DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

IDSA/PhRMA/FDA WORKSHOP

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9:00 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

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Richard Gesser, M.D.
Alan Goldhammer, M.D.
Donald Jaffe, Ph.D.
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. EDWARDS: Welcome to our second day. Today, we are going to discuss some topics where there, I believe, will be some more intense focus than yesterday and we are going to wind up bringing back into the discussions many of the points that we discussed yesterday.

I wanted to just make a very brief comment and that is to remind you that this is not an advisory board meeting. It is just a forum for scientific exchange. During the evening last evening and this morning, I have been searching for ways to sort of try to loosen up the conversation, if you will, and just diminish the formality.

One of the strategies I entertained was telling you my absolutely favorite biostatistical researcher joke. Then, the thought occurred to me that some of the biostatisticians here might not think it was funny.

DR. CHUANG-STEIN: We will survive.

DR. EDWARDS: It is the one about the three hunters who hunt with a bow and arrow. Has everyone heard that in this room? Under pressure, I cave in, but, it is so wonderful. Not only is it

my favorite biostatistician joke, it is one of my favorite jokes in any category.

So, to try to just reemphasize the fact that we really want to just encourage free-flowing exchange of ideas here without concern for--some of us might even express a bad idea on purpose just to see what the response is.

With those comments, the structure today will be similar to yesterday with our lunch break. We are going to try to summarize, towards the end of the meeting. I am anticipating, as usually happens in a meeting like this, that there are going to be some people who have to leave a little bit early. So we are going to try to structure the crux of the summary in such a way that we will be able to adjust for the fact that there may be some people who need to leave early.

So, with those comments, I would like to ask Dr. Goldberger to complete a thought that he developed last night related to our discussions and then we will move into our three points for discussion.

Mark?

Opening Remarks

DR. GOLDBERGER: Thank you. We were

talking a couple of times yesterday about using meningitis as an example about that issue of how could we get information in labeling that showed a relatively small study with a favorable microbiologic profile but clinical data that was harder to interpret perhaps as a result of the amount of data that was actually available or the amount of patients studied.

So there were several approaches floated in terms of just being able to put some information in the labeling, sort of leaving it then to clinicians to use this information as they thought best.

I proposed one alternative which was ultimately you would get some kind of what we call second-line indication. The reason I proposed that and the reason I am about to make another proposal is the idea of just putting it into the labeling in some section poses certain problems for FDA for the reasons we talked yesterday about promotional issues.

Therefore, it would not be an easy thing to achieve. One of the goals is always how can you take an idea an harmonize it in some way with the existing regulatory approaches so it fits in more

neatly and perhaps causes less problems and also, hopefully, provides its own longer-term solution.

I think, realistically, again thinking that such a clinical trial would have to go before an advisory committee for formal discussion to see what people thought about it is this probably best fits the model that you have heard talked about intermittently yesterday of an accelerated approval.

In spite of the concerns that were raised about what we mean by surrogates, et cetera, at the end of the day, I believe, what we were talking about, using meningitis as an example, is we have got the microbiologic data. The microbiologic data is very good of the experimental drug versus control.

What we are really saying is, even though we don't have that much clinical data, we believe that that high a level of microbiologic data really means that those patients ultimately would do well, although we don't have enough patients to fully demonstrate that.

If that is the case, then what we are saying is that that response in the spinal fluid would be predictive of a favorable clinical

response. Under those circumstances, that is something that is appropriate for an accelerated approval. That allows us to potentially take this information and fit it in to an existing regulatory structure instead of having to create something different.

It also, however, does, then, require something else. It requires the firm in question to do some type of additional study or studies or complete a study to confirm that this is the case. Ultimately, although this can be interpreted flexibly, it would require the submission of additional data of some type to confirm that the belief that people had that this good microbiologic result meant patients would do well to help strengthen that and show a better demonstration of it.

However, there is the opportunity to negotiate that with the company in question as part of the development process. I think that, if people think that this idea has merit, and I think it actually is the best way to achieve what Dr. Talbot had suggested yesterday.

One of the things I would like you to think about is, during at least the meningitis

discussion, probably because that may be the best place, is if were in such a situation, we had this good microbiologic result, we had come clinical data we thought was encouraging but, by no means, definitive, what would be the next step, what would you want to see next, even knowing you could get the information into the labeling, get an actual indication but what else would you want to finally sort of close the loop that you were satisfied about the performance of this product, what other information could be collected either preclinical, smaller clinical trial, more definitive clinical trial, or some blend of that to successfully accomplish that, that you thought would be useful and is something that, within some reasonable time frame which certainly can be several years, could actually be achieved by a commercial sponsor without it being overwhelmingly burdensome.

I would like to give you that thought to think about and consider. We can talk about it a little more with the meningitis discussion but I believe that that may be the best way to achieve some of the stated desires with regards to a difficult situation like meningitis.

I think it is worth some more discussion

and it does fit into the framework that already exists.

DR. ECHOLS: I would like to ask a question. I am familiar with accelerated approval for new chemical entities, but we might well be talking about what would be otherwise a supplemental NDA to a drug that is already approved for other indications

DR. GOLDBERGER: You want to know if that is a problem.

DR. ECHOLS: Is that a problem

DR. GOLDBERGER: The first accelerated approval ever technically granted after the regulation was put into place was actually one that I worked on personally and that was clarithromycin for the treatment of disseminated MAC in patients with HIV. Clarithromycin was already an approved product being dispensed, being available under a normal approval.

Yet this was an accelerated approval. In preparation for that, I asked more senior management in the Center to think about this issue and see whether it posed a problem and the answer, basically, was no. So there is no problem with that at all.

DR. EDWARDS: Very good. During the meningitis discussion, if it doesn't come up, I might as well warn both the IDSA and PhRMA people that I would like to ask for comments regarding Dr. Goldberger's suggestion during the discussion.

At this point, we will move on to the meningitis issue. I will call on John Bradley from IDSA to begin the discussion.

DR. GILBERT: I asked John, and he complied, to provide handouts of his slides because I think they will be useful as we get into the discussion portion.

Issues in Clinical Trials of Acute Bacterial Meningitis - IDSA Speaker

DR. BRADLEY: Dave saw how much information was on the slides and decided that it would be difficult if I was to keep within the time limit for people to read the slides and listen to me at the same time. So I took his advice seriously.

[Slide.]

It is a real privilege to be here to talk about bacterial meningitis on behalf of the IDSA. It is an area of great interest to me since I started my pediatric residency. Certainly, the

clinical field of IDE, with respect to meningitis, has changed dramatically since I started in the mid-70's with the change in organisms that we see and the development of critical-care specialty and the development of agents which are not antibiotics but antiinflammatory mediators which now have some role in the treatment of kids of meningitis and adults, I guess, as well.

I would like to thank both George McCracken and Dave Gilbert for going over these slides. Many of the concepts that are in the slides this morning have come from George McCracken's earlier presentation in February of this year.

[Slide.]

There are certainly a number of problems in performing studies in meningitis. There are a decreasing number of kids with invasive disease, pneumococcal disease. Certainly, we have not seen any Hemophilus influenzae Type B disease for the past eight years or so. With the increasing use of conjugate vaccine, we are seeing much less invasive pneumococcal disease. The CDC presented some data at the IDSA Meeting in Chicago just a few months ago regarding decrease in the incidence of disease.

So, given this fact, meningococcal meningitis is going to be the most prevalence bacterial meningitis that we see so the ability to do large-scale trials in the United States is going to be increasingly difficult. As I mentioned yesterday, even in the past couple of trials that we have done, most of the patients have come from non-U.S. sites.

The fact that there is increasing resistance in pneumococcus is something that we are all aware of and, in February, Dr. Soreth presented information on increasing resistance in pneumococcus. I had the opportunity to attend the Antiinfectives Advisory Committee Meeting in 1998 in which the committee felt that fluoroquinolones were an important class of drugs to use for meningitis should pneumococcus develop vancomycin resistance and standard therapy with a third-generation cephalosporin and vancomycin would no longer be considered effective for children.

[Slide.]

Bacterial meningitis is a serious infection and ineffective antibiotic therapy is not acceptable so we keep talking about the seriousness of infections and what the delta is. This is one

situation where you really can't afford to miss. There is a lot of preliminary work that is done before any drug has ever gone into the treatment of meningitis to try and assure that there will be no failures, extensive in vitro testing, extensive animal-model testing.

