients, or 300 patients?

DR. HARKINS: You would need approximately 180 per treatment arm if you had two arms, so you are increasing your sample size to, what, 360 from 100.

DR. RELLER: Thanks.

DR. CRAIG: Are we still on this issue or do we want to move on to another issue?

DR. RICE: I think we can probably move on to the next issue unless the committee has other questions, Dr. Craig.

DR. CRAIG: Obviously, we can take in a lot of written advice, too.

So what is the optimal time for test-of-cure? You had proposed something like three to seven days, but taking into consideration the half-life of the drug, so that if you had a drug that had a long half-life, you would want to go, I think like we have done before.

A drug could be in the urine I guess for a longer period of time at a higher concentration, so you wonder whether five half-lives is enough for a drug that had a very long one. I mean for three days you are looking at the drug would have to have a half-life of 12 hours to still have drug around at three days.

I think if you look at, for example, I can think of trimethoprim, if you look at that drug in terms of urinary concentrations, it has a half-life of about 12 hours, you can still find urinary concentrations that inhibit gram-negative organisms at three days, so the question is whether three days is a little on the short side for a drug that had a long half-life if you were trying to be sure that you were giving adequate chance for any urinary

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effects coming down, as well, besides the discharge of having some effect on the organism.

So from a pharmacokinetic point of view, I don't have any trouble with the seven days. I would wonder if you had a long half-life drug whether you might need a little longer. So I would probably aim for more like seven half-lives or something like that to be sure, a little safer to have a better chance that the drug is going to be gone.

I think again most of yours are going to fit in there. I would only be a 12-hour half-life that you would need to then maybe go five to seven days instead of three to seven days.

DR. RICE: I think that is probably very reasonable. Again, we, I think, should look at this on a case-by-case basis as newer agents come along the pike based on that.

DR. CRAIG: The longer you go, I think you also have the risk of, if they are sexually active people, of having a second infection, so you would like to get it early enough, but you would also like to not have it be too late or too early, that the drug, especially if it is secreted in the urine, could have some effect on the organism.

Any further comments on that one?

DR. RICE: I think we all agree.

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VOICE: Which secondary endpoints provide additional information?

DR. CRAIG: Roselyn, you want to try and take a bite out of that one?

DR. RICE: Could we have the slide back up that had secondary endpoints? I think John discussed this pretty well. The secondary endpoints - clinical response by site, microbiologic response by patient, and clinical response by patient. I think the gist is that given again the nature of this organism, if we depend on microbiologic response by patient or clinical response by patient, we can be pretty far off base.

I think that the latter two have very little role to play in assessing efficacy. Clinical response by site, again, is problematic, and I think other members of the committee, such as Dr. Thorpe, could comment, who care for women, because a symptomatic infection can become asymptomatic, and you can still have persistent colonization by the gonococcus, so I think the question of secondary endpoints has to be really downsized.

Again, I really don't feel that the latter two have very much to play in the question of efficacy.

Other comments or thoughts?

DR. CRAIG: Dr. Thorpe.

DR. THORPE: I have been of the feeling that the site-specific nature of this disease really does require that all sites be evaluated, and that includes both men and women. I think it also lends credence to this whole issue of emergence of resistance, and that it is not inconceivable that you could resistant pathogens at different sites.

For this reason, if we are going to look at therapies that have the action that we hope to have and in helping to stave off resistance, then, we really do need to look at all sites in all patients, and that is where I think the microbiologic cure certainly becomes the standard there.

DR. CRAIG: I guess the question I have, what do you mean by microbiologic response by patient? Is this other organisms, as well?

DR. ALEXANDER: No, it is not related to other organisms. It is related to taking a look at the patient as a whole and looking at all culture sites added together as opposed to looking at individual culture sites and getting a response as to whether they were eradicated, whether all cervical infections were eradicated or all rectal infection were eradicated.

DR. CRAIG: I see. Clearly there you might be able, as I say, with some of the drugs that have been used in the past, to possibly even show some differences if one

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had a concomitant arm or another arm that one was comparing the drug, a comparative agent.

DR. RICE: Something else while John is at the microphone to take into account is that with gonococcal infections, you can have mixed strain infections in different sites. For example, in some prior studies, we know that up to, say, 5 to 8 percent of gay men have more than one strain of gonococcus per site.

For example, you may have a PPNG and a non-PPNG in the same culture, ergo, the regimen may be to eradicate one, one strain, but you have persistence of failure in the same site by another strain of the gonococcus.

DR. CRAIG: I mean to use clinical, I mean I think what you would have to be able to do is be sure that there is not something else there as well, because as you mentioned, some of the symptoms and things may be related to a concomitant other organism, so I find it very hard to use clinical response in the patient without looking at other possibilities there.

For me, it is difficult to look at secondary endpoints, and I am still sort of left primarily with bacteriologic cure as your major endpoint for gonorrhoea.

I mean if you were able to eliminate the other possibilities, and there were some differences in clinical

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response, I could see it, but I am not sure that our science is such that we have that kind of information, and it doesn't mean that the companies may not want to look at that and try and provide that data, but it is not something that I would surely require and be able to interpret at this time.

Any other comments on that?

DR. RELLER: I agree. I mean for a given compound, they may very well want to systematically look at every patient for Chlamydia before and after, and show that this agent gets both of them, but given the very high concurrent infection rate, either of which, or both, may be asymptomatic or symptomatic or divergence between those, the microbiologic endpoint is the key here in contrast to on some other earlier issues the clinical endpoint was the key.

DR. ALEXANDER: Certainly as an endpoint, it does seem to be that microbiologic response is what we use as an indicator, but part of what this points out is that in other indications, in pneumonias, in otitis, or things like that, we really look at the patient and look for some clinical response as sort of an indicator, and that points out sort of the public health aspect of this disease is that a lot of our treatment is based on patients being asymptomatic, but

trying to treat them for the benefit, not only of themselves, but of their partners and others.

DR. RELLER: This raises also the important of the multiple sites that Dr. Thorpe mentioned earlier and the different strains and with different agents may be differing abilities to eradicate the organism for that public health aspect that would be important to find out.

Dr. Henry mentioned that whatever sites are sampled at the beginning need to be looked again, otherwise, we are going to have presumptions that we don't want to have.

DR. CRAIG: Other questions or are those the major ones?

DR. RICE: If we can go to the next slide, there is another question. I think we want to again reiterate again, and the IDSA Guidelines point this out, geographic variations in susceptibility and emerging resistance should really I think drive future guideline development.

I think we have covered pretty well the infection at specific anatomic sites, and there was a question of gender-specific indications, John, that was raised I think internally.

DR. ALEXANDER: That becomes a question when we are giving gender-specific indications for sites, and this

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is a little bit out of the purview of the evaluability criteria. We are getting more into the approval issues, but we know that there are differences between males and females in terms of the number of patients that we see with rectal infection, and part of that is felt to be sort of a contiguous general urinary spread in women, so that you have a certain proportion of rectal cultures that are positive.

Is treating a rectum in a woman the same as treating a rectal infection in a man?

DR. CRAIG: Do you know of any data?

DR. THORPE: I don't know the data specifically, but I think that this is what lends credence to culturing all sites in all patients, and I think it may help to resolve that issue is a rectum, a rectum, a rectum, and is the treatment adequate in both genders.

DR. RICE: I will try to respond to maybe two things. One question Dr. Craig had is a question of published data. A number of years ago, Sam Thompson looked at historical data relative to anatomic sites about the time that PPNG was emerging and the data are pretty soft. While they may not be specific large data sets, published data sets on differences in eradication, I think we know enough about the populations of strain-specific nuances that, for example, infections in gay men may be more symptomatic or

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due to certain types of gonococci or strain types more resistant to certain antibiotics that we wanted to treat the question of indications by gender stratification. So, I would say, no, and a rectum is not a rectum is not a rectum, and again, John's point that in women often you are looking at contamination or colonization, perhaps not truly microinvasive infection.

We should look at indications separately for men and women for rectal gonorrhoea.

DR. CRAIG: If there is some data that suggests that there might be there, I think it is useful to collect more data and to look at it separately.

Anything further?

Thanks, John. Let's move on the next one, which is acute sinusitis. Renata Albrecht will present the FDA presentation.

ACUTE SINUSITIS

FDA Presentation

DR. ALBRECHT: I had a nightmare that I saved my talk in the wrong version of Power Point, but it never dawned on me that I wouldn't even come up. There we go.

I will provide a summary of our proposed recommendations regarding the evaluability criteria for acute sinusitis

To start with, a very basic and fundamental definition of acute sinusitis would be an infection of one of the paranasal sinuses, most typically the maxillary sinus, however, there can certainly be involvement of frontal, ethmoid and sphenoid sinuses, as well.

Another caveat to this is that usually this is a complication of a preceding common cold or some other respiratory tract infection.

Acute sinusitis, much like bronchitis and pneumonia that we heard about this morning, has sort of gone through the evolutionary process of being subsumed in a big category and over time being identified as an entity of its own.

So back in the seventies, we talked about it and we approved agents for the treatment of infections of ear, nose and throat, or upper respiratory tract infections, as in the case of amoxicillin.

In the 1980s, we got smarter and we realized that sinusitis was an entity of its own, so we approved Augmentin for the treatment of sinusitis. In the 1990s, we became more specific. We actually approved agents for acute maxillary sinusitis, and the list is fairly long - Lorabid, Biaxin, Ceftin, Cefzil, and most recently, Levofloxacin.

This quote, when I came across it in Feigan and Cherry, was kind of my personal favorite, because I have always trying to figure out how otitis and sinusitis are the same and different, and so this particular quote says, "The pathogenesis of sinus infection is undoubtedly similar to that of otitis media. Both the middle ear, with its extension, the eustachian tube, and the paranasal sinuses are normally sterile, but their contiguous areas, the nasopharynx and the nose, have a dynamic microbial flora."

Therefore, it comes as no surprise to us to see our favorite three respiratory organisms again recognized as the common bacterial pathogens, in this case, in the etiology of acute sinusitis. They are, of course, Hemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis.

We are aware, of course, that occasionally other organisms are pathogens and etiologic in this process. For example, Staphylococcus aureus may occasionally cause this disease, Streptococcus pyogenes, and perhaps some I haven't named.

Although we recognize sinusitis is an entity, it is not a clear-cut entity, and I think as we think about the differential diagnosis, the differential diagnosis of acute bacterial sinusitis can be a viral process, a viral

rhinosinusitis or the common cold, chronic sinusitis, perhaps an acute exacerbation of chronic sinusitis, the term we are seeing more frequently nowadays, possibly nosocomial sinusitis, allergic rhinitis, and even asthma with complications involving the sinuses.

So because of the spectrum and scope of sinus involvement in various infectious, allergic, and other conditions, such as CF and asthma, it is important to agree on reliable diagnostic criteria for acute bacterial sinusitis when evaluating new antimicrobials in the treatment of this disease.

So whether the diagnosis relies on clinical and radiographic findings only, the clinical-only studies we mentioned yesterday, or on the clinical, radiographic, and microbiologic criteria, the findings are typically based on the history, physical exam, visualization, and culture of a specimen obtained from the maxillary sinus.

So what are the proposed criteria? We would propose that the patient have a clinical history of signs of symptoms which lasts a minimum of seven days, but no more than 28 days.

We recognize that the presenting symptoms may differ depending on the age of the patient. Adult patients typically have facial pain or pressure, a purulent nasal

discharge, possibly even nasal obstruction, headache, halitosis, and even occasionally fever may be seen with involvement of other sinuses, for example, the ethmoid, eyelid edema, and tearing may be seen.

In pediatric patients, on the other hand, cough may be the most prominent presenting symptom late in the course of an otherwise common cold, and the children may have a nasal discharge which may actually range from clear to purulent. They may also have a postnasal drip or fetid breath.

Radiology is helpful in confirming the diagnosis. Typically, x-rays are done, however, we have also had some experience with CT and ultrasound diagnoses. The findings that are looked for include mucosal thickening of perhaps 4 to 5 millimeters in thickness, sinus cavity opacities, or air fluid levels. Microbiology becomes relevant in the clinically and microbiologically directed study, as you can refer to in the Points to Consider document.

Direct aspiration from the maxillary sinus is considered the gold standard for obtaining the specimen for diagnosis. There are two approaches possible - one, a direct puncture below the inferior turbinate, another is an approach via the canine fossa.

Alternatively, if nothing returns on the direct aspirate, a saline wash aspiration may be attempted.

The organisms that we consider pathogenic are *S. pneumoniae*, *H. flu*, *moraxella* with probably *S. aureus* as well, and we look for quantitation. Now, let me momentarily digress and mention that yesterday, I acknowledged the participation in writing this document of all of our colleagues, and said all the fault was computer or something, well, I am very lucky that the biggest mistakes and typographical errors occurred in the sinusitis indications, so I can take all the blame for not getting the correct information in there, but the problems were in the document regarding microbiologic diagnosis.

This is area of controversy, so that section will clearly need to be updated and revised, as well as corrected. So let me clarify. What it should have said had I gotten it right is that quantitation of a specimen from an aspirate should show a colony count of 10^3 or greater.

Isolated organisms should be tested for susceptibility to the study drugs.

The issue of microbiologic diagnosis in endoscopy. This was a topic of a 1994 advisory committee. In fact, if I am not mistaken, it was in this room. We were fortunate to have Dr. Gwaltney, who is here today, present at that

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meeting, as well as Dr. Alan Wald, and industry representatives participated, as well.

At that time, several questions were asked, one of which was are there direct comparative studies showing that the information obtained by aspirate is correlated directly or has been with information obtained by endoscopy.

We learned at that meeting that there were two studies underway which we comparing endoscopic versus direct aspirate sampling in patients who had chronic sinusitis, but we were unaware at the time of acute sinusitis studies.

During the course of the meeting, we learned that one sponsor was actually conducting a head-to-head comparison of patients with these two modalities in acute sinusitis studies, and if they happen to be here, maybe they will tell us what the outcome of that study was.

So, in 1994, therefore the conclusion was that the data available to use were inadequate to consider an endoscopically obtained sample and culture equivalent to an aspiration-obtained sample in culture, but this is an interesting topic for all of us.

We heard during the open public meeting yesterday that the Agency is being asked to consider this again, and so the 1997 question is: what is the role of endoscopy in the diagnosis of acute maxillary sinusitis?

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In fact, I will even mention a proposal as to perhaps what is the role of endoscopy in the microbiologic diagnosis. The proposal reads as follows. If a sample is obtained by sinus endoscopy, may we consider Strep pneumoniae, H. flu, M. cat, and S. pyogenes as pathogens if they are isolated in colony counts of 10^4 or greater colony-forming units? Also, could Staphylococcus aureus be considered a pathogen if it is isolated in those colony counts, as well, in a pure culture?

So, the question is can we do this, are there new data in the last two-plus years, has the procedure for obtaining a specimen by endoscopy been standardized, and can we really definitively say that what we isolate by endoscopy represents the etiologic agent of the sinusitis, and if we can, what is the role of quantitating these specimens?

So, Dr. Gwaltney will hopefully tell us whether we are aware of new information and discuss this issue further.

Back to the summary of the document. The exclusion criteria, whom do we exclude from these studies? Well, it is the same, usual list of exclusions that we use in all protocols, and then, of course, the additional question of excluding patients who have other confounding illnesses that are not representative of acute bacterial sinusitis.