So I think that, as we go into a meningitis trial, we have more answers than we do if we are going into a skin-and-skin-structure trial with antibiotics.

[Slide.]

Clinical assessment in bacterial meningitis is largely a function of CNS inflammation and the resultant vascular insufficiency that results in CNS damage or inflammation. This is the first of a number of points talking about which is more important and easier to assess clinical or microbiologic endpoints in evaluation of drug therapy of meningitis.

It is certainly generally agreed that inflammation correlates with the presence of organisms in the subarachnoid space and the whole discussion of surrogate markers and whether microbiology can be used as a surrogate marker

again was discussed yesterday. It seems obvious to me that, if you don't have bacterial in the spinal fluid, there is no evidence of inflammation. When you get them there, there is. Once you treat someone effectively, the inflammation goes away.

But, in terms of doing a prospective trial, placebo-controlled, to prove that, I don't think that we are going to be embarking on that. At least, I wouldn't do that at our hospital.

[Slide.]

There are some data, though, that suggest that delayed sterilization may lead to increased neurologic sequelae. In the studies in which cefuroxime was used as a study drug compared to cefataxine, in Lebel's study out of Dallas, Texas with George McCracken, or cefuroxime compared with ceftriaxone in Schaad's study in Switzerland, there was an increased rate of hearing defects in children that had delayed sterilization in CSF. So there is one nice connection.

In addition, adjunctive therapy, which targets inflammation, like dexamethasone, may lead to improved outcomes with respect to hearing loss in H. flu which has been in our literature for a long time and, as of last week, the New England

Journal article which was a quoted multicenter study in Europe, improved neurologic outcomes in adults.

[Slide.]

The clinical outcomes in kids vary by country using the same protocol to treat the same organisms at all study sites. I had the opportunity to write up the meropenem meningitis trial that was done in North America and Central America with Carla Odio. The sponsor allowed us to go back into the database when the first pass of analysis showed that our clinical outcomes were worse than any other meningitis trial that had ever been done and it wasn't our experience in San Diego that we had poor outcomes.

In looking at the analysis by study site, post hoc, it was clear that, in the Dominican Republic, the outcomes were horrible. In Costa Rica and the U.S., they were actually comparable to all of the other previously published studies.

So the ability to use clinical outcome as an indicator of the drug's ability to cure meningitis became rather fuzzy because of all of these other factors that lead to differences in clinical outcomes became very apparent; access to

medical care, time to presentation, critical-care resources available to kids.

Many children in our institution are intubated and given mannitol to decrease brain swelling and, perhaps, prevent some of the complications attendant to that. So all of these clinical assessments may have nothing to do with the ability of the antibiotic to sterilize the CSF. Yet, it has traditionally been the primary endpoint for evaluation.

[Slide.]

The clinical endpoints, including neurologic, audiologic and developmental are global, all the way from death to complete cure. The clinical endpoints are vague and, in one of the earlier guidance documents, "The criteria for judging severity of neurological sequelae should be provided in the protocol," so it leaves each protocol, each person, to decide what the neurologic sequelae would be.

In my comparing our study with all the others, it is tough to compare apples and oranges if everyone uses a different yardstick for neurologic outcomes. The vague clinical-outcome endpoints may lead to differences in interpretation

in each study site, by each country. There are differences in the qualifications of the evaluators in worldwide studies.

The background of neurologists, developmental specialists and audiologists are not all standardized. When I was asking about qualifications in some of the other countries, I was reassured that everyone was well qualified. But there were no documents to standardize that.

In addition, when you do studies in many different countries, there are no standardized cross-cultural multilingual developmental scoring systems that can be used for children. So, using some of the adult scoring systems needs to be validated in pediatrics as well. They are not going to their jobs, and the infants are not going to schools.

[Slide.]

So the solution is a microbiologic endpoint which is defined at 24 to 48 hours. I know, in the handout, it is 36 to 48, but this is the most recent version. One can look at 24 to 36, 36 to 48, or 24 to 48, but the idea is to have a defined micro-endpoint.

These rates are clearly higher than the

clinical efficacy rates. They can be standardized across all multinational study sites. I know there has been discussion before this meeting on the value of quantitative cultures. I looking at those children who don't have sterilization by 36 hours, on average, there are two subsets, one in which there is a huge decrease, several-logs decrease, in the number of organisms present, so the drug is actually doing an excellent job of what it is supposed to do.

But a few children come in with extremely high bacterial loads and it just takes longer for them to sterilize compared to other drugs which work more slowly and the sterilization rate may be significantly less quick, which may give some insights into some deficits in drug activity.

[Slide.]

We now have greater sophistication in prediction of micro endpoints based on PK/PD data. I won't elaborate on that today. That certainly was well discussed yesterday and there are animal-model studies that Dr. Scheld has done and Dr. McCracken has done which are in the literature which give credibility to the fact that, if you can achieve drug in CSF and attain a certain drug

exposure, you are likely to have a good microbiologic outcome.

[Slide.]

The disadvantages of the micro outcome are that not all children who have classically been entered into studies have had positive CSF cultures. Some will have positive bloods but a negative CSF culture, but a CSF pleocytosis of a few thousand cells.

In the meropenem study, only 50 percent of the kids who are enrolled actually had positive CSF cultures. So it will mean fewer evaluable kids, if that is our primary endpoint, and the concept that might an early micro endpoint favor antibiotics which have concentration-dependent killing, as opposed to time above MIC. Again, Dr. Scheld went back to a concept that was floated ten to fifteen years ago when he and Dr. McCracken came out with data on CSF inflammatory markers and maybe you did more poorly if you killed all of the organisms very quickly and released tremendous antigen into the CSF.

The whole idea is rapid killing. The most desirable antibiotic effect is one which is discussed occasionally, however, with the use of

dexamethasone to blunt the inflammatory response, especially as we now use it, concurrent with antibiotic administration. Fortunately, this point is much less important now.

[Slide.]

Having made the case that micro endpoints are preferable, I still have some interest in clinical endpoints. In order to be able to take the current study with gatifloxacin or whatever new drug is coming along, I would like to be able to correlate what I am finding in the current study with what has been published in the literature previously which is largely clinically oriented.

So the rates of neurologic sequelae in developmental delay I would like to be able to correlate with previous publications. It gives me insight into the pathogenesis of meningitis by organism, study site, level of care provided and adjunctive therapy.

The blinding of the treatment arms in evaluating clinical outcomes, I think, is very important because there are soft neurologic outcomes, mild developmental delay and mild motor dysfunction which may or may not interfere with normal daily activities which is the catchword for

assessment of mild and moderate, which, if you know what treatment arm the patient was assigned to, may influence your evaluation.

Then safety assessments; if we have fifty kids in each arm, it gives us less ability to look at the safety of the drug and, as again mentioned yesterday, the doses of drugs used for meningitis are generally larger than those used for other systemic infections. So, I would like some number of patients that would be considered reasonable to evaluate safety data and to follow up on what Dr. Goldberger said, a study post approval which looks at defined data once the drug is out can actually fulfill some of these requirements, I believe.

[Slide.]

There are ways to strengthen clinical endpoints and these came up in a discussion between Dr. Powers and Echols and myself regarding, perhaps, tightening up the inclusion criteria, tightening up the clinical endpoint criteria.

[Slide.]

The delta we talked about extensively yesterday. I think, for serious infections, the 10 percent delta is appropriate, especially when the efficacy is not even 95 percent. That is just when

you do the tap. If you waited 72 hours, you should get virtually 100 percent micro efficacy.

[Slide.]

For the clinical endpoints, treatment success is defined currently as cure plus minor sequelae, as it was in the European study published last week in the New England Journal. A 10 percent delta would be unrealistic in terms of patient enrollment. Only 50 percent of the children who were treated actually had cure without any sequelae in both the meropenem-cefataxine paper and the trova-ceftriaxone papers.

An additional 20, 25 percent had minor sequelae which would lead to a clinical assessment of success. Biocreep, which hasn't been mentioned so far in this particular session, is less likely if you use a micro endpoint compared to clinical endpoints.

Dr. Powers, in our phone conversation a week ago, had actually mentioned the idea of using different deltas for different endpoints, 10 percent for micro and 15 percent, perhaps, for clinical.

[Slide.]

The clinical endpoints to be defined.

This is a difficult area, given all of the problems I have already mentioned. How do you define the neurologic deficits in children, which systems? The are motor, cognitive, hearing deficits. How profound? How to score them, especially in a six-month-old infant.

Developmental delay; we need standardized tests. We need qualified people to administer these tests because, oftentimes, it is just the subtleties of response of an infant to the investigator. And functional assessments; do the deficits interfere with activities at home, if the child isn't old enough to go to school, at school, if they are at school, and then how to assess the different degrees of functional disabilities.

It was very nice to see a Glasgow Outcome Scale that was the clinical outcome parameter for the study published in the New England Journal last week. But I don't know if the outcome scale has been validated for children. It is just a five-point scale with death on one end and cure with minor sequelae on the other and everything in between.

So I think that there is a chance that a group of people can come together and help decide

on exactly what the clinical outcomes would be. But I think if micro endpoints are the primary endpoints, that the importance that we have previously placed on these clinical endpoints is not nearly so great.

Thank you very, very much for your attention.

DR. EDWARDS: Thank you very much, John.

We will move now to Roger Echols from PhRMA. Roger?

PhRMA Speaker

DR. ECHOLS: Good morning.

[Slide.]

We have touched on meningitis several times this morning, or the last day and this morning, but I want to sort of back up a little bit away from some of the details of clinical microbiologics and, again, sort of provide a little perspective about how the three parties at the table might approach meningitis with a somewhat different perspective yet, at the same time, I think we are coming very nicely together with sort of a resolution which will be, hopefully, to the advantage of our patients.

George McCracken, John Bradley and others

have often talked about the need for options, for treatment options, for the treatment of meningitis whether it is bacterial resistance that is currently present or may be present in the future. There are always the odd-ball organisms and it is important to know that there is a certain number of drugs out there that do work in treating a specialized space such as the CSF.

As John has mentioned, from sort of the clinician's point of view is eradication of the causative pathogen is paramount. I am not unsympathetic to the FDA's point of view. They are the guardians of a very high standard which I think everyone in this room relies upon. As mentioned yesterday, if it in the label and it is approved by the FDA, people believe it and that level of confidence is very important to secure and maintain.

So proving what is safe and effective, intuitively, we think we know certain things but when you put the question, really, to the test, it can be much more difficult to prove beyond a reasonable doubt. That is why we have talked about noninferiority studies. Obviously, we can't use placebo control in this situation, and we all want

a high degree of confidence that we are not having biocreep, that we are not providing information that is not true.

Yet, at the same time, if we go for a surrogate marker, if microbiologic endpoint is a surrogate marker, the need or the test to really validate that may be a difficult one to also succeed in. That is why I think, somewhat mistakenly, I used the term "leap of faith" yesterday. But you still have to have some trust sometimes if you can't prove beyond a shadow of a doubt that a certain surrogate is valid.

From the pharmaceutical sponsor point of view, I would say, as much as we want to provide meaningful answers, because we have had failures as well as successes, we also want to know what is feasible. We are risk-averse, not risk-adverse.

[Slide.]

I think if you look at what studies have been conducted over the last decade, there is a relative lack of clinical trials and even those that I am going to present here, very briefly, are really to sort of demonstrate the scope and the degree of difficulty of conducting meningitis trials.

It has only been made more difficult through the success of vaccine programs for Hemophilus and Streptococcus pneumoniae.

There are three programs that I am familiar with over the last decade. The cefepime program, which was really two consecutive trials that took sixty-seven months to enroll a little over 350 patients. You can see that none of these patients were enrolled in North America, or at least within the United States.

The meropenem program was really four different studies conducted sequentially over fifty-six months. Three were European studies. One was a U.S. study. Then the trovafloxacin study, which was, as all of these were, an open-label study, was conducted in eleven countries as a global trial in fifty sites over fifteen months.

They all were roughly in the 300, 400 patients. These really represent tremendous efforts on the part of the companies to enroll these number of patients.

The top line there shows the evaluability rate of between 60 and 80-some percent. I will use, in some of my additional calculations, a 75

percent evaluability rate so not every patient that you enroll is evaluable for the primary endpoint. The clinical response tends to be generally in the 70 percent range, so, using 80 percent is really sort of the high end of what has been the experience.

As you can see, when you use clinical response as a primary endpoint, the confidence intervals are not as tight as we might like so the lower boundary, even with these pooled databases, these are not necessarily single studies, the lower boundary falls below -10 percent.

The other point I want to make is that our primary interest in terms of a pathogen is experience in the treatment of Streptococcus pneumoniae. There is a less of a need for new therapies for meningococcal meningitis even though it still can be a devastating disease and Hemophilus has been much less of a concern with the vaccine that is really being widely used, not just in the United States but in developing countries as well.

But the isolation rate in these trials of Streptococcus pneumoniae still was not 40 or 50 percent of the overall population. Again, the

experience with microbiologic eradication is generally around 95 percent if repeat tap is performed between 24 and 48 hours after the initial tap p.

So we have talked, in general, about two different paradigms. One is a clinical-endpoint study. Again, I support a high degree of confidence that the results we are seeing are true. I also--to comment on the power question that has arisen, it has generally been our feeling that, if you are going to risk your resources to do a study, you don't want to miss a positive result.

So we generally power things at a 90 percent level rather than an 80 percent which I know is acceptable but generally not acceptable within the industry. We want greater expectation of not missing something if it was there.

So these are actually fairly optimistic numbers. Expected response, 80 percent, as I mentioned, is on the high side. Evaluability is 75 percent, on the high side. But you still would end up with a total enrollment of nearly 900 patients to have a 10 percent delta and a 90 percent power whereas, with the microbiologic endpoint of sterile CSF or at least organisms not growing at 24 to 48

hours, you can achieve--with a sample size of around 270 patients with an expected sterile or nongrowing spinal fluid of around 95 percent, you can achieve a very tight confidence interval around a success rate of 95 percent.

[Slide.]

I do want to just throw out one alternative just to be complete, and that would be a noncomparative, basically observational study, prospective study using a very strict protocol criteria but, nevertheless, without a comparative arm.

You can achieve a very tight 95 percent confidence interval with a similar sample size. The advantage of this, besides being a less complex protocol to conduct--but the advantage is that all the organisms, particularly if you are interested in numbers of Strep pneumo, all the organisms would be receiving the investigational drug so you wouldn't be diluting your organism sample size by half with the organisms that presumably, in a randomized fashion, would fall out in the comparative arm.

Obviously, the cons are significant. You don't have directly comparative data. We know that

geography and many other factors will ultimately influence the overall success rate. Safety events, you can't balance against a comparator and so there are many problems with that.

But, again, just to be complete, it is an alternative that one might try.

[Slide.]

To summarize, there are sort of three options. The clinical option, which has been the traditional option, I don't believe is feasible. The sample size, and this is an 80 percent power rather than 90 percent that I showed you, but an enrollment of 700 to 900 patients is just not feasible today even with a very global trial with a tremendous effort.

The microbiologic endpoint with roughly 250, maybe 300, patients I think is about the maximum that can be achieved. But the number of Streptococcus pneumoniae that you might have experience with is probably going to be less than 25 for the investigational arm. So the noncomparative approach with an expected success rate, again using a microbiologic endpoint of 95 percent, you can have, with a sample size of around 290 subjects, you can have a plus or minus 3

percent level of confidence around a 95 percent success rate and you approximately double, then, the number of Streptococcus pneumoniae that you would have an experience with.

[Slide.]

So I do think we have several options but I think, again, from a feasibility point of view, I think sample size exceeding 300 subjects is unlikely. Again, I think we all want to have a high degree of confidence that we are seeing something that is correct in terms of microbiologic response.

As John mentioned, there are lots of problems with clinical response. I really would not do this study as an open-label study because of the soft subjectiveness of some of the responses, but even trying to do audiometry and certainly any kind of standardized developmental process in very young children in a global trial is very problematic.

So, if we are going to use clinical endpoints as a secondary, they need to be, I think, major clinical endpoints. Obviously, mortality would be one but, if we get into the minor neurologic sequelae and even how we define major

neurologic sequelae I think needs to be very objective.