Let me mention a quick comment. Chronic sinusitis. The IDSA does talk about both acute and chronic sinusitis in the IDSA Guidelines. At this point, we are only proposing the acute sinusitis guidelines and one of the questions will be, should we recognize separate categories, as well.

What about drug selection? The issues about selecting the test drug are the same as have been previously mentioned depending on the pharmacokinetic properties, the dose duration, and so forth, are selected. To be evaluable, a patient should have received about 80 percent of the proscribed regimen, however, a decision of failing drug therapy can be made after 48 hours of drug therapy.

As far as the control regimen, I still remember many years ago companies calling and say what can we use as a control, I mean you have only got Augmentin out there, but that dilemma has now been solved. There are many agents approved for acute sinusitis.

Certainly in selecting the agent, consideration should have been given to the spectrum of the organisms that the agent covers and also whether blinding is possible, especially in the clinical-only studies. The safety profile, of course, is always an issue.

What about the evaluation visits? These time frames should look fairly familiar by now. They are very similar to the ones we have proposed to the bronchitis and pneumonia indications, an entry visit, on-therapy visit three to five days into treatment, an end-of-therapy visit at 10 to 14 days, and a post-therapy visit around two weeks of therapy.

What is it that is proposed at these visits? Well, entry, of course, is to screen the patient for inclusion/exclusion criteria, obtain consent, randomize the patient, and begin therapy.

The on-therapy visit. This is when we make the first assessment of response, and just like in the other indications, is it necessary or is it not.

The end-of-therapy visit. This is when the patient has received maximal exposure to the drug, and this is really the optimal time to evaluate any laboratory or clinical adverse events to the drug.

Then, finally, the post-therapy or test-of-cure visit when we can assess the final response by the patients, have all the signs and symptoms of the infection resolved, or did the patient need additional antimicrobial therapy, if there were any adverse events, have they resolved.

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Having already heard some of the comments before about the role of the on-therapy and end-of-therapy visits, we again say do we need them or do we need to see the patient, what about the role of using the phone and calling the patient asking 20 questions, how do you feel, are you better, is the discharge gone, and so forth.

I used my graphic illustrations yesterday to sort of try to get a quick picture of where do evaluation visits affect evaluability. In a scenario where we presume that we need all four visits, both the entry, the on-therapy, the end-of-therapy, and the test-of-cure visit, we enrolled a hypothetical 100 patients, what we would have to see is all those patients coming at all those visits to say now they are fully evaluable.

In reality, what we tend to see is 100 patients get enrolled and then maybe 70 come to the on-therapy visit and maybe 65 come to the end-of-therapy, and maybe 80 come to the test-of-cure visit, and the question now is, so which ones do we count, which is the 65 that made all visits or the 80 that came to test-of-cure.

Well, the proposal is that the important ones at the beginning and the end with an assessment in between based on patients that we can evaluate, and so the critical visits are entry and test-of-cure, 100 percent compliance on

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those, and then the on-therapy and end-of-therapy could be evaluated via phone calls and other procedures.

Summary. In acute sinusitis, the diagnosis should be based on clinical, radiographic, and microbiologic criteria. To treat, new regimens should be compared. It is important to record, not just the test and control regimen treatment, but any ancillary medications that the patients may have taken.

We have proposed evaluation visits, and the other thing that is very useful is in the case report forms, to have not only the evaluation that the sponsor presents, but also what the investigator believed was the outcome.

The clinical outcome categories proposed are cure for patients who resolve all their signs and symptoms by the test-of-cure visit and failure, which would be converse of that. I have a quote from the IDSA, which recognizes that if a patient needs additional therapy, don't call it an improvement/additional therapy, acknowledge that this was a clinical failure and the patient needed additional therapy.

The question remains once you have a clinical failure, should retap the patient, should you do another aspirate, and this is a topic that was already brought up in the context of this morning's discussion.

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Radiology. How do we use that in interpreting clinical outcome, and particularly, what about the lag period?

For microbiologic outcome, clearly we need a baseline pathogen before we can determine whether a patient's microbiologic outcome is favorable or unfavorable, and the same outcome categories are proposed - eradication for absence of the pathogen whether from a direct repeat culture or based on clinical grounds and persistence.

So the questions that I think we could discuss, probably the hottest question is what about endoscopy and the diagnosis of sinusitis. Other questions might be are the evaluation visits proposed appropriate, is it all right to just have a before and after visit, or should we have the intervening two, as well.

What are the appropriate outcome categories, Q or failure, or are there others as well. I have already acknowledged that we have at this point not written guidelines for either chronic sinusitis or acute exacerbation of chronic sinusitis, what about that category, and then whether there are any other issues.

DR. CRAIG: Thank you, Dr. Albrecht.

Any specific questions? If not, we are going to ask Jack Gwaltney, and for those of you that have not read

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Clinical Infectious Disease, he has an excellent state-of-the-art paper there on acute maxillary sinusitis, and we appreciate his willingness to come down and help us on the committee discuss this issue.

Thank you, Jack.

Committee Presentation

DR. GWALTNEY: Thank you, Bill.

There is a very interesting paper that has been published, was published last fall, which I think has a tremendous amount of value in addressing some of the questions that Dr. Albrecht just raised, and I want to discuss that.

Before I do that, Dr. Albrecht asked that I say a little bit about the anatomy of the sinuses and its relevance to this question of endoscopic sampling for microbial culture.

As Dr. Albrecht pointed out, we are talking about acute community-acquired sinusitis, and that means we are really talking about two diseases. One is, as she said, the sinusitis that we now know is associated with the cold, which really, as she said, could well be called a viral rhinosinusitis, and this is a particularly striking example of a sinus CT scan and a coronal view of a young woman in

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her third day of a common cold, and as you can see, she has a lot of disease in the sinuses, the ones you can see.

This antrum has all the opacity you see here, there is opacity here, her ethmoid sinuses are badly involved. The infundibulum, the drainage passageways are occluded.

So she has got a cold, but she also has disease in her sinuses. I would just like to point out you see these little bubbles in this material, and that tells you this is thick secretions that are plastered to the wall of the sinus, not really mucosal thickening as we have all called this abnormality and as it still is continued to be called, but most of these findings you see really is thick gunk that is stuck to the wall sinus.

Now, these findings are surprisingly common and this is a summary of study we did a few years ago in 31 otherwise young, healthy adults; 77 percent had occlusion of the drainage passageway of the maxillary sinus, the infundibulum; 87 percent had the kind of abnormalities you saw, not that dramatic, but some type of abnormality, some degree of abnormality in the maxillary sinuses, 65 percent ethmoid, 32 percent frontal, 39 percent sphenoid.

Viruses have been recovered on aspirates from the sinuses. Whether the virus actually has to invade the sinus

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cavity to cause these changes or whether they can be due to disease in the ostial meatal complex is not clear.

Now, of patients that have a common cold, a small percentage then develop secondary acute community-acquired bacterial sinusitis, which is a disease that we usually mean and have meant traditionally when we say acute sinusitis.

We don't know exactly how many, but the information we have would suggest half a percent, 2 1/2 percent. These are two different studies. It is a relatively small percentage. But I think an important point to be made is when these people do get their bacterial sinusitis, they already have viral sinusitis, most of them, so we are really dealing with two diseases, and of course, the antibiotics are going to do nothing for the changes that are already there due to the virus as you saw in the CT scan that I showed you.

Now, there are a few people that have disease that starts, say, from a dental root infection who may have a pure bacterial infection of the sinus, but most of them really have a combination of a viral and a bacterial infection.

I want to say just a word about what happens when bacteria do invade the sinus. We don't have much pathologic material from humans, but work has been done in animals,

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particularly in a rabbit model, and this is a summary of some of those findings.

For the first two or three days, there is not too much that goes on. The ciliary bead frequency increases, but beginning on about the fourth day, there is destruction of the ciliated epithelial cells which line the sinus cavity, actually earlier for rabbits that are infected with pneumococcus day two, day four for Hemophilus influenzae, so that by four days, there is a tremendous amount of destruction of the lining of the sinus, and this is then followed by the sinus filling up with what the investigators call mucopus, and they point out that by the time this has occurred, this is a very sick sinus, it is not one that is going to be cured just by removing obstruction to the infundibulum and letting the sinus cavity drain.

We don't know if the same thing occurs in humans, but I think it is not unreasonable to think that there is similar kinds of destruction in the sinus cavity when bacteria invade that site.

We do know that the changes that occur based on imaging persists a long time in humans, which would suggest that similar events are occurring, and this is a result of a study by Leopold in The American Journal of Rhinology in

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which he observed humans with presumed acute community-acquired bacterial sinusitis using serial MRI.

He found the abnormalities persist after clinical complaints have resolved, and this is just a very brief summary. The mean aeration of the sinus begins to improve rapidly for up to about day 10, although abnormality persist, but somewhat surprisingly, by the time he finished the observation of these patients at 56 days, there was only 80 percent return to the amount of aeration that would be there normally.

So, again, this is evidence that there is serious disruption of normal function of the sinus in a human that has an acute bacterial infection.

Now, a little bit about the anatomy. The maxillary sinus is here, the nasal passages, the inferior turbinate, the middle turbinate, the uncinate process, and this structure here, the infundibulum, which is a drainage passageway about 3 mm in diameter enclosed in bone through which the contents of this 30 ml cavity have to drain.

Under normal conditions, 30 mm of water will go to 3 mm aperture in about 11 seconds, so things are fine, but when secretions accumulate in the sinus cavity of greater viscosity, and you can imagine molasses, obviously, they are not going to go out that small a hole very efficiently.

Now, in terms of the question of endoscopic sampling, as you can see, the endoscopist is faced with a serious technical problem of putting an instrument in the anterior nose, working up here through these narrow passageways, and I picked up the open side.

As you can see, they are even more narrow on this side, which is closed because of the normal nasal cycle, getting up here past the middle turbinate, by the infundibulum, making this acute angle, and then coming down this narrow passageway, which is about the same size as his endoscope, and getting in the sinus cavity.

Actually, the point is it can't be done, and nobody has claimed that they can do this. You cannot put an endoscope in the sinus through the natural ostium although as a non-surgeon, non-anatomist, non-internist, I didn't know that until I started looking at CT scans and began to understand the anatomy.

So what the endoscopist can do is sample this area here, which is called the middle meatus, and which is close to this site, but which is not exactly at that site and which is in the nasal passages. As we know, the nose, both the front, the back, and the nasal passages are colonized with bacteria, both pathogens and non-pathogens.

So the crux of the question is, is this area normally sterile, not only under normal conditions, but in an individual who has a runny nose from a cold where secretions are going back and forth with coughs and sneeze and snuffs and snerfs, and things like that.

There are some people -- and this is all the same patient -- this is the infundibulum, the normal passageway. This is an accessory ostium, which has occurred, and about 10 to 30 percent of individuals have this, and this is a second accessory ostium down near the middle turbinate.

These things probably happen in childhood when somebody gets a sinus infection, and these areas, these are fontanelles, these are just like the fontanelles in the head, they don't in many patients have bone, they are thin membranes, they blow out, and they are probably ways of relieving pressure in the sinus, so the infection doesn't dissect up into the brain.

It would be possible to come this route and stick an endoscope through here, and with care and in the 10 or 30 percent of people that have this, it may be possible, although one is still faced with the question of can you shield the part of the equipment that is going to take the culture, and not get it contaminated as you go up through the nasal passages.

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We know from studies of trying to obtain specimens from the lower airway, going down much larger passages, like the trachea, this is very difficult to do because the end of the device tends to get contaminated even though it is plugged with wax or has various ways of trying to protect the interior of that sampling device.

So the sampling targets in patients with acute maxillary sinusitis would be secretions lying in the sinus cavity itself, all sinus secretions which have been expelled from the passageway and are now in the middle meatus.

The approaches would be through the natural ostium by way of the infundibulum, through an accessory ostium when present, by blunt dissection through the intact nasal fontanelle. For years, otolaryngologists have taken their suction device, gone up to where that thin area is and actually pushed it through the wall of the sinus under local anesthesia, and many of said, well, I am going through the ostium, not realizing that really they were making a puncture site at that point, and then, of course, one can create a surgical antroscopy and this is done at the time of surgery.

Now, there are technical issues involved in trying to obtain samples again in the sinus cavity itself. As I

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said, the natural ostium is inaccessible, and this is just not possible because of the anatomy.

Accessory ostia are present, but there are difficulties, technical difficulties in getting there and getting into the sinus cavity, and getting out without contaminating the specimen.

The endoscopic puncture is actually a puncture, it is no different from a needle puncture, and involves contamination unless there is thorough cleansing of the site where the puncture is done, and, of course, the same thing applies with a surgical antroscopy.

Now, the technical issues in sampling the middle meatus are that the bacteria which includes the pathogens we are interested in, are normally present in the nose, the nasal vestibule, the nasal passages, and nasopharynx.

Therefore, specimens obtained by end oscopy, despite the attempts at shielding, and so forth, may inadvertently be contaminated through the procedure by the bacteria which are present in these sites.

Also, if there are bacteria there, which may have come either from the nose or from the sinus, they will grow, but if they have come from the due to the fact of the intranasal transport of material, then, they will give a false positive.

If there is a mixture of bacteria from both the nasal source and the sinus source, then, the results of the culture may often depend on which bacteria grow the best and which ones show up on the plates after several days of culture in the incubator.

That is just what I have said here. So, consequently, cultures of endoscopically obtained discharge, really, that should say may not accurately reflect the bacterial etiology. They will not if they are contaminated with bacteria that are in the nose.

So that has led to this difficult problem which was discussed in 1994, and which was again brought up this time. Some of the questions that came up, Dr. Albrecht has mentioned some of them, and the big one is, is there concordance between endoscopic sampling and puncture in the individual patient, not in one group of patients that have endoscopic sampling and another group that have puncture, because we would expect to see that because we know hemophilus, pneumococcus, and moraxella are part of normal flora, but in the individual patient, we need data to really answer that question.

People raise the question, well, what about patients without meatal exudates, because some of the endoscopists that spoke in '94, said that they didn't

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collect the samples unless they actually saw some pus coming down across the meatus, and many patients may have occlusion of the infundibulum, and may not have pus, and what would be done with those.

I think Dr. Schwartz raised the question of what about double infections. We know that about 10 percent of sinus puncture studies show more than one organism in the sinus cavity.

Then, two other questions that might be raised, as Dr. Albrecht said, what about standardization of the procedure, what kind of device will be used, what kind of cultures will be taken, and that type of thing.

Then, finally, I think a fifth and perhaps maybe most important question is will there be concordance in cultures taken after therapy, because what we have talked about up to now really is in relation to cultures taken before therapy.

The reason that I raise the question of after therapy is because I want to want to briefly review the results of this study by Lindback. This was a double-blind placebo-controlled study of approximately 120 patients with acute community-acquired sinusitis in Norway.

One group of patients received a gram and a half of amoxicillin, another group received a fairly large dose

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of penicillin, 1.3 grams t.i.d., and the third group received placebo, and this is a Kaplan-Meier graph showing the duration of illness in the three groups, and there are some very interesting things on this figure.

Number one, antibiotic treatment clearly is better than no treatment, and these are statistically significant differences between the two antibiotic groups and the no treatment groups. These patients, I emphasize received no treatment whatsoever.

Secondly, there is a trend that favored amoxicillin although there were no statistically significant differences between those two treatments.

Thirdly, without treatment these patients got well -- that is the good news -- and they got well at not too much of a different rate from those that received antibiotics. They got well. This is a self-limited disease, as we know.

The bad news is at the end of a month, one in five still had disease, still had symptoms, still complained of symptoms, and this would certainly be an unacceptable rate if there is a chance that these patients are going to go on develop chronic sinus disease.

Now, this is a summary again. This is a reference of Dr. Lindback's paper of the 44 adults who received

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placebo and of their evaluation of their progress and of the CT scan evaluation of their progress. They had scans taken prior to therapy and 10 days afterwards, and they had clinical evaluations at day 3 and at day 10.

As you can see, after three days, almost 40 percent of these patients who were receiving no treatment had some degree of subjective improvement, and at the end of 10 days, three-quarters of the patients had subjective improvement and said they felt better. This was confirmed by the sinus CT exam, which showed that two-thirds of them had objective evidence on the sinus CT exam that they also had improved.

So I think this study raises an important question of the reliability of clinical information as a measure of bacteriologic cure, and this would appear to suggest that it is not very good.

The second question would be the reliability of sinus imaging studies, in this case sinus CT examination, again as a measure of bacteriologic cure, and again these results suggest that also is not very good.

Well, now, you might say these patients were cured, they have cleared their infection spontaneously, and so, in fact, these clinical and radiographic parameters really are associated with a bacteriologic cure.

I am not convinced that that would be the case, and I wanted to show a brief summary of some studies done with pre- and post-therapy puncture in which either what was considered adequate antibiotic therapy was given or inadequate therapy.

The first is one by Caren Felt in 1990 when sinus aspirates were obtained, as I say, in these studies, where patients were thought to have been given an appropriate antimicrobial in terms of spectrum and of dose, and those that were given a suboptimal dose, and in this instance, the antibiotic was Cefaclor, and as you can see, the cure rate here was 91 percent, here 74 percent.

We had a similar experience. Again, it just so happened with the same antibiotic, where we gave what we thought was an appropriate dose of antibiotic. Again, the cure rate high as we expected, and again with the lower dose patients still had titers of bacteria in their sinus cavity up as high as 10^6 or 10^7 after 10 days of what appeared to be inadequate treatment.

These two slides are out of order. Actually, this study was done earlier. In this one, an attempt was made to actually measure the antibiotic concentration in the sinus aspirate and determine how it related to the MIC of the causative bacteria.

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Here, the concentration was higher than the MIC, here it was lower. Again, you can see the difference in cure rates. These are bacteriologic cure rates based on puncture and culture, 90 percent, 45 percent, and again here, 96 percent versus zero percent, and these were six patients that received clindamycin who had Hemophilus influenzae, and that was not a very wise thing for us to do, to treat patients with sinusitis with clindamycin, but we made that mistake and we realized it wasn't a good idea, because these patients were all infected and still had high titers of bacteria.

So I would guess that those patients that were reported in the Norwegian study, many would have had bacteria still frozen in the sinuses had they had punctures done.

In the draft guidance document, this issue is discussed several times, and I think it is pertinent to what I have just talked about, and I wanted briefly to comment about this. This relates to the discussion that we had here about gonorrhea, and the question that if patients become asymptomatic, is that satisfactory as a criterion that one would wish to go by in testing antimicrobial treatment.

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It says on page 6 of the guidance that criteria considered important are not the same for each indication, and it gives examples where the focus is on the culture results, and one is asymptomatic infection, and I would suggest that where you have spontaneous resolution of the illness, certainly is another example that may fit that category.

Then, on page 19, it says the presumed microbial eradication outcome based on clinical response. I would say that would also seem to be questionable, again based on what we have seen from the Lindback study, and the issue is addressed again on page 21 where it says the amount of discordance between clinical and microbiological outcomes, where that is discussed and where it is stated that although a small amount of discordance would be acceptable, a larger amount would not be, and I think it is an important issue to decide what degree of discordance there is in these cases of acute sinusitis.

Just a couple other comments I would make if presumably you want to hear them, since I was invited, I haven't had a chance.

DR. CRAIG: That's right.

DR. GWALTNEY: Page 40 talks about the fact that granting approval for antimicrobial agents that only are

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effective against some of the bacteria that cause acute sinusitis, and there is a precedent and that has been done. I think this raises a very important question. How does the doctor know what the patient has? How does the doctor know the patient doesn't have pneumococcus or has H. flu?

The doctor doesn't know, obviously, and so how can he select an antibiotic which might cover one of the bacteria or two of them, but not all three. Even if he does sinus cultures, he doesn't know. Maybe his Gram stain will tell him, but often it won't. He won't know until the culture is back.

So I think that is an issue that I think really should be readdressed.

Finally, one of the things that did come up was the other bacteria, and we do know some of the alpha strep, Strep milleri, Strep intermedius, all important pathogens in the sinus, and actually the proportion of these cases can be relatively high, 10, 15 percent, and I think that it would not be unwise to include them in the bacteria which are of importance and which we judge our antibiotics.

One of the major problems if you do believe in doing sinus punctures before and after, as I do, is collecting cases, and so you need to make it easy to get the numbers, and not that you want to ignore the important

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pathogens, but I think these should also be included, and finally, in that same light, I would certainly think the idea of cutting down the number of visits is an excellent idea. These patients that come in and have the two punctures, and they will do it, if they are recruited, they will come in and have it done. We did 150 last year, but you have to make it easy for them, and to ask them come back four times is really too much. I think the initial visit and the test-of-cure visit really are adequate with telephone contacts to make sure the patient is doing all right.

So that concludes my remarks. Thank you.

Questions and Comments

DR. CRAIG: So do we want to take these issues again one at a time in terms of the committee.

Go ahead.

DR. RELLER: Could we ask Dr. Gwaltney questions?

DR. CRAIG: Sure. Sorry. I can't let you off that easily, Jack.

Dr. Reller.

DR. RELLER: To help with the subsequent discussion, it is just too good of an opportunity.

At what point in the anatomy does the infundibulum down into the sinus in health become sterile, that is, from

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the middle meatus, one coming up the hairpin turn, down the infundibulum, into the sinus, what is the analogy, if it is appropriate, with cricothyroid membrane in health, when we discussed earlier the issues of secondary bacterial infection with acute bronchitis versus chronic exacerbations, so that we understand what the underlying natural state is that we would aspire to return to with any kind of therapeutic intervention.

DR. GWALTNEY: Well, I think that is a very important question and as far as I know, we really don't know the answer to that. Most of these studies that were done in the past concentrated on the nasopharynx and the nasal vestibule. Some cultured what they called the nasal passages, but as far as I know, no one has tried with any precision to answer that question that you just raised, and I think it is a very crucial one, not only in health, but I think it is important in disease because that is when we are talking about taking these samples is in someone who has already got a cold.

DR. RELLER: Other than the technical difficulty of not being able with an endoscope to get around the hairpin turn, if we knew where sterility normally began, one could, it seems to me, help assess whether there is any

utility to attempting pus observed, pus not observed, with sampling by endoscope in the middle meatus.

The second question is has anyone yet done the study that everyone wanted to see in November of 1994 here, of best endoscopic sample, however defined, versus direct maxillary antral puncture for microbiological comparisons?

DR. GWALTNEY: Not that I am aware of, but those data may be presented today, but I haven't seen them. I may have missed them.

DR. MOLEDINA: Dr. Reller, about four years ago I reviewed some data that was present in the NDA, but the investigator was a Canadian investigator, and he had done nine endoscopic cultures. The technique he used was a double lumen. That means he put like so that he can decrease the contamination. He cultured nine patients and did simultaneous sinus taps also. He recovered organisms from all the nine patients by nasal endoscopy, but by the antral puncture he could culture only three patients.

So like two-thirds of the patients were considered contaminant in spite of using a double lumen. I had to call him actually to find out what kind of technique he had used, and he said that it was really practically impossible to do nasal endoscopy. He was supposed to do a larger study, and I don't know if somebody from Abbott is here who can comment

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on that, whether he did that or not, but that was done for Biaxin. It was nobody from U.S., he was a Canadian investigator, and I can't remember his name because it has been like four or five years since I reviewed that application, but if there is somebody from Abbott who knows whether he has done anything extra, I have no idea, but he was supposed to do a study.

DR. RELLER: If antral punctures are done, given the less frequent but real Strep milleri, et cetera, plus the usual pathogens in acute sinusitis, with that quality specimen, do you think that quantitation adds anything to interpretation if one has an antral puncture?

DR. GWALTNEY: I think the main thing quantitation does there is with Staph aureus, and in spite of the fact that people with puncture make an attempt to sterilize the wall, will still get stabbed in some of the specimens, and without the quantitation it is hard to interpret those. Occasionally, you get gram-negatives, but I think most of those you would throw out anyway and think the patient either had chronic disease or was contaminated, but staph is a large enough problem in terms of numbers that it does help considerably with that.

DR. RELLER: At what quantitative point does one separate contamination from real with Staph aureus?

DR. GWALTNEY: When we were doing them in the hospital where we were, we were using 10^4 or greater, although many were much higher. When we had to take them across town in a taxi, and they sat around a while, we dropped down to 10^3 , and I think that has been a pretty reasonably good way.

I don't want to forget one thing, though. There was a study done by Dr. Talbott and others from Rhone-Poulenc. That has already been presented to the committee. It was published in an abstract. As far as I am aware, that has not been published, the full paper, to give actual details, just to remind you of that paper. If they looked at all of the bacteria recovered -- and I don't have the numbers -- anyway, comparing the two techniques in the same patients, it had a sensitivity of 65 percent, a specificity of 40 percent, a positive predictive value of 38 percent, a negative predictive value of 67 percent, and an accuracy of 49 percent.

If they only looked at the results with the Big 3, the sensitivity went up to 79 percent, the specificity to 85 percent, the positive predictive value to 69 percent, the negative predictive value to 90 percent, and accuracy of 85 percent, and we don't know how they were selected. We don't really know -- I haven't seen the actual data of the actual

number of bugs to look at that in a way I think it would be desirable.

DR. CRAIG: Dr. Schwartz.

DR. SCHWARTZ: Yes. Jack, could you put on your CT scan of the sinus anatomy and go over. I think it would be very illustrative to the people in the room how a sinus aspirate is actually done, not so much for the gory details, but where the needle is in the sinus cavity and how, if you have only a partial filling with fluid, how the needle can be above the fluid level or it depends on the patient's position, sitting up or lying back.

There are so many variables even when you do a direct sinus aspiration, that is why I hope that people here don't get confused when you are only getting 50 percent positive results back versus middle ear taps where there is 85 percent and 90 percent. It is an extremely difficult thing to actually get the needle to where the pus is.

DR. GWALTNEY: Well, the procedure actually is very simple. The area here on the medial nasal wall is anesthetized and sterilized, and then with either a large -- and this would be like 14-gauge needle. Well, now, there is a commercial device available which is a spring-loaded stylus, a trochar that pushed through the bone into the sinus cavity, and then the aspirate is aspirated, or if they

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cannot be aspirated, then, a small amount of saline is put in there, enough to obtain to obtain a specimen, and they are taken out.

This is not the kind of thing I like people to do to me, which is take a big needle and point it at my face. I do believe it is honest to say this is not a painful procedure if done properly, but I have to admit there is a crunch when the needle goes through the bone.

It has been a safe procedure. The danger would be if the surgeon puts the needle in the wrong place, obviously, but otherwise, it has been a very safe procedure, there have been hundreds of patients, and this was the traditional way that sinus infections were treated before we had antibiotics. This was the way they were treated because this was considered an abscess, and just last week I did do this therapeutically on a woman who had had a dental abscess in August and still had disease in one of the sinuses at the bottom of the root. We punctured her. Not surprisingly we didn't grow anything out of her, but by washing her out, I think we did a very useful therapeutic maneuver and hopefully she will not progress to chronic sinus disease.

In Europe, this procedure is done with a device that shoots the trochar through the wall. A plastic catheter is then placed into the sinus. It is cut off at

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the nose and left there for several days, so the patient can come back and have the sinus irrigated, and then when the disease is cleared up, they pull out the plastic catheter.

Americans are more sensitive than Europeans.

[Laughter.]

DR. CRAIG: Dr. Henry.

DR. HENRY: I would like to ask you more about the quantitative cultures that are proposed. The IDSA Guidelines say that they are labor intensive and maybe not helpful, but if they are done, you talked a little bit about how you came to, you know, with Staph aureus, 10^4 organisms per ml was important, but how did you arrive at that, and why not, if these are supposed to be sterile sites, why any organisms, why do you have to quantitate?

DR. GWALTNEY: Well, I have a slide and I didn't bring it. There are at least three criteria which we have used in infectious disease to establish pathogenicity when we have an area which may not be a closed space.

One of these would be concentration of bacteria. We have seen this holed up in urinary tract infections, in burn wound infections. I think it is well established now in sinus infections. We have used this in osteomyelitis where quantitative cultures have helped us distinguish pathogens from non-pathogens.

Secondly, Gram stain is used, and where Gram stain correlates with the quantitative culture, I think that has been very helpful, and then finally, evidence of inflammation. In the original studies that Frankie Evans did in the puncture studies, he correlated these elevated titers with the presence of white cells in the nasal aspirate, and there is a very good correlation between elevated cultures and pus, lot titers and no pus. So I think is well-established.

Now, I would not necessarily say, though, that because you had elevated titers in a specimen obtained from the meatus that that would necessarily allow you to say, well, that implies infection. I still think the head-to-head comparison would be necessary in order to reach that conclusion.

DR. HENRY: I guess my only caution would be that if a study was designed, and quantitative cultures were something that were requested or desired, that, as Dr. Schwartz pointed out, depending on where that needle was placed to get the aspirate, you might not get a very good sample, and if you were doing washes, which may be actually more accurate where you could actually instill saline and flush the sinuses, that that sample might be more representative, you might get something, but then it

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obviously would affect your quantitation in terms of trying to find a cutoff of what would be significant.

DR. GWALTNEY: Well, quantitative cultures are not really -- I mean now we have labs that are highly automated, and so they don't fit into that, but, you know, to do a quantitative culture, you put several tubes in a rack, you put saline in, you do tenfold elutions and you plate them out.

So, really, it is no big deal when you consider all the sophisticated laboratory testing we do in the hospital. That is primitive stuff, and there is really no reason it can't be done. A routine lab doesn't like to do that obviously. In studies, I think there are reasons that those are useful things to do.

DR. CRAIG: Yes, Dr. Rakowsky.

DR. RAKOWSKY: To follow-up on Dr. Schwartz' question, is there a difference between a canine fossa approach and a middle meatus approach in terms of, one, adverse events, and, two, pathogen recovery.

DR. GWALTNEY: You say the canine fossa?

DR. RAKOWSKY: Or like a Caldwell-Luc approach.

DR. GWALTNEY: I think most otolaryngologists would not use that. That is almost of historical interest. The bone is much thicker there and the crunch is much

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louder, and the otolaryngologists have to be much stronger, so if you do a puncture, the place to go is under the inferior turbinate.

DR. CRAIG: Let's try and get back to the questions. The first question is endoscopy. At least we haven't heard of any new information, and it was suggested that possible there was some sensitivity and specificity, if you just limited it to your three organisms, that has never really been published for anybody to look at yet, and the committee sort of feel that right now we still don't have sufficient information on endoscopy.

And that is what you would say, too, right, Jack?

DR. GWALTNEY: I would agree with that.