Then, in a randomized study, our experience with Streptococcus pneumoniae would be about twenty subjects.

Thank you very much.

DR. EDWARDS: Thank you very much.

Now, Dr. Ibia from the FDA will proceed.

FDA Speaker

DR. IBIA: Thank you very much. I really thought you were going to try to pronounce my first name.

DR. EDWARDS: I thought about it seriously.

DR. IBIA: Because one of the first tests I give to people is really to get them to try to pronounce my first name. I try to simplify it, really, by shortening it to I-m-o.

[Slide.]

One of the great advantages of speaking after giants like John Bradley and Roger Echols is really that they do the hard job. They laid a very solid foundation that even some of us can essentially summarize, sort of bring out the issues.

Another point is that I would say almost the entire workshop has virtually been on meningitis. Given that, I thought it would probably very efficient if I just present two slides.

[Slide.]

That is my title slide.

[Slide.]

And my summary slide. Then we can get on with meningitis, spend a lot more time on meningitis and talk about it. But the meeting has been so structured and I don't think, in the spirit of the structure of the meeting, that that would be allowed.

[Slide.]

So I thought we should raise the issues again at the risk of redundancy. Also, what are the current issues in drug development for the treatment of meningitis. Let me just refocus us here by saying that we are referring to acute bacterial meningitis due to the usual organisms, Strep pneumoniae, maybe Hemophilus, given that a lot of the data come from outside the country.

Group B Strep, meningococcus, Listeria. Again, we are not really talking about meningitis

in a unique situation. For example, if you have craniofacial trauma or craniofacial surgery or people with intracranial devices, that is not the kind of meningitis that we are talking about.

[Slide.]

As an outline, my talk is going to touch on entry criteria, treatment, timing of assessment, endpoints as well as, to some extent, population as well as statistics. Given the fact that not all these carry the same amount of weight, I will probably focus again on endpoints and statistical considerations.

[Slide.]

John Bradley and Roger Echols did mention things about changing epidemiology in meningitis. But I just thought I should bring up this issue of concomitant medication in clinical trials as well as in treatment of meningitis.

Here I present you recent data from the Canadian Surveillance Unit that looked at meningitis over a period of time in Canada. The point here is adjunctive dexamethasone and empiric vancomycin treatment. The red line is for vancomycin while the green bars represent adjunctive dexamethasone. What the graph

illustrates is the fact that there has been a significant decline in use of adjunctive dexamethasone as well as a tremendous increase in the use of empiric vancomycin certainly since about 1996.

In fact, in this data by Kellner and colleagues in 1999, 100 percent of the meningitis they wrote in that study were actually on empiric vancomycin at the very beginning. I know John Bradley did say that, in their institution, they still use adjunctive dexamethasone. I wonder how many practitioners here still use adjunctive dexamethasone.

I have also read the paper that was recently published by DeGans and colleagues from Europe. What one is not shown, indeed, whether that paper will have a significant impact on the practice of clinical care of meningitis in terms of use of adjunctive dexamethasone.

[Slide.]

On protocol entry criteria. The 1998 Draft Guidance Document does recommend a separate protocol for neonates and young infants because of the specific differences in etiology and clinical manifestation of meningitis in that age group. But

the question really is should older children and adults be enrolled in a single or a separate protocol, in particular, given the decline in the incidence of meningitis in this country and other nations that vaccination has been used.

Again, let's also think about clinical care of patients with meningitis and the fact that often, when these kids come in, some of them may have been on some antibiotics for maybe otitis media or maybe something else that was not very clear to the practitioner. So the question is what role, if any, should antigen testing, Gram stain and all other non-culture-based tests play in enrollment, especially given the decline in incidence of meningitis and also the fact that a lot of these kids could have been on antibiotics prior to the time that they have been seen for possible enrollment in meningitis trials.

I guess the question that I should also bring in at this point is the fact that, even what I just referred to in Bullet No. 2, whether we should place a certain rank order in certainty of diagnosis of meningitis, for example, as we do in fungal infections like candidiasis or invasive aspergillosis to say possible, probable and

definite bacterial meningitis as you enroll patients into the study.

[Slide.]

There has been a lot of talk on choice of comparator. Since yesterday and even this morning there have also been talks about it, but one thing that comes up frequently is the fact that blinding could be a major challenge in meningitis trials. Here I present an example of a trial that enrolls two drugs. On one arm, for example, vancomycin and ceftriaxone on one arm against a single agent that is also given intravenously but has the potential to be stepped down to oral therapy maybe after seven or ten days of treatment and the patient is doing very well.

The question then has to do with the impact that sham infusion that might have to be used under that scenario, sham infusion on patients who may have cerebral edema. Is this a big problem? Could this be a big problem?

I guess the other question that one needs to ask is, given this kind of scenario that I have presented, which could be a challenge in a clinical trial, is that kind of trial trying to ask too many questions all at once? The point I am making here

is that why don't you just see whether the drug is effective as against looking for something else in terms of the potential for the drug to be stepped down to oral treatment.

[Slide.]

On evaluations, at the agency, we have grappled with quite a few things as we think about meningitis. One of those things that we constantly think about is what is the best time to repeat lumbar puncture in meningitis trials? Is there data to establish that best time? This morning, that has been alluded to. Is it 24 to 48 hours? Is it 18 to 36 hours, 24 to 36 hours? Is it 30 hours?

Is was interesting that I believe it was Mike Scheld that mentioned an earlier study that when they added beta lactamase to what was considered to be eradication, a lot of the children actually had positive growth. It also reminds me of the trial done by Lebel McCracken that was mentioned earlier in 1989 published in the Journal of Pediatrics that, even though ceftriaxone had clearance at about 24 to 36 hours, when they added a beta lactamase, 7 percent of those that were eradicated actually had positive growth.

But the interesting thing is that when that lumbar puncture was repeated at 48 hours and beta lactamase was added again, all of them, including those on the ceftriaxone arm had eradication. So is 48 hours the best time to repeat lumbar puncture?

What other factors could impact the time and how should they be factored in when assessing patients in meningitis trials? We think of the organism, itself, the baseline quantity that has been mentioned earlier, the drug, itself and other host factors; for example, the age of the patient involved.

This is another issue that comes up quite frequently and that is what really is delayed sterilization and how should we use it in evaluation of meningitis trials? I know that the IDSA Guideline of 1992 said something like, if there are few organisms and you repeat lumbar puncture at 24 to 36 hours, and the patient is doing well, that should be considered a delayed sterilization because usually these patients do not require additional antibiotic therapy.

Now, how comfortable are we with that definition from ten years ago? Should that still

be the standard? The other thing, the Guidelines said, in 1992, was the fact that quantification of baseline pathogens should be considered. It is relevant, but it should be considered optional.

The point that John Bradley did say something about the fact that microbiologic tests can be standardized across all multinational sites. But the point is in terms of quantification of baseline pathogens, how feasible and how consistent could that be across sites even in this country, not to talk of across sites in other countries that may be involved in enrollment of patients with meningitis.

[Slide.]

Still on evaluation, the next question is when should follow-up evaluations be done and should all patients come for all visits. Here, I will refer us back to the 1992 IDSA Guideline that recommended five to seven weeks for the first early visit to be followed by six to twelve months for all patients.

It is interesting to recall that at the 1998 Advisory Committee Meeting, two weeks was sort of--it wasn't a consensus, that the majority of opinion at that 1998 Advisory Committee Meeting did

say that the test-of-cure visit should be at two weeks and that there should be a six-month follow up of a subset of patients that "were abnormal at the two-week follow up."

The question is, then, is there data on the long-term outcome of patients that are "normal" at the early visit of two weeks or five to seven weeks as the case may be and what do late neurologic sequelae tell us about differences, or potential differences, in drug efficacy in meningitis.

[Slide.]

Here, I present, for illustrative purposes, a hypothetical two-drug, Drug X versus Drug Y, trial where the bacteriologic and clinical outcomes are shown. Drug X had--you know, both of them had a fairly good bacteriologic outcome, 95 percent versus 94.6 percent. The clinical outcome was a little bit different, not too different, a little bit different, 72 percent and 80 percent.

As you can see, the difference in outcome between Drug X and Y is -8 with a 95 percent confidence interval around the difference of -16.3 to 2.5. We have a lot of issues with these and I believe this is not an uncommon kind of finding.