DR. CRAIG: One of the questions came up on evaluation visits that she brought up, and I think Dr. Gwaltney said that he thought we are going to make it more difficult in terms of getting samples, that we did need to make it a little give and take, so again, in terms of evaluation visits, as was suggested at the beginning and at the end were the primary times, and that some of these others could be done by telephone.

Do people feel at ease with that?

The next question was on outcome. Here is where we see some differences from what is listed in here and from

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what Dr. Gwaltney presented in terms of using clinical response alone as compared to getting bacteriologic response and doing a repeat puncture.

Yes, Dr. Schwartz.

DR. SCHWARTZ: There aren't that many Dr. Gwaltneys in the United States, and while you might get a few who will do the initial tap, you are going to be looking high and wide to get some that are going to be doing the follow-up tap, but that is not to say you can't get Dr. Gwaltney to do the follow-up tap.

DR. CRAIG: Jack.

DR. GWALTNEY: Well, I have never done a sinus puncture in my life, and I don't think I ever will, but I really want to emphasize something that I think is very important.

Our studies are done with several groups in Virginia and several groups in North Carolina, and these are people who just began doing the studies in recent years. Many of these doctors are willing to do the punctures, both initial and final, and I really think that the trouble in getting enough patients in many of these studies is a recruitment problem.

It is not so much that patients aren't willing to do it, but if you wait for the average doctor to get enough

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patients that come in, then, it really takes a long time to get them, and we actively recruit in the newspaper with a 800 number, and all that.

So, although there are some patients who are unwilling to have the punctures done, most of them are getting free antibiotics, they want to know what is causing the infection, and most of them will have it done and a surprisingly high percentage will come back and have the second one day to see if the infection is gone, et cetera.

The way the protocols are now written, I think one thing that really should be changed is that when the doctor and the patient is willing to have the second puncture done, it is not in the protocol, and the study monitors discourage the doctors from doing it, and that has been more of a problem than trying to get the punctures done.

So, in the second of the two studies that are in there, that has talked about looking for bacteriologic cure, I would hope that that would have in there at least that the second puncture is desirable or optional at least.

I do think you would be able to get enough to give you the kind of data --

DR. CRAIG: And what is enough? How many do you think you would need in order -- you know, is nine out of 10 okay, that we have bacteriologic cure?

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DR. GWALTNEY: That is good enough for me. Your number is in here like 25. I think those are reasonable. I think you are in the ballpark. I don't think it is hard to get that kind of numbers. You don't need huge numbers. Nine out of 10, you know, 15, 20, 20 is great, is plenty as far as I am concerned.

DR. CRAIG: Yes.

DR. ALTAIE: I have a question for Dr. Gwaltney.

We said that the quantitation would help to decipher the Staph aureus issue of being contaminant or not. Let's say theoretically, if we have a patient with a Hemophilus influenzae in their aspirate of 10^3 and a Staph aureus of 10^4 or greater, which is the culprit?

DR. GWALTNEY: Well, you know, I can't tell you what is the real truth, but in that instance, I would call both of them pathogens. All we can do is set our standards and then go by what our standards are, and if both of them really were there in those titers, because coinfection, it does occur. We have many examples of that with all kinds of combinations. I would say that patient probably had both bacteria in there causing disease.

DR. ALTAIE: So, otherwise, if it is an aspirate, can I say any organism that we know they are pathogens, are acceptable as pathogens regardless of their counts?

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DR. GWALTNEY: Except for staph, I believe that. I am sure you are going to get some false negatives, but I think most of the time you grow a pneumococcus out of a sinus aspirate specimen, it is a pathogen.

DR. ALTAIE: So you would like to see quantitation on an aspirate to even then decipher the Staph aureus issue?

DR. GWALTNEY: I think the staph and maybe some of the other strep, and there are a few gram-negative, but staph is really the major one.

DR. ALTAIE: Right. Thank you.

MR. LEROY: I have two questions regarding sinus puncture. If it was used in the past as a therapeutic procedure, do you think that it could impact the results of the clinical study that you are performing, first, and the second question -- and this, for example, could have been the reason for the high success rate of the placebo group in the Lindback study published in the BMG -- and the second question is, when you don't have Strep pneumoniae-resistant penicillin in the center performing sinus puncture, can we think that the other methods could represent evaluable alternative to obtain bacterial documentation?

DR. GWALTNEY: The first question, I think is a good one, and people have said, well, you get these cures because you are going in there and washing the sinus when

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you collect the specimen, and I think that is a reasonable idea.

The reason I don't think that is entirely true is because when we have had the failures, for example, with clindamycin and H. flu, those patients did have the aspirate and had the material aspirated out, and they didn't have a big wash.

You know, there is a difference. You can take the patient and put that needle in and leave that, and then put a lot of saline in there, and they put their head over the pan, and then a large amount comes out of their nose after you have collected the specimen.

We have not done that, but we have tried to get everything that is in there, out, and the otolaryngologists have felt like it is kind of unethical not to do that. But where we have used the wrong antibiotic, like with those H. flu, they still were infected in spite of that. So, I don't know that that is totally true, it is a good issue.

I am not sure I understood the second part of your question.

MR. LEROY: The second question is if the epidemiology of the center that do the sinus puncture -- I am referring, for example, to the Swedish investigator -- if in those centers, it could be in some centers in the U.S.,

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if in these centers there is no Strep pneumoniae resistant to penicillin, how can we try to evaluate the effectiveness of the new antibiotics against those strains?

This is important because it is the major question as to the new antibiotics.

DR. GWALTNEY: Well, I think part of evaluation has to be done in the laboratory, and where we know that strains are resistant to antibiotics, there really is not much sense even in doing the clinical trial. So, I think we want to start with antibiotics that are sensitive, that show reasonable in-vitro sensitivity to the antimicrobial that is going to be used, and then I think really the critical reason for doing the puncture study is to make sure we give them the right dose, because we don't have good correlations between plasma levels of drug and sinus secretion levels.

So, I think at this point, and maybe these can be worked out, although we have tried, and others, and it is hard to get specimens where you get good, consistent antibiotic levels in those sinus aspirates because of sampling problems.

DR. CRAIG: Yes, it makes a problem. I mean it brings up the thing that is nice about getting some of this kind of data, bacteriologic cure, enables you a chance to see if you can model it like we have done with otitis media,

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and if one was able to get the same kind of model to fit, then, at least you might be able to draw more of an association, is that if we can get ear specimens from kids on repeat puncture, as is done, in areas where there are resistant organisms, then, we can sort of -- you know, if the same model tends to fit, then, you can tend to go back and say, well, it is probably then also going to apply for sinusitis, as well.

But, again, you would still like to have some data later down the line that would help to confirm that and eventually send a ENT doc down to Virginia from an area where they do have a lot of those to learn the procedure and to go back and to do it to try and get some of that data.

So that you would be happy with using, as proposed here, primarily clinical endpoint, but to try and encourage to get at least 20 patients or so in which one could get bacteriologic data?

DR. GWALTNEY: Yes. I think the two studies make very good sense. I don't particularly like the category of assumed microbial eradication. I would just rather say clinical cure of patients with known H. flu or known pneumococcus or whatever, and let the bacteriologic cure be a real bacteriologic cure based on the puncture results in a small number of patients.

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DR. SCHWARTZ: Dr. Craig, are you talking about the initial aspirate?

DR. CRAIG: No, I am not talking about the initial aspirate, I am talking about the follow-up aspirate. I think we decided before that endoscopy isn't far enough yet for that.

The other question I would have is, is x-ray at least -- I remember from reading your article -- it seemed like if you had a CT scan that actually showed an air fluid level with sharp edges, that that was much more likely to yield bacterial infection than one where there is roughened edges or where there is just thickening.

Are we to the point where CT scans are cheap enough now that we should really prefer those over the old Waters' views?

DR. GWALTNEY: I think we are at most places, and I think that is really what is being done. You can get these limited CT scans with seven or eight exposures, and the cost is really not too much different from a complete set of sinus x-rays, and with new shielding and things like that, why, I think they are very satisfactory, so that if you are going to get any imaging study, unless they are exorbitantly expensive in your institution, I would go and get the CT scan.

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DR. CRAIG: Would encourage and design to try and use those people, then, that have air fluid levels as compared to those that do not, to try and increase the yield of bacterial pathogens?

DR. GWALTNEY: Well, the problem is that there are only a relatively small proportion that have that kind of finding, so you would lose a lot of patients, and I think that wouldn't -- I mean you almost could say that you really don't need the radiographic studies. I mean the early studies, we just used to do clinically and do the puncture before and after.

The CTs are very nice, but they really as far as collecting cases that can do bacteriology on, they really don't add too much.

DR. CRAIG: So you are questioning whether it is one of the inclusion criteria?

DR. GWALTNEY: I honestly don't think it adds very much. I know from the point of view of recruiting patients, it makes it harder because then the patient has to be scheduled for the CT, and they have got to get the babysitter, and, you know, all that stuff.

DR. CRAIG: How about just a regular x-ray, would you still get a regular x-ray?

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DR. GWALTNEY: Well, our culture recovery rates don't vary whether we get x-rays or not. We get the same 50 percent pretty much, 50 to 60 percent just based on coming in with seven-to-10-day history, and it sounds like they have got sinusitis. Whether we get the x-ray or CT scan or not really doesn't change that.

DR. CRAIG: So in order to get a few more punctures, you would be willing to give up some x-rays?

DR. GWALTNEY: I would. I would from my point of view.

DR. SCHWARTZ: May I make a comment on that?

DR. CRAIG: Yes.

DR. SCHWARTZ: I think the x-ray is helpful, and I have done sinus punctures on studies, a different route, but I have done them.

What the x-ray does is give me the confidence to go ahead and drill, and give the patient the confidence to go ahead and that they are making the right decision because they, in fact, have sinus disease.

Other than that, it may not be too helpful because, as you could see, on the CTs that Dr. Gwaltney showed on adult patients, and we have probably about 27 on pediatric patients, early in the course of a normal cold, by day four, if there is purulent material anyway, which is our

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target population, 70 percent had grossly positive CTs, and not sinus disease. I mean the sinuses were involved, but not necessarily bacterial sinusitis.

DR. ALTAIE: This is Sousan Altaie again.

DR. CRAIG: Yes.

DR. ALTAIE: I would like to hear from Dr. Reller about the quantitative counts in a sinus aspirate, if you would give us his view of count, I would appreciate it.

DR. RELLER: That is why I asked Dr. Gwaltney.

[Laughter.]

DR. CRAIG: So you just want to say amen.

DR. RELLER: I had always envisioned that with a pristine pure specimen, that is sort of like a suprapubic aspirate of urine, anything that you get may be important. Actually, I was a little surprised to hear that there is as much confusion as there is with Staph aureus given that that is a player, but a relatively -- I thought from your published work -- a relatively minor player.

A lot of people say acute sinusitis, Staph aureus, but when you look at the literature, it is not a major pathogen with acute sinusitis. Am I correct, Jack?

DR. GWALTNEY: It is not, no, it is a small percentage, maybe 1, 2 percent.

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DR. CRAIG: But in colonization of the nose, it's a high percent.

DR. RELLER: I understand. Most of the time -- I mean I realize technically it is simple, but it is so different from what the usual processing is. There are good data if one uses a defined, reproducible loop of the regular streaking out with the same loop versus quantitation, and given the kinds of number differences that we want, I would like to see the data that one couldn't do just as well with looking at how many staphylococci there are with a properly plated-out specimen from a direct aspirate.

A single colony, I am not very excited about. If they have really got acute sinusitis owing to Staph aureus, I mean I think it would go out into the second, third streak, and there would be a lot of them.

You know, if you see these things in practice, it is not hard to say there is a lot of that one, and that is real, and I am more comfortable with the semi-quantitation in interpreting a colony or two versus a lot of it if the specimen is good. I mean to me it is much more important. You can't make a good specimen out of any kind of quantitative separations.

I am very much in favor of before and after direct puncture, and I would be willing to look at how many

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colonies there are to tell, separate, to give some aid for the occasional nose, I mean because you are cleaning this off as well as you can. I mean it is sort of like you are taking a sample of mucosa in the process, so there may be a couple of them, but if you have 3 or 4+ growth, is that what you see with the acute sinusitis owing to Staph aureus when they actually occur given as infrequent as they are?

DR. GWALTNEY: Well, I am not an expert on the techniques you are talking about, and what you say makes sense to me. It isn't mucosa, though, we have got skin in there. The nasal vestibule is skin, and I imagine it's like those people that are trying to find how many bacteria down in the pores of the skin, and they put the tape on, and they pull it off, and it takes you many layers before you get rid of all those bugs, and I guess when they go in to get this specimen -- because they are not much further behind the vestibule when they put the needle in -- that there is just so much Staph there, they are getting it in the specimen, but it sounds reasonable to me that if you did good semi-quantitative cultures on a plate, that would give you the right answer most of the time for staph.

DR. RELLER: Let me make another analogy just to bring this together. Let's take a lumbar puncture. I mean occasionally get one or two colonies of Staph aureus, the

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Gram stain doesn't show Staph aureus, and we ignore that. I mean I think any clinician would ignore that.

We do get patients who have staphylococcal meningitis in conjunction with drug use, endocarditis, et cetera, or shunt infections. I mean you have got lots of organisms. I mean it is not a single colony.

So I think with excellent technique in obtaining the specimen from a presumed sterile site other than the new acute disease, that semi-quantitative cultures allow one to have the interpretive information that is necessary.

That is my own feeling and that one doesn't need to do a quantitation to make that determination. That doesn't mean that quantitation isn't important in making the determination, but one doesn't need the quantitative cultures to make the quantitative assessment is what I am saying.

DR. CRAIG: Brad.

DR. LEISSA: I can hold for Dr. Melish, because I have a different question, if you want to go with that.

DR. MELISH: I do a lot of quantitation of staphylococci, and I agree it is not very accurate, just to about one log when you do dilution methods, and you can use a loop and be very, very accurate with quantitated loops, but you can't just say, oh, this is 2+, 3+. I think you

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could devise an easy and cheap way for any lab to use a quantitative loop and answer the question are there more than or less than 10^4 Staph aureus, but you would have to streak the whole plate in a way you do for a urine culture.

So, it doesn't have to be done with the dilution method, but if Dr. Gwaltney is certain about the 10^4 and that is the standard, that is not a hard standard. The other question is can they just do qualitative cultures for all the rest, and that is probably true.

DR. CRAIG: And I think that was the question that was brought up yesterday by the presentation from industry, was specifically not to have quantitative counts for the major organisms. Am I correct on that?

DR. SCHWARTZ: Yes.

DR. CRAIG: Is this still related to this issue?

DR. SCHWARTZ: Yes.

DR. CRAIG: Dr. Schwartz.

DR. SCHWARTZ: I do a lot of ears, not that many sinuses, but I have done thousands of ears, at least more than 1,000, and sometimes I will get a single colony of pneumococcus or five colonies of pneumococcus, and if I were held to the standard should that particular patient or those patients be on a study, I would have to exclude them, and yet I am very certain that they had pneumococcal acute

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otitis media. I mean it is in absence of anything else. I have to sometimes hunt on the plate with a magnifying glass.

DR. CRAIG: I would agree with you. I mean I think that is an organism that is a more delicate organism, and clearly can be seen with a Gram stain and not grow out, but staph, on the other hand, tends to be a relatively hardy one, and so I think it is much less likely to have that discrepancy between being the cause and having a single colony come out.

Yes.

DR. LEISSA: I just wanted to revisit for a second for clarification. In the Points to Consider, which talk about there being two trials, one being a clinical trial, a large clinical trial, the other one being the clinical micro, relative to the comments to the discussion about x-ray being done, sinus films.

Dr. Gwaltney, do I understand you to say that you do not think that they should be considered evaluability criteria for someone to enter into a study with acute sinusitis or did I misunderstand?

DR. CRAIG: And you are still going to do one of them, is this going to be a clinical trial where there is no puncture at the beginning?

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DR. LEISSA: Right. That is the one I am really asking about, there is no puncture and you are saying how can you increase your specificity if they have the condition.

DR. GWALTNEY: I would think that if you are not doing punctures --

DR. CRAIG: That is the question that I also brought up, would you even want to further specify what you see on the x-ray, in other words, would you want to see CT scan with certain findings to try and increase the yield that you are dealing with, a bacteriologic infection, and not just a sinusitis, or the fact that, as you also mentioned in your article, if you wait out, so this is past seven days, the time that the cold would resolve, that alone tends to -- which I think is the criteria that are listed here, you were talking out beyond seven days, that that alone with x-ray is enough to ensure that you are batting about 60 to 70 percent.

DR. GWALTNEY: I honestly think that is about as good as you can do, but I think what Dick said does have some -- well, he was using it a different way, but to give the patient the competence that a puncture was indicated, I think there is some value in that, but what I said was really that when we did them or didn't do them, the recovery

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rate of bacteria, using mainly then a very experienced otolaryngologist, it really didn't change.

DR. CRAIG: Yes.

DR. ALTAIE: Being a microbiologist, I can't get away from counts or not counts. I want to sum up the idea of having an aspirate being the sample, nicely collected like Dr. Reller would like to see, and have the three major organisms considered as growing in there, not considering their counts at all, as a positive culture, and when you look at Staph aureus, require a count of greater than 10⁴.

Would that proposal be acceptable?

DR. CRAIG: I think that is the hint of what I have been getting from the committee here, is what they are looking at, yes.

DR. ALTAIE: So if we have three pathogen, no count consider --

DR. CRAIG: They are organisms that are more difficult to grow at times, so you could see situations where you would only get a few of them out, and so the presence of the organism is fine.

DR. ALTAIE: Is significant.

DR. CRAIG: Yes. Is there anything else that we have, did we cover -- I guess I am trying to get back -- the question of chronic sinusitis?

DR. ALBRECHT: The question of acute exacerbation of chronic sinusitis.

DR. CRAIG: Sort of like the infectious disease, the ENT's man chronic fatigue syndrome.

[Laughter.]

DR. CRAIG: What was the specific question you wanted to ask on chronic sinusitis, should we develop criteria for it?

DR. ALBRECHT: Is it an entity, and how do we study it?

DR. CRAIG: Jack?

DR. GWALTNEY: Well, first off, I think it is important to separate patients who have and who have not had surgery. In the first group, the ones who have not had surgery, as far as I know, we really have virtually no information from puncture studies on these patients as to whether bacteria have anything to do with this or not.

I think we all assume that chronic sinus disease comes from acute sinus disease, but I think there are other ideas people have that maybe there are various categories and some of these patients have more problems with allergic problems or other things, and it is not just a simple thing that sinusitis didn't get treated properly, although I don't know that.

I mean the first thing I think we really need is to have some studies done, and it would be very easy to do these studies, patients that are going to surgery to functional endoscopic surgery, have a puncture done first and see what grows. It has not been done. If we could get the otolaryngologists to agree to do that, that would be a wonderful piece of information to have.

Then, you would know whether it is reasonable to try to treat them with antibiotics because then you would know what is growing or not.

DR. SCHWARTZ: But so many of them have been treated and retreated, and treated again, and treated a fourth time.

DR. CRAIG: The ones that I have clearly had problem with are the ones that I have seen after surgery, where they have been told to flush this out with saline or something, and they decide, well, I will just use the tap water around, and then all of a sudden we have a Pseudomonas or something. I mean there is crazy things like that, that get the organism or unusual organisms up there, but you are right, getting taps and finding out what you are dealing with at the time of surgery would be the time to do it.

DR. GWALTNEY: The ones after surgery, like you say, they have Pseudomonas and/or other gram-negative

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Serratia, and they have staph, and they are continuously infected. I don't think colonized, they are infected, they have crusts, they have the thick stuff that we have all seen, and I think those bacteria are a major part of the ongoing disease. I don't think that is why they originally the chronic sinus disease.

There certainly could be trials to see if those patients could be cured. They also have osteitis, and Dr. Kennedy and otolaryngologists in Philadelphia, is working with some of the people at Hopkins, and the distortion of their facial bones, those little bones, is as great as it is in bones in the spine with osteo, so we may be dealing, not only with a soft tissue infection, but with a bone infection in those patients, and there have been no real control trials.

We have tried to treat some of those patients long term with the idea we are going to treat them six or eight months, and we have had a terrible time trying to get that long, they get reactions, all these problems happen. So whether that would cure them or not, I don't know.

DR. LEISSA: Dr. Gwaltney, are your comment applied both to chronic sinusitis and acute exacerbations, or do you distinguish the two, and where one might be more amenable to antimicrobial therapy?

DR. GWALTNEY: Well, you really can divide patients with chronic sinus disease into three categories. We have talked about two of them. One is post-surgery category. The pre-surgery category, some of those patients, if you puncture them, you will grown pneumococcus, H. Flu, moraxella, and Dr. Gross in Charlottesville did a study in patients who were going to surgery, they were getting operated on, did the punctures. Lo and behold, they grew pneumococcus, H. flu, out of these patients.

Now, I don't know how to interpret that. I believe the results. Is this the original cause of their infection, were they just unlucky and had the exacerbation, but if they were having exacerbation, they shouldn't have been being operated on, so I don't want to get into that, but that is what they found.

DR. CRAIG: Dr. Reller.

DR. RELLER: Dr. Gwaltney, for chronic sinusitis before an acute exacerbation, what is the state of the flora or absence thereof, is there an analogous situation that once one gets to a certain amount of damage from the middle meatus over the curve infundibulum that, in fact, what is in the nose is in the sinus, whether or not there is new activity with some superimposed organism, is there an analogous situation to chronic obstructive pulmonary disease

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with colonization of the airways at all times with periodic exacerbations?

DR. GWALTNEY: If you accept the fact that in order to answer that question, we have to do punctures on patients who have not been operated on, don't have antrostomies, if you accept the fact that you really have to do punctures and maybe quantitative cultures to answer that question, we don't have any information.

There are studies done at the time of surgery, but as you know, by then, they are grossly contaminated tissues, they have been in and out, in and out, so when you snip off a little piece of stuff and throw it in the pan, there is obviously no way you can interpret that, so we don't know the answer to that question. That is the study we need to do.

DR. CRAIG: The workers that work with anaerobes always have tended to imply that anaerobes are an increased problem in chronic sinusitis. Is there data to support that?

DR. GWALTNEY: Only one investigator has really found that, it has just been one person, and the others have found that. The other point would be, as you know, anaerobic infections are pretty obvious, when a patient

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opens their mouth, that they have got a true anaerobic sinusitis, you know it.

So these infections in the average chronic sinusitis patient does not have those kind of clinical things to go along with it, so I am somewhat skeptical of that. I know that is considered as one of the causes, but I really -- the answer is the studies have not been done.

DR. CRAIG: Any other questions, Dr. Albrecht?

DR. ALBRECHT: No, I think that covers it, thank you.

DR. CRAIG: Let's take a break. We will start in about 20 minutes.

[Recess.]

DR. CRAIG: The last topic we are going to cover today is acute otitis media. Brad Leissa will be doing the FDA presentation.

ACUTE OTITIS MEDIA

FDA Presentation

DR. LEISSA: The last for today. I have given to the committee members handouts or copies of the slides because there is some differences between what is in the guidance document and what I have on the slides. Some continued thinking since those were finalized. There are also a few copies down at the end of the table there if any

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of the sponsors would like a copy, and also our design is to have these available on the worldwide web site, CDER's home page, so you will be able to access all these slides, as well.

DR. CRAIG: That is the biggest response I have seen from the people out there today. We have been hoping that you people would make a lot more comments about things.

DR. LEISSA: Well, at least you know they didn't need to stretch, they just had a break.

Here, we talk about the evaluability criteria specifically for the systemic anti-bacterial drug products. I put in parentheses "bacterial" between the acute and the otitis because obviously for anti-infectives that is what we are looking for and that is what we are trying to recruit in these clinical trials, knowing that we are not going to be perfect, but that is still our goal.

I am going to digress just for a minute for everyone to kind of rethink where we are, why are we doing these evaluability criteria, why are they important.

If you think about what goes on in the whole drug development scheme, you have the drug developer who is doing planning of their studies. They go out, do the clinical trials. That information then goes back for analysis, then, for future planning, back again to the sponsor for further

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analysis, and then, hopefully, if everything goes smoothly, over to regulatory review at FDA; then down for, hopefully, again approval, labeling for that drug, and then on for eventual, and the world driver here is promotion, what is it that a sponsor can say about their product.

Now, where there have been challenges in the past is this point here, where the expectation of what the developer is doing, and what the Agency is reviewing, aren't necessarily on key, and that is what we are trying to achieve here with the evaluability criteria.

So off my soapbox for a moment, this is a closed book pop quiz now, so, please, all papers done on the floor, and we will be grading everybody here, and also whoever gets a perfect score gets a signed autograph copy of the evaluability criteria document from all the people in Anti-Infectives.

So here is the first question. Name a systemic anti-infective drug product whose only approved treatment indication is acute otitis media. Now, some of you already know the answer. Go ahead, Dr. Craig. No.

[Laughter.]

DR. LEISSA: Anybody else?

DR. CRAIG: The only approved?

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DR. CRAIG: The only approved indication. It is not approved for anything else.

DR. SCHWARTZ: Pediazole?

DR. LEISSA: Yes, but you saw the sheets, didn't you?

[Laughter.]

DR. LEISSA: That's okay. We will assume you knew the answer. Very good.

DR. SCHWARTZ: You didn't say I couldn't cheat.

DR. LEISSA: Actually, I had the hint here. It was approved in 1979, but, indeed, it is Pediazole with the only approved indication.

Okay. Extra credit. From the following list, identify all approved pathogens in the Pediazole package insert. So, of those five, it can one, or two, three, four, five. Which of these are approved for the Pediazole package insert? Extra credit. Any ideas?

[No response.]

DR. LEISSA: I don't have a hint for this one, I am sorry.

DR. SCHWARTZ: I will keep mum.

DR. LEISSA: In the interests of time, the answer is Hemophilus influenzae is the only approved pathogen for Pediazole.

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Question No. 2. Name at least two systemic anti-infective drug products which are indicated for the treatment of middle ear infections due to staphylococci. Name at least two, but the correct answer for extra credit would be there are four that have that.

Anybody want to throw out some drugs that are approved for staphylococci?

Keflex, one. Ceftin? No. Augmentin? No. Biaxin? No. Ceclor? Yes.

The full list, well, we got two there. The full list are Amoxil, Ceclor, Keflex, and Spectrobid or bacampicillin, and the caveat is that for Amoxil and bacampicillin, it's for non-penicillinase-producing staphylococci. There aren't too many of those around nowadays.

But the reason we are doing this is there is some obviously history about labeling that we have done for this indication that has gone on over the years, and some things may seem out of sync today, but it is still interesting, and we have to keep that in mind from where we have been to where we are going.

So, how about the labeling timeline for acute otitis media? Back in the 1960s or so, I don't have the exact date, but we began seeing approvals labeling that

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reflected otitis media or ear infections and up here to most recent.

So, in the 1960s to 1970s, we saw two different types of labeling that occurred. It was either reference to pneumococcal infections of the upper respiratory tract, including otitis media or infections of the ear, nose, and throat due to whatever organism, so pretty global claims.

Then, in 1997, Anti-Infectives came out with this Clinical Evaluation Guidelines. In there, there was about a two-paragraph thing about what you needed for otitis media, and probably the important things that happened back then was that you had to have four weeks of follow-up to be able to make an assessment, and anybody who was to be considered evaluable had to be microbiologically and clinically evaluable. There was no clinical-only population.

In light of this guideline and discussion of a term of otitis media, you actually see the use of otitis media or acute otitis media in labels.

In 1990, you see the first of those two drugs that are currently approved, that have acute bacterial otitis media, and that was seen in 1990, and then in 1992, as we all know, there was the Anti-Infectious Points to Consider document and the IDSA/FDA Guidelines.

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It is funny, often I hear here, even though they really are the IDSA/FDA Guidelines, because it says on the blue binder of Clinical Infectious Disease, my colleagues here, we refer to it as the IDSA Guidelines, and when you go down to IDSA, they call it the FDA Guidelines. I don't know what that means.

Here, of course, here we are in 1997, talking about evaluability criteria.

So, again, why are these important? The otitis media labeling history has been varied and diverse. We have to think about that as we move forward with regards to labeling and why we are talking about evaluability criteria as pertains to future labeling and promotion.

Of course, what is studied and what data are collected determines what can be stated, labeled, and promoted about a drug, that simple.

Let's dive into the thick of things. This is the definition that is currently in the document, and based on some conversations with people, this can obviously be improved upon as the definition, but the definition in the document is "Inflammation of the middle ear, manifested by localizing signs or symptoms such as ear pain, hearing loss, nonspecific symptoms like lethargy, fever, irritability, nausea and vomiting, and characterized on otoscopic

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examination by inflammatory changes in the tympanic membrane."

Some of the symptoms that we are referring to here, because language is very important, and definitions, we are talking about acute bacterial otitis media, acute suppurative otitis media, acute purulent otitis media, and acute otitis media with effusion (AOME), but we are not talking here about the serous otitis media or secretory otitis media, and we are not talking about chronic otitis media with effusion where a middle ear effusion is present for at least two months, nor chronic suppurative otitis media where there is a perforation of at least six weeks. Those are definitions that are frequently used.

Study considerations. In 1992, the Points to Consider came out, and we have mentioned that many times so far in the last day and a half. Although these were previously addressed by the advisory committee and we are not obviously here to rethink the Points to Consider, but we can't think about them in isolation either.

So in that guidance, it talked about there being two trials suggested, the first trial being a clinical-only comparative study where you only tapped through the tympanic membrane those children that failed; and then a open clinical/microbiologic study where you had patients that

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were tapped at entry, and you tapped the failures, and that at least -- and this is the only place that is really discussed in terms of numbers of bugs, but for this indication it talks about there being at least 25 Hemophilus influenzae, 25 Strep pneumoniae, 15 Moraxella catarrhalis, the Big 3, not to be confused with Dr. Brown's the Big 3 for febrile neutropenia yesterday.

Also, it discusses about the use of restricted labeling, i.e., not for first-line therapy. There actually hasn't been a drug yet that has this specific wording, "not for first-line therapy" for this, but there are two antimicrobials, cefixime or Suprax, and ceftibuten or Cedax, where the main pathogen in acute otitis media, Strep pneumoniae, is not included as one of the due-to organisms in the indication for acute otitis media.

One thing you should ask yourself is, well, if back in 1997, the Division was requiring that to be evaluable for this condition, you had to be microbiologically evaluable, and now we were saying clinical only is okay, but tapping the failures, what happened in that interim period.