John Bradley alluded to it in the meropenem trial and I believe other trials have failed in a similar scenario. The question arises, in my opinion, how do we explain these. I know there are lots of issues with the subtlety or the subjectivity of clinical evaluation that could potentially explain a finding like this.

But let me ask the question, because inflammatory response in the subarachnoid space has come up quite frequently. Could Drug X--indeed, it is a good drug. It caused rapid eradication but, indeed, in doing so, it generated a lot of inflammatory markers that resulted in poorer clinical outcome.

Or the flip side is could Drug Y also have had a good response but it was not as rapid as Drug X and so the clinical outcome for Drug Y did come out better than the clinical outcome for Drug X.

The other question is could Drug X have only suppressed and not really clearly eradicated the organism from the subarachnoid space and that is why we have a poorer clinical outcome.

I don't know. I don't have answers to these. We are just bringing up this illustration for discussion purposes.

[Slide.]

Here I present some of the strengths of clinical endpoints as well as limitations of bacteriologic endpoint. I know this has been discussed at length yesterday and this morning, but let's also look at the fact that clinical endpoint is what really is relevant to practitioners and to patients. Drug traces disease and not necessarily just the organism. It also enables us to compare differences in host effects on cure rates as well as allows a measure of safety which had been mentioned earlier.

Limitations of bacteriologic endpoints are the potential for misleading appraisal of drug benefit in a serial disease like bacterial meningitis. Often--and this is a point that I really have to emphasize--often, in clinical trials of meningitis and many other conditions, that repeat lumbar puncture that we talked about may not be available and so we use clinical outcome to presume eradication.

If you look back at almost all the trials of meningitis in the past, there have been a lot of patients that have had no repeat lumbar puncture and so eradication had to be presumed.

I know it is possible to standardize. I know it is possible to insist on having that done, but I am just talking of the practicality, in the clinical setting, of having a repeat lumbar puncture always.

In addition, bacterial endpoint only lacks the ability to estimate the impact of drug on inflammatory response as I brought up in my illustration. Again, it is completely uninformative when it comes to the safety of the drug being tested. As we alluded to earlier, there is no individual-level data that correlates bacteriologic endpoints with clinical response.

I know it has a lot of advantages, too, and those have been mentioned in earlier presentations including the fact that a bacteriologic endpoint will certainly make the trial a lot easier to perform

[Slide.]

Still on outcomes, I did data to show that bacteriologic outcome is a good surrogate for clinical outcome. We have been talking about that the whole of last evening and today we have been saying the same thing. With bacterial endpoint alone means the potential differential effect of

drugs on inflammatory response and how should clinical success/failure be defined, and what should constitute the primary efficacy population?

That issue has not been emphasized. The fact that some trials could use intention-to-treat or modified intention-to-treat while other trials could use the protocol or evaluable patient population to assess primary outcome.

Finally, how best can preclinical and early first-clinical trial data be used in meningitis trials to help address some of the issues that I have highlighted? I think Dr. Goldberger's earlier suggestion comes in directly here.

[Slide.]

Now, on study design, sample size and statistics, the relevant question here rests on the amount of evidence that is needed to show efficacy in meningitis trials. Should pivotal trials be randomized, active controlled and blinded? From our end, that is the kind of trial that we would like to do.

From the end of the investigators and the sponsors, how feasible is that? How practical is that and what role, if any, should noncomparative

studies play? That certainly dovetails into the alternative trial design that Dr. Echols mentioned and Mark also mentioned earlier.

What are the appropriate noninferiority margins and sample sizes that we should use in meningitis trials?

[Slide.]

Here, all I have done is to try and bring what I thought I heard yesterday into one single slide, and that is if we look at bacteriologic outcome and clinical outcome and also consider a 90 percent power, the numbers I present there are for 5 percent delta and 15 percent delta, 5 percent delta for bacteriologic outcome and 15 percent delta for clinical outcome are numbers that we think are not necessarily unfeasible.

If you look at the bacteriologic outcome and if you recall the meropenem trial that Dr. Echols presented, the bacteriologic outcome was 98 percent. If we look at the trovafloxacin trial that he presented, the bacteriologic outcome for the control arm was 96 percent. However, if you add the input delayed sterilization to the 96 percent outcome for most of the trials, you get a bacteriologic outcome of about 98 percent for most

trials.

So, 5 percent delta is not unachievable in terms of bacteriologic outcome rather than the 10 percent delta that has been thrown out and 15 percent delta for the clinical outcome is probably a fair balance between the 10 percent delta and 20 percent delta.

But these are just facts that I am throwing out for consideration at this discussion.

[Slide.]

Finally, there was a recent publication that came out of the University of Michigan that looked at clinical trials in meningitis that have been done, I believe, since 1980 to the Year 2000. I think what was very interesting in that clinical trial was that if the delta and clinical outcome was defined as 10 percent, it was only one of sixteen studies that were done in this country and Western Europe that could meet a delta of 10 percent in terms of sample size.

Fifteen of the sixteen studies could meet a delta of 20 percent but only one out of sixteen could meet a delta of 10 percent. The point I am making here is that meningitis trials in the past have had sample sizes that have tended to be on the

small side. So this is nothing new, generally, in terms of looking at all the trials that have been done as reviewed by the investigators from the University of Michigan.

[Slide.]

Finally, I just want to summarize my presentation by asking the questions again so that it will lead us into discussion. What are the strengths and limitations of bacteriologic and microbiologic endpoints? I guess we can spend the whole day talking about this point alone; what is an acceptable loss of clinical efficacy related to the control arm for meningitis trials and what are the issues in study design that deserve consideration when designing a trial in meningitis.

Thank you.

DR. EDWARDS: Thank you very much.

Discussions

DR. EDWARDS: Before we actually begin the discussion, the points that we have been provided for discussion are brief enough that I would like to read them. Much of this Dr. Ibia has just already described, but let me just go through them.

What are the strengths and limitations of bacteriologic and microbiologic endpoints in

clinical trials of acute bacterial meningitis? Please include in your discussion how one would measure differences between drugs and other parameters such as release of inflammatory mediators which may affect clinical outcome. This would be a bit of an extension of a nonclinical outcome and, perhaps, in addition to the bacteriologic outcome.

The appropriateness of using surrogate markers for clinical efficacy when the clinical endpoint is measurable, the practicalities of performing meningitis trials, we have really very beautifully heard discussed already. Given the benefit of drug therapy over placebo, delta 1 is presumed to be large. What is an acceptable loss of clinical efficacy relative to control? Delta 2 for meningitis trials balancing the serious nature of the illness with the practicalities of performing clinical trials in this disease entity?

What other issues of study design deserve consideration when designing a trial of meningitis, issues relating to blinding of the trials, standardization of concomitant therapies and issues related to oral stepdown therapy?

We have in this room the absolute highest

level of expertise to discuss the issues of trials of meningitis and a golden opportunity of approximately an hour where we can do that in great detail.

Reflecting back on the comments that Dr. Powers made yesterday regarding balance, this would be an opportunity to really explore issues related to balance in these trial designs now.

So, Bill?

DR. CRAIG: I would ask Roger, or I guess even the FDA, has anyone ever taken all the studies there and looked at the patients that did not have eradication at the time period compared to those that did have eradication and see if the clinical outcome was statistically different? It is not enough in any one of the single studies but if you added them all up, one might get enough in the nonelimination group that you would have enough patients to see if there is any impact on the clinical outcome.

DR. POWERS: That is a really good thought and that is why, a couple of months ago, we asked a lot of the companies around this table to provide us with all the information they had down to the patient level because what you see in the clinical

trials, you will see these totals of percent eradicated.

What we want to see is that the people who are eradicated, what happened to them, and the people who didn't eradicate, what happened to them, at the patient level. So we are in the process of collecting that data but, as you can imagine, it takes a long time and we are really grateful to the companies for sending us this information and we are going to pool it altogether and look at that over time.

DR. EDWARDS: Yes, George?

DR. TALBOT: I was very interested by the presentations and specifically two points that Dr. Bradley mentioned. One is that it appears that assessment of the clinical endpoints in meningitis trials is fraught with difficulty. So I think one has to ask, looking at any of the data such as Dr. Powers was mentioning, whether the endpoints were assessed properly.