One of the things that happened was that the Division was approached by many sponsors saying that it was very difficult for them to go out and recruit investigators

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that were willing to do tympanocentesis, and that if we really wanted tympanocentesis, they were going to have to do these studies overseas in Europe. So that was part of the thinking that went behind saying, well, let's see if we can get by with this clinical-only study and just make sure it is a really well conducted study and design.

DR. SCHWARTZ: Brad, just a quick question. These 25, 25, and 15, it is my understanding that a single child with bilateral acute otitis, that has both ear taps, two of those 25 can be accounted for by that single child.

DR. LEISSA: In terms of from a counting perspective? You mean if they had Strep pneumo in both ears?

DR. SCHWARTZ: Yes.

DR. LEISSA: No. That wouldn't be something I would expect to see in the Division.

DR. SCHWARTZ: Okay.

DR. LEISSA: Inclusion criteria. We are talking about children here obviously, males and females, typically over 12 weeks of age, and in some cases we have had a few adults that have been studied, but it is pretty rare because the condition obviously is fairly infrequent.

Baseline clinical assessment. Signs and symptoms consistent with acute otitis media. Pneumatic otoscopy

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where one would hopefully be looking for a bulging tympanic membrane, and that the critical thing, though, here is that hyperemia or redness of the TM alone is insufficient.

Everybody knows that any child that cries has a red TM.

Loss of light reflex is mentioned in the document and decreased TM mobility. This obviously brings up the issue about, well, how good are clinicians at assessing dermatoscopy. Some studies have said that in the best hands, that investigators are wrong 20 percent of the time, and that is in the best hands.

Tympanometry or electroacoustic reflectometry, which are two techniques to assess TM mobility. I have here the optional, and it is going to be an issue for discussion with the committee later.

Other criteria. Thickening of the TM indicates a chronic process and should be noted.

Otitis externa should be distinguished from acute otitis media.

Bilateral otitis media should be distinguished, should be noted from unilateral left, right otitis media.

Children with a perforated TM may be included. The caveat here being in the clinical, clinical-only study, and I know that Dr. Schwartz will have some comments about that later, but the idea being in a perforated TM and a

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micro, will you really be able to assess the microbiology of that.

Antihistamine and decongestant use during the study period should be recorded and reported.

Microbiologic assessment. Identify which middle ear effusion was sampled, left versus right, although if bilateral otitis media, we would expect that both ears, the attempt be for both ears to be tapped, because they can be discordant in approximately at least 20 percent of patients, i.e., you could have Strep pneumo in one ear and Hemophilus influenzae in the other ear, or one culture negative and one culture positive.

The report in-vitro susceptibilities relative to study drug and the active control, and, of course, if one of the study drugs is the beta-lactam, report the beta-lactamase activity for the Hemophilus influenzae and Moraxella catarrhalis.

Exclusion criteria. Tympanostomy tubes present at baseline. Another issue which is somewhat open to discussion is how much time do they have to be off drug before they come into the study.

The idea that in the clinical-only study, you could say no drug for the previous seven days, but in the clinical microbiologic study, where the child is coming in

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and having failed another drug regimen after having three days knowing that you are going to get a positive culture to make the child evaluable, that that should be sufficient.

The caveat here is that children with recurrent episodes of acute otitis media may be enrolled but should be analyzed separately, recurrent being defined as at more than three episodes in the past six months.

One of the key things in terms of us doing our number counting or rule counting in determining evaluability of patients is where do they fall in the evaluation or evaluability windows that Dr. Albrecht already went over in her slides. So we have here obviously entry, and I am just calling that arbitrarily here study day 1.

Then, on-therapy visits being study days 3 to 5, and I have what is listed here as optional phone call not required for evaluability, but clearly to have the contacts, so that if the child isn't doing well, they know to come back in, so the child is protected in the study.

Then end-of-therapy visit, and I have here stipulated this is not the test-of-cure visit, because we have had applications come in where all the analysis was centered around end-of-therapy when we really want to see what the efficacy is off drug.

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Then, early post-therapy being days +7 to +14, 7 to 14 days post-therapy after finishing the therapy, and obviously, as other people have discussed, that may change depending on the pharmacokinetics and dynamics of the drug and the bug, and that being the test-of-cure visit, remembering that back in 1977, at that time it was stated that the test-of-cure visit was actually one month post-therapy.

If persistent middle ear effusion, then late post-therapy visits, days +30, +60, and +90. I know we are going to have some interesting discussion about this, and this is something that I am putting in mostly because it is something that is in the IDSA/FDA Guidelines. The implication that I read from those guidelines is that monitoring middle ear effusion persistence is important somehow related to antimicrobial therapy, and I personally have some questions about that, and I know other people do, too.

So, in contrast, the IDSA Guidelines specifically say that the visits should be -- so you have some contrast relative to what we are proposing -- study days 3 to 5, and obviously, there would be the entry visit, study days 10 to 14 four weeks after entry, and 6 to 8 weeks after entry.

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In terms of assessing clinical outcome, the key thing here, the overall clinical assessment is based on the patient, not on the ear.

So you have clinical cure, signs and symptoms resolved, and the effusion resolved.

You have clinical improvement where the signs and symptoms are resolved, but the effusion persists, and then you have clinical failure.

And clinical failure and all failures should be carried forward. Clinical failure is defined as "Lack of improvement or worsening of symptoms within 72 hours of entry."

Concurrent systemic anti-infective drug use during the study period, entry and study period being defined as from the entry to their last observation. It is not the time that they are on antimicrobial, but the study period.

And insufficient improvement or relapse by end of therapy or the test-of-cure visit; TOC, test-of-cure.

And then there is obviously the issue of relapse, reappearance of signs and symptoms after therapy concludes. Well, one, of course, should ask the question, well, is that really essential to making an assessment a drug's efficacy, do you want to distinguish failure from relapse or do you just lump them all together as failure.

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Again, so you have the perspective of IDSA/FDA Guidelines, failure is defined as lack of resolution within 72 hours of the onset of therapy; relapse, as being reappearance of signs and symptoms after initial response or during or within 4 days of conclusion of therapy, and they make this additional definition of recurrence, which is more than 4 days after therapy if the signs and symptoms reappear, then, that is considered recurrence.

How about microbiologic outcome? Unlike the clinical, microbiologic outcome can be per ear as long as you do capture which ear was tapped, and the microbiologic response in otitis media naturally is often clinically driven. Even in the failure sometimes, the parents will refuse to let their child undergo the tap.

So you have eradication, documented whether the tap was done versus presumptive. For persistence, you have the documented tap, again presumptive. Then, there is the issue of superinfection and whether or not you want to distinguish superinfection being that new organism that occurs on therapy versus a new organism that occurs post-therapy, whether that distinction should be made.

Again, IDSA/FDA Guidelines. These are the four that are defined - eradication, which they have listed as presumptive; then, there is an entity called suppression,

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which is the baseline pathogen not identified on therapy. What I learned from that or my understanding is that if a child fails clinically, and they retap the ear, but the bug isn't there, it is not that it was eradicated, it is that it is suppressed.

Persistence - presumptive versus confirmed following at least 72 hours of therapy.

Superinfection - new pathogen following at least 72 hours of therapy.

So, who is evaluable after all this? Let's look at the clinical-only study first.

Well-documented signs and symptoms of acute otitis media, require baseline tympanometry? Again, this is an issue I think we need to discuss.

Eighty to 120 percent of the proposed (labeled) dosing - unless early failure.

No concurrent anti-infective drug use during the study period.

Assessable at the test-of-cure visit, earlier failures carried forward.

No systemic anti-infective therapy for the previous 7 days. Again, the clinical-only study.

No tympanostomy tubes at baseline.

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How about the clinical/microbiologic study? Most of the things that I just said in the clinical-only study apply plus isolation of a susceptible baseline pathogen, again, one of the Big 3, using appropriate sterile technique, although we must keep in mind as we are going through this discussion that at least one-third of otitis medias will be culture-negative at entry.

The baseline treatment failures are acceptable as long as the baseline pathogen is susceptible to the study drug. If they failed the previous drug therapy, the baseline pathogen should be resistant to it.

Perforated TMs, the idea in the document is that they not be evaluable, but I am sure there will be some discussion about that, as well.

So, we are to the end where these are some of the issues I would like to leave with the committee to ponder.

The first issue to ponder is for the clinical-only acute otitis media study, in the interest of increasing diagnostic specificity at entry, are there minimal baseline clinical findings and/or tests that should be required for evaluability, for example, tympanometry or electroacoustic reflectometry where age appropriate, the idea being obviously we want to be able to distinguish bacterial from viral from other causes.

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Issues to ponder No. 2. What is the appropriate timing for the acute otitis media test-of-cure visit, knowing that again 1977, it used to be a month post-therapy? This issue I would like to raise, knowing that PK and PD is obviously critical to making that determination, but can we come up with some idea independent of the PK/PD about what is at least a minimum time to make that test-of-cure visit.

Is one to two weeks, as proposed in the document, sufficient time to assess a drug's efficacy in the treatment of this condition?

Issues to ponder No. 3. In light of Anti-Infective's Points to Consider document, for the clinical/micro study, it is currently recommended that 25 Strep pneumoniae be monitored, is that sufficient depending on the drug in light of increasing concerns about resistance or should greater Strep pneumoniae experience be sought in designing clinical trials?

Really, a follow-up to that, the same question is depending on the drug again, for example, beta-lactam, should acute otitis media clinical studies be conducted in geographic areas where Strep pneumoniae resistance and/or beta-lactamase resistance are known problems?

That means would one require that at least X percentage of the studies or the patients enrolled in the

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studies came from areas where it was known that resistance was an issue.

The last issue to think about is in IDSA/FDA Guidelines. It states that, "Patients should be followed up clinically and by otoscopy biweekly until the middle ear effusion has completely resolved. The time to resolution of the middle ear effusion should be recorded."

This implies, if I read that correctly, that a drug's efficacy claim for the treatment of otitis media should somehow be linked to middle ear effusion. So the issue is, should otitis media clinical trials for drug approval be designed, and therefore an evaluability criterion, to assess the time to middle ear effusion resolution.

That's all.

DR. CRAIG: Thank you, Brad.

I guess for the committee, Marian Melish is going to discuss.

Committee Presentation

DR. MELISH: Hello. I am Marian Melish. I am an infectious disease clinician in pediatrics. I am also board-certified in pediatric emergency medicine, and I work in the emergency department once a week. I am not an expert on otitis media, but I do see a large number, and I am going

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to try to bring a skeptical approach to the problem of design of clinical trials. We are actually trying to see whether my new computer actually made my slides.

First of all, one of the biggest problems with the diagnosis of otitis media for study purposes is to actually confirm that you have otitis media as the clinical problem at hand.

We find otitis media is routinely overdiagnosed in children who are under the age of four years. The associated symptoms are not specific. Children of this age often cannot or will not tell their doctor or even their parents that they are having ear pain.

I continue to be amazed at the variability of the appearance of the tympanic membrane, a very small membrane, but it can look very, very different from child to child. Pneumatic otoscopy, which is mentioned as very important in the Points to Consider and particularly the IDSA Guidelines is definitely subject to observer bias, and in the case of an investigator, the investigator himself is rewarded for subject accrual and may overdiagnose otitis media.

Therefore, two of three observers might be needed to actually confirm if you are going to go on clinical grounds alone in the diagnosis.

The response to this, to my way of thinking, means that we should objective studies, and tympanometry and reflectometry are practical, and a trial has been published just recently in Pediatrics in January of 1997 from the Boston Multicenter Otitis Media Group in which they had objective studies on all patients. So this is definitely practical.

I think there is no way around it, but tympanocentesis should be encouraged. This is a way of making certain that we have an objective diagnosis.

I question that tympanocentesis is such an invasive procedure. Certainly we can't describe any horrible sorts of things to the audience as far as tympanocentesis compared with antral puncture, which we are agreed should be done.

The tympanocentesis probably has a significant therapeutic value maybe for all children, but certainly for older children who complain bitterly of ear pain and can get instant relief.

Something that hasn't been mentioned is that blood culture is positive in a considerable -- well, a small proportion -- but a certain proportion of patients who are diagnosed with otitis media, and this could also be of value

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as an additional test, particularly if blood is going to be taken for monitoring of toxicity.

The current clinical practices are quite at variance with finding objective studies, and diagnosis is made by unconfirmed clinical judgment, usually by one clinician. This includes many patients who don't have acute otitis media, but have nonspecific fever with red TMs, frequently in this age group have human herpes virus 6 and 7, the most common causes of febrile illness in children under 18 months, URI perhaps with sterile effusion, enteroviral and multiple other illnesses.

Although clinical practice guidelines are pending, in general, amoxicillin and Bactrim are considered first-line drugs.

In looking at response to clinical trials only, there is a high frequency of spontaneous resolution of acute otitis media that is probably much more frequent than the 30 percent that was cited in the IDSA/FDA Guidelines.

In the United States at the present time, there is a very low frequency of serious suppurative complications, so this certainly would be an example of a significant failure, but it would take a large study to demonstrate very many people who are on some form of therapy who had serious suppurative complications.

It is very common to have persistent middle ear effusion beyond therapy, and there are local differences in antibiotic susceptibility, although as time goes on, these local differences are really blending out, and large proportions of the country are experiencing pneumococci that are resistant.

The question is what are the aims of the antibiotic treatment, and I found it necessary to remind myself, well, we wish to sterilize middle-ear fluid, but we haven't set up our studies to demonstrate that we are able to do that.

We wish to relieve the associated signs and symptoms. We wish to resolve fever in three to five days, a very important time point, but not all patients have fever. To me, the older children who have the worst looking eardrums and most complaints of pain, and the ones you can make the most secure diagnosis are frequently not febrile.

In the young child, by contrast, you wish to relieve the pain and the irritability, but you may be unable to assess this or distinguish it very well from whatever else may be going on.

Certainly early it takes more than three to five days to improve the appearance of the tympanic membrane, and

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the question about resolving effusion is one that will take much more time.

So, my recommendations are that we should think of every way we can to enhance the diagnosis, so that we are studying patients who actually have the condition that we are most interested in studying, so I think this absolutely requires objective measures - tympanometry and/or reflectometry.

I think that it would be important to see that there are multiple observers for clinical descriptions, particularly to agree on whether or not there is abnormalities by pneumatic otoscopy, and if there are no objective measures, there certainly need to be much more observer standardization. This could be done by clinical centralization and investigator education.

I think that if we are going to seriously ask -- and I think it is an important point -- that patients who fail should tympanocentesis. This means that we need to encourage and provide investigators with education to perform tympanocentesis, and I think we should enhance diagnosis precision and improve our microbiologic association perhaps by blood cultures at study entry.

I was startled the first time I saw a presentation at the FDA about otitis media treatment to find that a drug

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that is not considered a first-line drug in the pediatric clinical community was used as the comparator drug.

I am uncertain as to what should be the comparator drugs, but it does seem important when you are looking at patients who are referred for otitis media, who have not necessarily had recent clinical failures, that they should be compared with what they would be likely to get in clinical practice, which would be most likely to be amoxicillin or sulfa/trimethoprim.

We don't honestly know how important penicillin intermediate and resistant pneumococcus are in treatment failure. There is general advice that you should choose a comparator drug that will respond to local susceptibility patterns, but this may not be appropriate in this time of flux with increasing amount of resistant penicillins, and of course, if we are going to be comparing, as have been recently done, things like injectable therapy with oral therapy, short-term therapy with long-term therapy, there are going to have to be some way to maintain the blind.

We are facing a major challenge with antibiotic resistance, so I think that at this point, it is clear we have to increase the number of patients that are evaluated in clinical microbiologic studies, and there needs to be special attention to see that we have a considerable number

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of organisms that are penicillin intermediate and penicillin resistant that are actually causing disease in patients.

In order to facilitate increasing this number of patients with microbiologic evaluation, I think it might be important to nest the clinical-only and the clinical-microbiologic studies. That is, if all investigators who are carrying out a study for a sponsor were knowledgeable and committed to doing tympanocentesis on the failure patients, they could also choose an appropriate subset of patients in which to do clinical microbiologic studies at the same time.

Therefore, the clinical sites could be the same, and that would probably increase geographic diversity in patient accrual.

There were questions about what should be adjunctive therapy. At least I think that antipyretics are well established in the care of sick children and antipyretics do not remove fever in children. They definitely lower it. Except for the fact that you may lose the ability to measure fever at an office visit, something which is variable anyway on study day 3 to 5, parents should know that their child is much better, their fever has resolved or not, even if they are administering antipyretics.

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There is abundant evidence that there is no value to using decongestants, and I don't think they should be allowed. Antihistamines, however, might be needed by certain children for other indications, but they shouldn't be used as part of the treatment of URI or acute otitis media, so I think it would be important to explain their lack of usefulness in those conditions to patients who are enrolled.

I thought we should clarify outcomes, and as I have been listening this afternoon, I think probably the most important thing would be to clarify outcomes by clinical cure or treatment failure, and leave this category of clinical improvement, which Brad and I both put on our slides, but leave this category out and instead look at the question of persistent middle ear effusion as a separate question altogether.

Finally, I would like to say that in terms of the visits, I am thinking that in order to also get the information and make it easy for the subjects to comply, the entry visit is important. The 3- to 5-day documentation of how the child is doing with the absolute requirement to see the patient if they are not doing well is important.

I am not at all certain that an end-of-therapy visit does very much. The longer I see patients in follow-

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up for otitis media, the longer I like to wait before I decide whether they have had a good response or not, and so I am not sure that much is gained by an end-of-therapy visit, but a test-of-cure visit at least 7 days and perhaps as long as 15 to 20 days after completing therapy seems reasonable.

Then, I think a flexible follow-up with a defined endpoint for determination of middle ear effusion would be very reasonable. You could see the patient probably monthly, every two weeks is perhaps too often, and at 3 to 6 months, if the effusion has still not resolved, then, that could be counted as an endpoint, middle ear effusion either present or no longer present.

I would just like to say I think this has been a very exciting day. I think that we have been talking about bringing more science and tightening up a lot of evaluation guidelines, and when I look at otitis media and the progress we have and haven't made, I think in the area of therapy, we very much need to make certain that we have got as objective criteria as possible to identify which patients are actually afflicted with the illness we are trying to study, and I think we have to be very careful of the choice of comparators.

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I think Brad gave me a list of at least 16 antibiotics that are approved for use in otitis media, 2 of which, well, at 3 or 4 of which are probably inappropriate, so that if we don't choose with care the comparators to reflect the current clinical practices, we are also going to be perhaps comparing one ineffective therapy with another ineffective therapy.

Thank you.

DR. CRAIG: Dr. Schwartz.

DR. SCHWARTZ: To be last is a joy. I will try to make my comments as brief as I possibly can. I would probably like to say a lot more than the time is allotted.

First, Brad, you had a list of some questions that I would like to make some comments on for people to at least think about and possibly for discussion if we have time for that.

One is the diagnostic criteria. It is often said that one-third of cultures of the middle ear when tympanocentesis is done are expected to be negative, and I believe this to be entirely erroneous. If one has good criteria to begin with and knows how to perform tympanocentesis and knows how to get the specimen to the laboratory, and the laboratory knows what to do with it, I

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really think that only 10 percent or less of acute middle ear infection should not yield pathogenic bacteria.

I have shown this in about 250. We have reported it time and time again. The better you are at your criteria, the smaller that one-third will become.

Regarding criteria as far as what constitutes acute otitis media, the most important thing is the thing that is often left out, and that is the contour of the eardrum, so that if you don't have a bulging or almost bulging contour of the eardrum, with the eardrum going out towards you, fluid under pressure the best definition, because of presumably rapidly multiplying bacteria and inflammatory products of that reaction, the chances of you getting viable pathogens from the middle ear decrease significantly.

The Scandinavians in this decade did 1,000 tympanocenteses -- I gave Brad lists of the reference for that -- and they looked at which ones were likely to have pathogens, and when they found eardrums in the neutral position, although immobile and maybe red versus those that are under pressure regardless of the color, but they must be opacified, they are going to get 85 to 90 percent pathogens in the bulging group and about two-thirds pathogens in the other group.

As far as symptoms, there has to be more than something -- I think it should be quantifiable, something like a 25 percent change in the baseline behavior of a child -- we are talking children now, whether that be sleep, eating, periods of happiness or periods of unhappiness and consolability, some way of consoling what is pain, merely a wrinkled brow or crying for two minutes versus crying for an hour.

A lot of that I think we need to know what each child has, because a drug may act differently in the very, very toxic-producing bacteria in the middle ear. Give me a rip-roaring pneumococcus versus a quiescent pneumococcus, and I will show you one even if you don't cure the disease, there is not going to be much difference in the child, whereas, the other one, if you don't cure the disease, we had just last week two cases of mastoiditis on treatment with antibiotics not known not to be very effective against the pneumococcus. These were surgically treated children in the middle class, definitely took their medicine, and we will begin to see that very thing again.

Those were the only two I had in 25 years, by the way, one was mine and was another one of the doctors.

Mobility, talking about the pneumatic otoscope, the original description of that in 1864 by Dr. Siegle, and

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it's called the Siegle otoscope, was a biphasic maneuver, so that Dr. Siegle's description in German was you first seal the otoscope speculum into the ear and then you rarify the ear and the ear canal by sucking gently and to do that several times in succession in order to see if the eardrum is retracted, and then and only then are you allowed to gently puff in a very, very small way to see if the eardrum responds to positive pressure.

For instance, a child who has middle ear fluid, some degree of inflammation, a red eardrum, and a very retracted eardrum, will have immobility by every criteria that is used for evaluating antibiotics, and that is ridiculous because you are not going to find pathogens very often in that ear, so you have to have biphasic pneumatic otoscopy the original way it was intended, and the only way that it is going to make sense.

Tympanometry, I agree is very, very important, more important perhaps in the clinical trials, but also important in the bacterial trials. It gives an objective tracing or at least an objective enumeration in the acoustic reflex instrument to the parent that, in fact, this is a fluid-filled ear.

They are mightily impressed when they see that, they can understand that this is not just a earache from an

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insect bite, and it also gives an objective tracing, so that if a doctor is about to stick that eardrum with a needle, and the tympanogram shows a perfect A curve, I would hold my hand and say, gee, maybe I really have to take a second look, maybe I was too hasty in making that diagnosis. So it keeps me honest, and it should keep everybody honest.

There is one proviso or one caveat with the tympanogram. It doesn't have to be flat all the time. I am not sure what to do with C or negative pressure tympanograms because I don't think they correlate at all with acute otitis media, but there is a phenomenon called positive pressure peak tympanogram where the tympanogram is still positive in a peak, but it is in the positive pressure zone, +100, +150, and these correlate very well with otitis media with a thin, purulent fluid that still is still compressible and allows the curve to develop before the fluid thickens out later on in the course of the disease.

I believe perforated eardrums, as long as they are within the first two days or the first day, if you want to be more rigid, as long as you don't have a tube, it's a fresh perf, you have pus in the ear canal, you culture that pus and from that culture you have the Big 3 plus I would certainly allow Group A strep, the Big 4 middle ear

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pathogens, I see no reason why those should be excluded from analysis or not put into the study.

The mid-therapy visit, I find to be very important, the 3- to 5-day visit. I look at failures sometimes parents may not have realized that their children are as ill as they otherwise appear on more direct questioning, when one looks at the eardrum, it allows me to predict which antibiotics either have a very slow rate of efficacy of nonrate of efficacy, and will do a tympanocentesis on that ear if the child remains symptomatic. If not, I mark in my record watch this one more carefully. Perhaps they will get a phone call a day or two later, I will allow for some antibiotics to have a slow rate of clearing, but also this could be a true failure.

So if I didn't see that child until the end of therapy, and to me the end-of-therapy visit is not that much value. The test-of-cure visit is of value. The middle-of-therapy visit of value for reasons that should be obvious. The others you can easily do by telephone call or any other way. I will continue to see them if the committee insists, but I don't think they are productive visits, and they cause the patients extra problems and extra time in a very busy schedule.

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The time off of drug before entry, in my opinion, I think those that are microbiologically proven or bacterially proven studies should have a 3-day limit. If you are off in three days and a new onset increase in symptoms, a bulging eardrum, I am perfectly happy to say that that child has acute otitis media, and would be happy to enter that child in the study as long as the antibiotics tested were not in a very, very similar microbiologic spectrum as the one that they just came off of.

For clinical trials, I think the 7 days is perfectly fine.

I believe that in 25-25-15 should be at least 100 of pneumococcus scattered around the country, selected to be at least a few of the areas of high pneumococcal resistance, 100 nontypable H. flu, and maybe 25 or 30 moraxellas.

There has been some people that go around the country saying moraxella is the pathogen that doesn't have to be treated -- and that may or may not be true -- it doesn't go anywhere except the middle ear, it never causes mastoiditis, and basically, when we are including that, we are looking at the 85 percent that would resolve spontaneously.

I can't speak to the last issue, but what I can say is we had an abstract just accepted for the upcoming

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ambulatory peds meeting. We looked at 50 children with moraxella acute otitis and 60 children with nontypable H. flu, and we looked at every little variable that we can see, type of fever, duration of fever, color of eardrum, extent of pain.

There was no difference between those two pathogens in every single criteria. So, therefore, if you don't want to treat moraxella, I urge you not to treat non-type B hemophilus.

I believe that, in a final statement, that after 28 days or 30 days need to follow a middle ear effusion and an antibiotic trial is of no value whatsoever. The failure of drainage has nothing to do with the antibiotic even if it is supercillin, it is a problem of other dimensions, and has nothing to do with evaluation of the drug that I am expected to evaluate.

Thank you.

Questions and Comments

DR. CRAIG: Questions?

Is there a difference between pneumococcal otitis media and hemophilus and moraxella in terms of progression in symptoms?

DR. SCHWARTZ: Well, two of them stay where they are. One of them, if it is a virulent strain or you have

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host problems, can cause havoc. It can cause a necrotizing acute otitis media, especially Group A strep is the archetype villain for that, and can lead to rarely acute mastoiditis, and if you look at -- there is a Dr. Neilsen in Denmark, right after the Second World War, that reported on thousands and thousands of non-antibiotic, it is the best natural history study, and what he found, if the children had Group A strep, at least 5 to 10 percent of them were going to go on to horrible middle ear complications.

So you don't fool around, as I am sure you know, well know, that is one you don't fool around with, and of the pneumococci that are the bullies, the tough guys, you don't fool around with those. The other two, let them today, treat them tomorrow, treat them next week, I really don't care.

MS. COHEN: Do diseased tonsils have anything to do with this?

DR. SCHWARTZ: Not with ear disease as far as we know.

MS. COHEN: Not with ear disease at all?

DR. SCHWARTZ: No. Adenoids possibly, but not tonsils.

MS. COHEN: Thank you.

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DR. HENRY: I have a question as long as you are up at the podium. What are your thoughts about your comparator drugs?

DR. SCHWARTZ: I couldn't agree more with Dr. Melish. The words, I mean they were beautiful words to me. I think the comparator should, at least in some trials, should be amoxicillin. We are doing everybody a disservice. Here, we are saying amoxicillin is the drug of choice, yet, go back 10 years, show me the study that has used amoxicillin as the comparator. There isn't any. So we have to be honest to ourself. I think amoxicillin is going to work just fine, and what you are going to do is pull the rug from underneath the marketing people that are using antibiotics with a high rate of diarrhea as the comparator drug. They say, well, our drug didn't do any better, but look, it caused less diarrhea. That is nonsense.

DR. MELISH: And the Boston Group decided to use sulfa/trimethoprim --

DR. SCHWARTZ: Fine. I don't have a problem with that.

DR. MELISH: I agree as well. I just wanted to get your ideas documented on the record.

DR. LEISSA: Dr. Schwartz or Dr. Melish, you seemed to both agree that tympanometry or the

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electroacoustic reflectometry are both important. Is one better than the other, do you have a preference of either of the two in terms of specificity?

DR. SCHWARTZ: I have done studies on both. I think there are advantages and disadvantages of both. You have to understand that under six months, your take rate with either of those is going to be low. The probe tips are too big, the ear canals are small, the kids are wiggly.

If I had to pick, I think probably the tympanometer is more accurate, but the other one, even without a tracing unit, the tracing unit makes somewhat more accuracy in the acoustic otoscope, but even without that, it is good enough and it gives me objective evidence and apparent objective evidence.

DR. MELISH: I would agree that that could be part of the trial. I think it would also be important to see that there needs to be extreme standardization in the clinical evaluation of the middle ear, and I don't think this is often done.

I think all the investigators need to get together, they need to agree, they need to find some sort of protocol of ways of having two or three people check on any clinical judgment, and one of the things about the objective

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measures is that they tell you whether you have a bulging tympanic membrane.

It is not a question of whether you think it is or whether you want to enroll 25 patients in the study because you get a bonus when you do. You just have to use some objective measure. It is just an incredibly overdiagnosed condition.

That is why I am not so sure about the business about looking at the children who have had a history of recurrent otitis. Some of them have and some of them haven't, some of them have just had febrile illnesses in the last six months.

DR. CRAIG: Dr. Reller.

DR. RELLER: It is my understanding that these documents are at a point that we can speak freely and open to change. Given the overwhelming interest and potential importance of the serious pathogens and that no clinical study is going to be yield information about those, and the pleas for more objectivity in the clinical studies to make them more worthwhile, are we at a point, because of the changing epidemiology of the organisms, to face reality and say we are really not getting much information from the clinical studies and scrap them altogether?

DR. LEISSA: Back to 1977, right.

DR. RELLER: Well, maybe that is the appropriate thing to do. Dr. Schwartz, what do you think? It would be better to have useful information including the microbiological for the resistant pneumococci and given the changing epidemiology of Group A streptococcal infections in this country, to have that information on fewer patients, more information on fewer patients, where we know what is really going on.

DR. SCHWARTZ: I would have to see, I would have to walk in the shoes of the manufacturers. I don't know if they are able -- I think they should be able to get qualified people, I can think of probably 10 given enough time, who can do tympanocentesis or some way of getting middle ear fluid.

The clinical studies give lots and lots and lots of patients, but you have such a wide variability of what people are calling what, how they are determining it, I wish I had a Bible to put their right hand on each one and say I promise I will only give you real otitis media, and not, oh, I can get an extra thousand bucks from my next three or four patients. It is open to abuse, a lot of abuse, and that is my major concern.

DR. CRAIG: Yes.

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DR. MELISH: I think, however, that we should strengthen the microbiology, but I think we need large numbers of patients, because we have, you know, as you said, a couple of the pathogens have a very rate of spontaneous resolution, and it takes large numbers to demonstrate equivalence, but if you beefed up the microbiologic studies and did clinical studies with the appropriate comparators, I think that we would be getting the answers we need as to whether we are really using the right ones, so I think there is a role for both, but I don't think they have to be exclusive either.