It sounds like there are a lot of issues there which does speak to considering a microbiologic endpoint although that has some problems, too. So that is a potential weakness of clinical outcome.

A potential strength that Dr. Bradley mentioned of the microbiologic outcome is the ability to control biocreep. It is not clear to me that the clinical outcomes have that ability so much given that methods of assessment, methods of supportive care and so forth change over time. So controlling biocreep with a microbiologic endpoint seems to me an important consideration.

DR. EDWARDS: Roger, did you want to comment?

DR. ECHOLS: Just to comment on Bill's question, I think the FDA is in a unique advantage to be able to request that detailed information. I am not sure I would get the same response from my competitors. Unfortunately, the publications which I have tried to go through don't provide that level of detail.

Certainly, to me the toughest question right now is the one that Imo's has mentioned and we have talked about, the whole issue of whether rapid sterilization necessarily translates into clinical response benefit--not relative benefit but not a problem, a negative, in terms of inflammatory mediators.

As much as I would like to even think

about designing a clinical trial to prove that one way or another, many have tried that long before and I am not going to tread there. The only thing I can think of is really the animal model, or the various animal models, where you can better measure these things, a more appropriate place to answer that question.

I think Mike and others might have the answer to that.

DR. SCHELD: I don't think we have the answer to that question even in animal models, as Roger has alluded to. We know, at the present time, which inflammatory mediators are most responsible for the development of meningitis, per se. In other words, if you use tumor-necrosis factor alpha or IL1 beta, you can induce meningitis with those cytokines by themselves.

There are other cytokines and chemokines which do not do this. We also know that there are chemokines and cytokines that appear to be rather specific for bacterial versus viral disease and some of them have actually been entertained as a diagnostic test.

We also know that they are released in an orchestrated pattern over time, just like they are

in sepsis or septic shock and some are gone by the time, say, a patient would be arriving at your doorstep. So I am not enthusiastic about trying to measure a particular cytokine response, say, in CSF that would predict outcome in patients with meningitis because I have a feeling that that would be very difficult and would take a lot of patience in order to show that.

I think it probably could be done in animal models. The problem there has always been that most of the studies that I am aware have been done in rabbits. The endpoint is usually a microbiologic endpoint and not a clinical endpoint and we don't let the animal survive for days and follow them neurologically or audiologically to understand what those endpoints are.

I think the evidence is very strong that TNF alpha causes apoptosis of hippocampal neurons which causes memory loss and other issues related to the neurologic sequelae of meningitis. I suppose that if you had a small animal model and you studied the inflammatory response, you could answer this question of whether rapid bacteriolysis or rapid bactericidal activity without bacteriolysis and, therefore, the attendant

inflammatory response led to a change in neurologic or--well, that probably--neurologic sequelae or death.

Like Roger mentioned, in clinical trials, which I wholly support, it should either be death or something easily measured as major and lumped together and everything else is over in another category.

So I think it is feasible to do those experiments. I am just not aware of any that have been done. Mouse models in meningitis are difficult. They abrogate all of the natural pathogenesis because the organisms are either directly instilled into the cerebral cortex or hyaluronidase or some other enzyme is put in the internasal cavity and that is followed by the bacteria and they get bacteremia and they get meningitis, but only a proportion get meningitis.

So it won't be easy to get this answer from an animal model is my main point.

DR. EDWARDS: Let me ask you to comment further in this context regarding the issue of other additives to bacteriologic sterilization such as a Gram stain or antigen detection which might strengthen the use of a non-clinical endpoint.

DR. SCHELD: I would support the Gram stain as an entry criteria. It is only going to be positive in about 80 percent of patients, but if I had a patient who had pneumococci or meningococci in the blood stream and had a positive Gram stain in the CSF, that patient would be entered in as a definite meningitis case.

We don't even do antigen testing in our hospital anymore. Most hospital laboratories either have stopped offering it or the sensitivity and specificity is so poor, or the cross-reactivity with some of the organisms is so bad, that I couldn't recommend it.

I would throw out an idea which is probably not going to have any validity but there is a pretty strong growing literature using inflammatory markers which are nonspecific to try and separate bacterial from viral meningitis. This is very important to clinicians, as you know, because if you have got partially treated bacterial meningitis, the spinal-fluid formula can look a lot like viral and patients with viral meningitis can have a high CSF pleocytosis due to neutrophils.

They are things like CRP and procalcitonin. NPR, last week, was talking about

CRP but it was mainly in heart disease. But you can show that there is a fairly good separation, especially for procalcitonin, between proven bacterial meningitis and viral meningitis. You can separate these groups out.

What I don't know is if you followed the response to how the patient did over time with serial procalcitonin measurements whether that would be predictive of how they would do. Somebody ought to do that experiment.

DR. DERESINSKI: I know in the U.K., PCR for meningococcal diagnosis is widely available. I am not suggesting that this would be done at point of service but, in terms of deciding post hoc which of the patients enrolled in the trial actually had bacterial meningitis, if PCR were available for the array of pathogens that were of interest, then that would possibly be useful.

Can you comment on that?

DR. SCHELD: PCR is useful. It is sensitive. It is highly specific. The problems in some of the assays in the past have been that they are too high a false-positive rate. But meningococcal PCR, I think, is very valuable. We don't have one that is as good for pneumococci at

present.

While we are on this subject, the data is very old. It is back in the 1960s by Roger Feldman and a number of others. But there is, in human beings, a correlation between the height of the bacterial concentration in the spinal fluid and ultimate outcome. The higher that number, the worse the patient is going to do.

There is one exception and that is Listeria. For reasons that are not completely clear to me, Listeria tends to have a lower concentration of bacterial in the spinal fluid than do the other three major meningeal pathogens. Yet, the outcome of Listeria meningitis in the United States is quite poor. 25 percent mortality rate is not unheard of.

But, for the other pathogens, it holds pretty well.

DR. GILBERT: It is more intracellular.

DR. SCHELD: That is another good interesting question. At least in animals, that is not the explanation. We did an experiment a number of years ago, or my idea was use a drug that had intracellular penetration and, therefore, it would eradicate Listeria more rapidly from the

spinal fluid in an animal model so it shows rifampin which is highly active against Listeria.

It didn't work. The reason it doesn't work is because over 95 percent of the Listeria in your spinal fluid are actually in extracellular location. So can't explain it.

DR. DERESINSKI: Actually, in a way, related to the issue of the prognostic implications of large numbers of organisms, is it possible, John, that the difference, the inter-country difference, in outcomes in the study, the meropenem study, might be related to the frequency with which children get antibiotics prior to admission to the hospital in the different countries? Was that checked? Were urines looked at for antibiotic?

All the studies that have looked at self-reporting or parent reporting of antibiotic administration suggests that it is highly inaccurate and you really need to check the urine.

DR. BRADLEY: The urines weren't checked in that study. The one thing that correlated with poor outcomes was time from the onset of symptoms to hospitalization.

DR. SCHELD: That is a critical variable in resource-limited settings because you can show,

time and time again, that the time from onset of symptoms to the initiation of the first dose of antimicrobial agents in a society such as ours is far shorter than it is in a resource-limited setting.

Another thing that we have been interested in very much recently has been the impact of micronutrient deficiency in bacterial infections, in particular. Malnutrition is very common in a setting like the Dominican Republic, which you mentioned earlier. If you look at the data, for example, in West Africa, which is published in Lancet, pneumococcal meningitis in West Africa, both children and adults, has overall death or severe neurologic sequelae in 78 percent of patients.

So 22 percent of patients escape unscathed, which is horrible. But it is mainly related to the poor comorbid conditions, malnutrition, et cetera. What we have just shown recently, if you take animals and you make them zinc deficient or glutamine deficient, that not only do they have more bacterial in their spinal fluid, they have more bacteremia and the mortality is twice as high as if they have a normal zinc

concentration.

So just that one variable affects the animal model profoundly. I can't imagine what it must be doing in human beings.

DR. EDWARDS: John?

DR. BRADLEY: First, I would like to say that George McCracken would have been here today except he is presenting a talk in meningitis at the International Pediatric Infectious Disease Meetings in Santiago, Chile today. So he couldn't make it.

In addressing the issue of dexamethasone use empirically in meningitis, there isn't unanimity in the pediatric ID community. There are two schools of thought. One is led by George McCracken where his retrospective data with pneumococcus suggested a benefit. There weren't enough cases of pneumococcus in his clinical trials in contrast to Hemophilus to show a statistical benefit.

So people wanted proof that it worked before they used it. There are two papers, one from Egypt and one from Turkey, which are prospective which show benefit but the disease that is present in those countries is a little bit more severe, a little bit different, so some pediatric

ID people here say, well, that is not relevant to our population.

Now, with this new paper from Europe in adults, I would think it would give more impetus to the use of dexamethasone but I can just hear my colleagues saying, "Well, that is in adults. That doesn't apply to children." So we still have the issue.

In terms of markers of inflammation in the central nervous system, the CSF, the kids that come in already have significant inflammation present, many of them, and with damaged central-nervous-system tissue, you are going to have markers of inflammation being produced just based on damage.

To be able to control at the 36- to 48-hour point, how many of those inflammatory mediators are a function of death of organisms stimulating white cells or death of cells stimulating white cells I think will be very difficult to separate out.

It is a very good question, a very tough question. But I don't know that we can get at it necessarily in these human models. So, in terms of trying to take a clinical outcome parameter and

make it more scientific by measuring inflammatory mediators, I think, I think will be very difficult. There is such a huge background in clinical presentations from CNS inflammation and damage that I think it will overshadow the signal from killing of organisms.

Again, ten, fifteen years ago, we were looking--when the data on IL-1 and TNF came out, we were looking at drugs, perhaps, which wouldn't cause as rapid an inflammation and everyone was thinking, "Gee, ceftriaxone and cefataxine may not be the drugs of choice anymore." But, again, with the use of drugs like dexamethasone to minimize the impact of exploding organisms, I think that those concerns are a bit less appropriate now, especially if we can standardize dexamethasone use prospectively.

Now, we also have the issue of dexamethasone effect in meningococcal meningitis which still is not well characterized. In some Brazilian studies that remain unpublished, dexamethasone decreased hearing loss in a prospective controlled trial. I wish they would publish that information.

So I think there are a number of

unanswered questions but I think the micro endpoints are the most defined endpoints that are most likely to be correlated with clinical outcomes. It is important to raise all of these other issues, but I think focusing on what we can do is still very, very important.

DR. EDWARDS: To just sort of clarify--I want to address this question to you, Mike, but I will invite anyone to respond. If our goal were to design a study, to create a study design, that would maximize using and endpoint like microbiologic cure and allow flexibility in clinical outcome, so making the study feasible, at this point in time, what would be your selection of the nonclinical outcome parameters to be measured.

Can you add things other than just sterilization of the CSF?

DR. SCHELD: Without any other prospective or retrospective information from animal models as to whether other inflammatory mediators would predict outcome, I don't think so. I think the microbiologic response, preferably quantitative, assay would be the best defining method.

DR. TALBOT: Just along that line, I think that is a question that is important because the

sample-size considerations that have been presented are based on dichotomous outcomes. So the question I was going to pose is similar to yours. Is it feasible, clinically, and in the clinical-trial setting, and meaningful to, for example, look at time to reach a certain colony-count threshold or to look at a two- or three-long drop at a certain time.

So, for example, could you get a cohort of 75 patients, would it be reasonable to randomly assign a third, a third, a third to have a tap at, say, 24, 36, 48 hours or 36, 48 to determine whether or not there is a difference in the profile of drop of counts or time to get to a certain count?

DR. EDWARDS: Dave and then Roger.

DR. GILBERT: You have convinced me that it is incredibly difficult to do a proper controlled statistically valid study of purulent meningitis. Even if the microbiologic endpoint is accepted as a valid marker, it is still going to take, if I read these numbers right, hundreds of patients, many years, many different sites and the like.

So, it strikes me, if our goal in this

free, open-flowing discussion is to push the envelope a little bit to see how we can help the clinician help the public that our thinking has to go a bit farther.

Dr. Goldberger started out this session suggesting that we could use microbiologic endpoints to, perhaps, get into the accelerated approval sort of format. Again, I think that is doomed just because of the numbers. Yet, what is clinically relevant is that clinicians--academicians, as well, of course--but clinicians want whatever data can be easily accrued.

We need to know as well--clinicians also need to know that it is unlikely, it seems to me, that they are going to quickly get a prospective, randomized, double-blind trial. The image of the FDA is wonderful. As somebody said earlier, it is the regulatory agency with respect to drugs that is the envy of the world. It is stamped as safe and effective by the FDA, everybody responds to that.

On the other hand, it could be a bad image if the current regulations or the interpretation of the regulations block the flow of pertinent information to the users, to the clinicians. So I

would like to, at the risk of having criticism rain down upon my head, suggest that maybe there ought to be a new section in approved package inserts.

We have got black boxes with adverse-event warnings and so forth. Could we have a grey box, Pertinent Data of Import for Unlicensed Indications. Now, that is just sitting here dreaming up a name, but so that it is absolutely clear that this data is not data that has been part of the usual prospective, randomized, controlled double-blind study.

But, in the process of evaluating new drug X against drug Y, we enrolled 50 patients with pneumococcal meningitis, either comparative or noncomparative, but we only got 50. But we don't want that to be buried in a vault somewhere. We feel like we ought to share that information.

I don't like the word "surrogate" because it means so much to different people. So, again, and I have been scratching around here, bacterial eradication does not necessarily correlate with survival or residual organ or tissue injury. Since it is not feasible to promptly assess clinical outcomes in a large number of patients, bacterial eradication is postulated or presumed to provide

clinical benefit or words to that effect.

This is my postulated grey box. And then the data. Then I don't see how we lose. It doesn't fit within the paradigm of existing regulations and that, of course, always creates angst. But to have pertinent data buried doesn't make sense to me.

To wait, the study that we are all quoting in the New England Journal took eight years to do. How many different countries and investigators in five different countries? I mean, that is not prompt service to the American public.

DR. EDWARDS: Roger, I have got to ask you to just relax for a moment.

DR. GILBERT: You wanted this to be provocative and free-flowing, Mr. Chairman.

DR. EDWARDS: Well, you have really introduced a whole conceptual idea here which I really think we need to turn to for a moment before we come back to Roger.

Mark?

DR. GOLDBERGER: I thought those comments were very interesting. My actual response sort of started yesterday and I think it continues now as I have for, for instance, been on any number of USPHS

working groups to look at issues related to therapy of PCP, therapy of Mycobacterium avium, therapy of opportunistic infection in AIDS. There have been many of these groups over the years.

The purpose of those groups, in fact, has often been to take information both that is in the product label, information from clinical trials, information from clinical experience of experienced clinicians, et cetera, et cetera, and formulated into recommendations by an authoritative body.

More recently those recommendations carry with them some information about where the data was derived from, how strong the recommendation is and that those recommendations are then made available publicly and are available, obviously, on websites, et cetera.

It seems to me that the approach that you are outlining fits very well into that type of strategy for making information available. It is, on one hand, very encouraging to now hear that people believe that the product label is the greatest source of information from which all practicing physicians obtain everything they know and, if it is not there, nobody will know anything.

Experience has suggested that,

regrettably, that is not always the case and that, in fact, if the working group of the IDSA, other major organizations, a combination of one of the neurologic organizations in IDSA were to have a working group and develop such guidelines, they could be made freely available and they would provide enormous help to practicing clinicians and would include, in fact, the kind of information, the strength of the recommendations, et cetera.

Truthfully, it seems to me that, actually, is a more effective way of getting information out there than trying to talk about developing a new section of the product label. So that would actually be my simple response.

DR. EDWARDS: John?

DR. POWERS: Could I add something to that as well? There are two different issues here. One is getting by the regulatory hurdle of getting your drug approved for a specific disease. The second one is how clinicians view that information once it gets out there. There is actually a fair body of information that says what makes clinicians change their practice patterns to use a new drug or an old drug in a new way is a randomized, controlled trial.

I can give an example in the recent past where we have looked at things. Caspofungin, an antifungal, was approved for admittedly a different indication, namely as a secondary treatment for invasive aspergillosis based on 60 patients in a historically controlled trial.