Anyplace that is doing a clinical trial can learn to do a trial with tympanocentesis. It is not that difficult a technique, and I think you could easily decide not to look at children under six months of age in the study, and when you get older than that, you get to the point where you can do the tympanocentesis more easily. Older children, too, are a particularly good source for being able to do tympanocentesis. They can sit still, and they will get immediate relief.

Do you agree with that?

DR. SCHWARTZ: It depends on the tolerance of pain, the extent of inflammation. There is just a lot of variables. What I have found is I was a beast before I

started using something to make these kids pain-free during the procedure. They are not pain-free, but at least pain-blunted. Anybody has to use something to make that procedure, which is a very painful procedure, much more humane.

DR. MELISH: I actually thought that drawing blood was more painful for these children.

DR. SCHWARTZ: No way. I will show you if you want.

DR. CRAIG: Yes.

DR. SORETH: I think that in some respects, we may have painted ourselves into a corner in changing from the 1977 guidelines to the Points to Consider and having a large clinical-only trial and then a smaller trial with tympanocentesis and microbiologic data obtained.

What has happened -- and Brad alluded to it in his talk -- is that in a couple of cases, we find that in the clinical-only trial, equivalence is demonstrated when compared to an FDA-approved comparator.

Obviously, implicit in a clinical-only trial is that a certain percentage of children will not have their otitis media due to a bacterial pathogen, but viruses or other etiologies, and depending on how tight the clinical criteria are, maybe that percentage is 5 or 10 percent and

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maybe it is 30 or 40 percent, but nevertheless, in the clinical-only trial, equivalence is demonstrated to an approved comparator, and then you take a look at the smaller trial that has microbiologic data, and you see a hole.

You see that your test drug is really not equivalent to the comparator, that maybe one bug in particular is not well covered, in a couple of cases Strep pneumo, so you have the conundrum of clinical equivalence being shown in a trial, the larger trial, and then microbiologic data that is disconcerting, that ends up in an approval that read acute otitis media due to susceptible pathogens, and then two of the three are listed.

I think it is problematic.

DR. MELISH: Well, it is problematic in a lot of ways, because there is probably a lot of patients in that trial that didn't have otitis media to begin with, and there is a lot that would have responded anyway, so that can't see even in inferior agents, you can't see it in trials that are carried on in that way.

That is why I am saying that you need objective criteria, you need to standardize your clinical objectives, and you need to get as much microbiologic material as you can. You may be in a corner, but things have changed, and that is, we have a very high frequency of at least

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intermediate resistance to pneumococcus all over the country, and in certain areas, a high frequency of very high-level resistance.

The second thing is when we had our meeting about antibiotic susceptibility problems, it seemed to be the cephalosporins, and the daycare centers and the children who are nearly constantly on antibiotics that are predominantly blaming for the place where this arises.

So it isn't the same situation anymore. It is time to -- you know, it has really got to be urgently addressed with larger microbiologic studies and more rational use of antibiotics and study of antibiotics.

DR. CRAIG: The other possibility is maybe to use a more sensitive indicator if you can do repeat punctures, where you are looking at bacteriologic cure instead of looking at clinical cure, to at least pull the numbers down, but use an indicator that would potentially be much more sensitive for looking at antimicrobial response.

DR. LEISSA: Again, historically, as I have stated, that in 1992, when the Points to Consider document came out and gave birth to this clinical-only study, that the basis for that responses were coming to us and saying we can't find people who would do tympanocentesis in this country, if you want micro studies we will do them, but we

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have to go overseas and would you prefer to have U.S. children or would you prefer to have foreign children studied, so that was the genesis.

It doesn't mean we can't go back or change things, but that is important history.

DR. CRAIG: Dr. Reller.

DR. RELLER: When we discussed sinusitis, the plea was that we can't do antral punctures, and we didn't buy it, and I don't think we should buy this one.

I am concerned about accuracy in every particular. I think that was the word used, about the labeling the implications. I mean I am very bothered by an approval of a drug -- and I mean I understand the basis and how it came about -- of leaving out except for, for example, the very pathogen that Dr. Schwartz mentioned is the serious one. Given in practice that no one is doing or few are doing regularly -- most of the time it is empirical therapy without the tympanocentesis, even the tympanometry in many practices not regularly done, so that to have an approved drug, I mean it implies that it is useful, but if an exclusion, a very important exclusion is something that no one can know a priori except with a failure, I think that is a dangerous situation.

DR. CRAIG: Dr. Rakowsky.

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DR. RAKOWSKY: Just a little background here. I guess the way we approve drugs now is based on a statistical model where you take a comparator, compare it to your study drug, show statistical equivalence, and then it gets approved.

I wonder if another model to look at this would be an animal model -- and I am not, I am going to ask Dr. Craig the status of the animal models at this time for ear infections -- and do smaller studies where you actually find the pathogen and then repeat the tap, and then compare your results to the predicted results based on your good animal models.

In that way you can have smaller trials. You basically don't compare against the comparator, but compare it to an animal model per se, but a lot of it depends on the accuracy of the animal models that you have available.

DR. CRAIG: Not only the accuracy of the animal models, is how predictive they are of human disease, and what you are going to see in human response to antimicrobials, so I think you would still need to try and find some parameters that correlate with efficacy in the animal model, but you would also like to be able to see if those same parameters correlate with the human animal model.

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So, you would still want to be able to get some data in humans to be able to still show that the animal models are applying.

That is one of the things that was mentioned before, of doing pharmacodynamics and trying to get some of these parameters out, is to look at them and see if they are predictive in a variety, that the animal species is not an important determinant of that response, so that you can gain some insight, some information that then you can reconfirm in clinical trial.

Dr. Feigal.

DR. FEIGAL: I just want to comment, and I don't know if this helps with your concern or not, Dr. Reller, but the way that one of the products that doesn't have as good strep coverage was labeled was that it was labeled in settings where Strep pneumo had already been covered, so the notion was that it could be used empirically if you already had another agent that would have covered that, or if you had the organism or if there had been a failure in the face of good Strep pneumo coverage, and so you thought that you probably had some other organism.

So, that was our attempt to deal with that.

DR. RELLER: There is a tremendous hole in that thinking, and the hole is something that -- let's say

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amoxicillin. In the old days, I could trust amoxicillin to hit Strep pneumo. In my area now, in vitro, we have 22 percent, 21 percent. Of those, maybe 4 percent are going to really chew up that person's ear and continue to cause problems if I use amoxicillin and continued on amoxicillin, at least that is what it seems, it is a lower percentage.

So what you are saying is if they have already been through amoxicillin, let's say for Strep pneumo, and they still have a problem as soon as amoxicillin stops, have a recrudescence, I can switch to this antibiotic with known poor coverage against Strep pneumo, because presumably it would have died it with antibiotic A, but if it is marginally susceptible to antibiotic A, because of the emergence of resistance in increasing percentages of absolute resistance, that blows a hole in that theory.

DR. FEIGAL: I take your point and I think in this era, I think we assume that when we say you need to cover Strep pneumo, that people understand that there is resistant Strep pneumo that has to be empirically covered, that they can't assume that it is all sensitive, but it still is a problem when you have an antibiotic that has utility for part of the spectrum, either to say that the only antibiotics that will be marketed will be ones that have the full spectrum or if we know that it is effective in some

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settings, do we try and provide some type of restricted labeling, and whether we have the best wording or not, I think that is one level of the issue.

The other issue is are there serious enough safety concerns about partial spectrum antibiotics that they don't even have a role on the market, and that is a tougher one.

I think the other comment I would just like to make is just another variation on this theme, and it relates again back to standards and relates to the difficulty with power and study size, is that many of the trends over the last decade have been to simplify regimens and to increase dosing intervals, and so we are commonly asked to comment on and approve study designs that will go from t.i.d. to b.i.d. dosing or will lower the total amount of drug from a certain milligram to another to be more competitive in this price-conscious world, and then we are asked to actually design a study that is large enough, that will actually tell us if we are able to distinguish between what is safe and what we can get away with most of the time, and how far we can really back down, and because there we are actually dealing with the same active ingredient, probably the differences are going to be quite small.

But to use empiric studies with all of the problems that you alluded to in that kind of setting is also

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very problematic in terms of how much of an assurance is it to show that two regimens look very similar in a setting where you don't have the kind of precise measurements. So, i think there are many difficulties in this area.

DR. CRAIG: Dr. Wikler.

DR. WIKLER: Matt Wikler from Ortho-McNeil.

I want to discuss two possible points. The first is talking about the comparative agent. We are saying people are using amoxicillin, trimethoprim/sulfa, on the other hand, we are saying the organisms are changing a great deal, and now we are seeing a great deal of resistance.

Well, what happens is if you run a study and you say we have to exclude patients who supposedly have a resistant organism, then, what happens is, in theory, you can't study your new drug versus penicillin-resistant strains because they would be resistant to amoxicillin or the increased numbers of strains resistant to trimethoprim/sulfa, so I think that raises one interesting issue that needs to be considered.

I also think that maybe some thought should be given to placebo-controlled studies, and the reason I say that is we know the rates of cure are very high, and it is only specific problem organisms that are a problem, and frequently those organisms are the ones that aren't going to

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be susceptible to amoxicillin or trimethoprim/sulfa anyway, and so maybe the reason the trimethoprim/sulfa was considered as a comparative agent was because it works really great and patients would get better anyway or where frequently antibiotics aren't needed, and therefore, some thought should be given to those issues.

DR. PARKER: I have a question for you about your treatment of the microbial data, where you wish to do it on a per-year basis, that has certain statistical implication, not the least of which is I don't believe the ears are independent, and that if you use that data, and you compute things up in the usual way for your confidence intervals, they are no longer valid.

I am suggesting that if you wish to use that, that you must have failure on both ears, success on both ears, and if you have a discordant pair, then, you have got a choice. One resolution is to not evaluate it, so it doesn't count in the numerator and denominator, and one other method that has been suggested is to count it a half in the numerator and a half in the denominator.

That doesn't do as much mayhem, but I would really rather throw it out, but I think you have to address that issue before you proceed. It is a great way to double your

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sample size, but FDA wouldn't let me do that with the teeth in my dental study, and I don't think it is fair.

[Laughter.]

DR. CRAIG: How about the question of placebo?

DR. MELISH: Well, I would like to address that a little bit. There is a move in Europe for nontreatment of otitis, at least an observation for a period of time.

I think compared with what we were talking about before, we know that if you select the patients correctly, that this is a bacterial infection, it does have suppurative complications. We know that in certain populations in the United States, such as Native Americans, we can see it in certain groups of people in Hawaii and in Alaska natives, provision of antibiotics is very important, and I also have seen some patients with mastoiditis over the past few years, and I think the reason we have seen less is because we are perhaps overtreating otitis.

I don't think we should continue to overtreat otitis, and I think that we should not have a placebo arm in otitis media treatment in the United States at this time, but I very strongly agree that pneumococcus is our biggest problem and what has been happening in our nation has been that drugs have been sold to physicians because the so-

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called spectra of resistant hemophilus, and actually it is the pneumococcus that is the biggest problem.

Now we are in a new era. We don't know what we should be using to treat these patients, and I think we should be comparing it with either sulfa/trimethoprim or amoxicillin, because the kind of kids we would be recruiting into this trial would be the kind of kids, not the super, multiple infections patients, these would be the kinds of kids that physicians would be putting on amoxicillin and sulfa/trimethoprim, and I hope that we have some better agents.

Augmentin, which seems to be the comparator of choice recently, isn't going to do very much better for the resistant pneumococcus, it is not going to do anything.

DR. CRAIG: I guess that is one the things I worry about is some drugs have gotten approved for hemophilus that theoretically could have no activity at all against the organism, but just because of the very high cure rate, spontaneous cure rate, that you would get the numbers down.

For example, you could start with 200 patients, have 60 percent that have positive cultures, 20 percent have hemophilus, and you are down now to 24 patients. Fifty percent of those clear spontaneously. Now that brings you down to 12 patients, and half of those will still have a

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clinical response even without eliminating the organism, so you have got 6 failures out of 200 patients, and that is just not going to show up as being a significant problem, and as a result, a drug is approved for an indication where it has no absolutely no activity at all.

That is why I still come back to again trying to get better data at least in some small group of patients where we try and get bacteriologic cure, so that we can get that additional data to go along with what we are seeing in terms of clinical to really be sure that the drug has significant antimicrobial effect on the illness.

DR. RELLER: Do you want to get to the heart of the matter and require microbiology with a very limited number of comparator choices, and if one wants to do a clinical-only trial, require that it be a placebo-controlled trial?

DR. SCHWARTZ: Eminently clever. I would go for that.

[Laughter.]

DR. RELLER: I mean let's get the honesty out on the table here.

DR. SCHWARTZ: I think that would be wonderful. You would have to exclude the very, very ill from the clinical trial. There are those you can predict who might

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have a real tough bug, they are going to have more pain, they are going to scream, not merely have a little change in behavior, the eardrum is going to be this color and bulging, and weeping because there is a transudate from the capillaries within the drum, it is going to melt the ear wax, it is going to have little plaques of epithelium because there is desquamation because of the virulence.

Exclude those and I think you have got a wonderful study.

DR. RELLER: Let's include them with the tympanocentesis and get the resistant pneumococcus.

DR. CRAIG: Any other comments or questions?

DR. LEISSA: I think the big issue still has to be the last slide, the last issues to ponder. This has to do with the issue of linking middle ear effusion resolution to antimicrobial efficacy.

DR. CRAIG: I think we heard, at least the impression I got is that it is not related at all and we should forget about it.

DR. MELISH: No, I am not sure that that is true. I think we should study it.

DR. SCHWARTZ: How do you study it?

DR. MELISH: Well, you just watch and see whether one drug or another --

DR. SCHWARTZ: But that is never shown to have an effect. It is never antibiotic-specific. I mean you have enough data now. If I am wrong, then, somebody really needs to write on that subject, drug X gives a greater resolution faster than drug Y, but that doesn't happen.

DR. RELLER: Why don't you just include the MEE in the clinical placebo trial?

DR. MELISH: Well, that is a different issue, and there are guidelines for otitis media. These are patients who started with what we hope we will have the way of diagnosing it as acute otitis media.

DR. SCHWARTZ: D r. Melish, of all people, you see them once in the ER, I see them for the rest of their lives.

[Laughter.]

DR. MELISH: I do see some kids in follow-up, but what I was saying, you know, I did say that we should separate the question of the middle ear effusion, but I wouldn't object to following it for a limited period of time to see whether there is a difference.

DR. CRAIG: Any other comments?

DR. LEISSA: I guess what I am hearing from that is that it is something of interest, something to be studied, but relative to an evaluability criterion, where you have patients required to follow-up for monitoring

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resolution of ear effusion, that is a different issue, that is not what we are looking for.

DR. CRAIG: I think that is it in general.

Again, let me encourage people that were silent, didn't get up to the microphone, to at least send in your comments because we do want to hear from everybody, to sort of get everybody's idea on this, not just those of us that were sort of forced to comment or those that felt really called on to say something, but we do want to get your input in trying to make this document as useful as we can.

We will close and we will see you tomorrow.

[Whereupon, at 5:35 p.m., the proceedings were recessed, to be resumed on Friday, March 7, 1997.]