Voriconazol was approved as primary therapy for invasive aspergillosis based on a 400-patient trial that was randomized and prospective. Both of those drugs were approved by us. However, in talking to practicing clinicians, they view the strength of that data very differently. So it is not just getting by us. It is, then, what would clinicians do with information based on twenty pneumococci eradicated out of the spinal fluid and would that give them the information they needed to actually make a change in their clinical practice.

DR. EDWARDS: I interpreted that response as a negative.

DR. GILBERT: You are very astute. Nobody will argue about the value of prospective, randomized, comparative trials. However, what we are hearing is that, for this very, very serious disease, it is not feasible. If I was

industry--and industry is sitting over there like they are deaf and dumb here. I know neither is true, but I am not going to invest money in a trial that is going to take me eight years to accomplish, to get even to minimal statistical power.

We have got to come up with something creative.

DR. POWERS: Let me ask the flip side. When we had this discussion at the BAMSG, we said, oh, nobody is going to put anybody on the spot. Jack Edwards turned to me and said, "John, let me put you on the spot." So I am going to do the same thing to Roger at this point.

DR. EDWARDS: I was going to do the same thing.

DR. POWERS: He has been waiting to talk anyway. When Imo showed his last slide, what we are talking about--I am just looking at these numbers. This is 80 percent power, so I got the numbers wrong, I will admit.

When one looks at a 90 percent bacterial eradication rate for a 10 percent delta, that is 141 patients. When we look at an 80 percent clinical rate--I'm sorry; that is a 90 percent--yes; 90 percent bacteriologic cure rate at

a 10 percent delta with 80 percent power is 141 patients per arm; correct? Did I say that right?

If we look at an 80 percent clinical success rate, and I am basing that on the trovafloxacin trial that was published in January, an 80 percent clinical success rate for 80 percent power with a 15 percent delta is 112 patients per arm, less than the microbiologic part of the thing would be.

So I guess the question is are those numbers unfeasible to do.

DR. ECHOLS: Feasibility--no one has a crystal ball. Certainly, judging from what Trovan or the Pfizer folks were able to do in a relatively short period of time, relatively being a 15-month enrollment period--so I certainly would not even embark on a study that I thought was going to take five, six, seven years.

So whether it is 15 months or it is 18 months, I am certainly looking at an enrollment time of less than two years. You would have to put the resources behind it but that is our expectation in terms of number of sites, number of countries.

So I think we can come up with some meaningful prospective, randomized data with about

a 300-patient sample size which I think will satisfy both a tight confidence interval for microbiologic endpoint and a somewhat less tight but still not uncomfortable, a lower boundary of 15 percent or something like that, for clinical endpoints as long as the clinical endpoints are hard or relatively hard, or relatively hard.

If you start getting into soft clinical endpoints, and you end up with an efficacy rate of 70 percent, then the numbers change again. But just to answer, I think, a couple of the other--not to diverge, but just to give you my real idea of what needs to be done.

I am convinced, looking at the data, that blinding is really critical here. As much as we would like to demonstrate the option of being able to step down to oral therapy, I think that complicates the study to such an extent that we wouldn't be able to maintain a blind in a global program.

So I think the step-down issue should wait for another study or other experience. So I think we can do a double-blinded trial which will then help in some of the clinical evaluations that are not then biased.

But my other real concern in as much as we love to quantitate things no matter what it is, quantitating the microbiology in a study conducted in ten different countries is, I think, going to be very, very difficult if not impossible. We can't use a central lab. We have to depend on the local labs. The techniques are--just even trying to train people how to do it, I think, would be a problem.

I am also envisioning that many of these cases, they will have already taken the spinal fluid, spun it down and then seen that they have a positive Gram stain. Then they enroll the patient, so you can't go back and even quantitate in an unspun sample the original isolate, the original spinal fluid.

DR. TALBOT: What about time, somehow incorporating time, to--

DR. ECHOLS: Again, it is going to be very difficult, I think, to even get people to do the second tap within a specific window, to try to then break that out into three different cohorts. I think it just, again, gets a level of difficulty that--the most important thing, in some ways, is almost whether the patient is enrolled on a Friday

and then the 48 hours falls on a Sunday, depending on what country and religion you are in, that that may create a bigger problem than anything else, just having the staff available at a specific window to do it. It would be tough enough even with everyone doing it the same way.

The only other thought I had is that to get information sooner. We will have a safety board. We will be doing an interim analysis probably after the first hundred cases, or something. If the agency felt that that information would somehow be useful, and they were willing not to penalize us, obviously, for breaking a blind in an interim analysis, somehow that information could be available sooner than the whole study. The whole study would still be running. It wouldn't be that we would stop the study prematurely. It is just that information could be available a little sooner.

But it probably wouldn't be available that much sooner. We are not talking years sooner.

DR. EDWARDS: This conversation seems to be heading towards a zone of balance, in my opinion. I think that it would be very valuable if we tried to fine-tune the balance issues. So,

John, I am now going to put you on the spot. I would like to have you all respond to the comments that Roger has made regarding quantitative bacteriology and what would be the hard clinical endpoints that you would use.

DR. POWERS: I think that is actually, to answer your second question first, quantitative microbiology, I think--I guess what we are coming to, the balance I see, is that both clinical and microbiologic endpoints lend something to determining the drug's efficacy, both in a little different way. So they are complementary but different.

The quantitative microbiology would add something to the microbiologic endpoint in terms of--as Mike said, there is some prognostic significance to it. However, if it is not practical, then we are back to the feasibility issue. I agree. I think it would be very difficult to get fifty centers, like the trovafloxacin study, and get all that information sent to a central lab and get the quantitative information.

It would be helpful, but we don't require it currently. So that gets to the practicality

issue of actually doing that.

The second question is those hard endpoints, I look to this group here to help us to actually design what those hard endpoints would be, what do clinicians find relevant and can we do this in a way that is more dichotomous of, yes, the person is cured or no, they are not, instead of getting very fuzzy in between.

The blinding would help tremendously because, as Roger said, then we don't have this issue of was there any potential bias involved in determining those outcomes, both clinically and from the safety point of view. So I think all those things would help us in the long run.

DR. ECHOLS: In terms of the clinical endpoints in the evaluation of previous studies, the major neurologic sequelae is certainly mortality but the one other variable that is, I think, soft is if someone gets an additional antibiotic or has their antibiotic treatment changed, you can, really, at any point--in some protocols, they are automatically considered a failure whereas, in another way, you might consider them nonevaluable.

I think, by double-blinding, you can get

away from some of that but I think, clearly, in the Trovan study, because people knew they were on either the standard of care and maybe not doing as well as they might like, but, since they were on standard of care, they didn't change therapy whereas, if they were on trovafloxacin, they were a little less sure, they changed therapy even though they were getting better.

We just need to avoid that kind of confusion. I think blinding will help, but I still think, unless a patient is getting worse or having a clear outcome, maybe nonevaluability or not including them in the analysis rather than automatically calling them a failure.

DR. POWERS: I think a lot of what would help with this, too, would be to define in the protocols ahead of time what actually is a success and what actually is a failure. Dr. Bradley and I talked about this on the phone. One of the issues in the trovafloxacin trial was certain investigators called subdural effusions a failure.

If it was specified in the protocol, that is not a failure. That might actually help the clinicians to decide. Having done these trials, myself, before, if the CRO comes out and tells you,

why did you put this down there on there, and actually questioned the physicians about why they are putting these things down, it would be helpful.

The question still remains, why did that happen in one arm of the trial and not the other. But part of the reason might be, as you said, it wasn't blinded.

DR. EDWARDS: John?

DR. BRADLEY: I agree exactly with what you have said. I think we can put together hard clinical outcomes rather than going into all of the subtleties of developmental delay and degree of disability. We can define outcomes which would be easier to measure, something along the terms of the Glasgow Outcome Scale.

With respect to the blinding, we talked about this as well. In the trovafloxacin study, we were less comfortable with the safety of the drug and any child who was on trovafloxacin who had joint problems during treatment, we wanted to be able to do an MRI on and the company said, "Any time any of you want to do an MRI because of joint concerns, do it."

So the safety of quinolones, in general, is far better understood at this point. Far more

patients have been treated, kids, so I am no longer interested in identifying the safety issues. So the double-blinding, now, I think is far more important.

Getting back even further to the micro versus clinical endpoints, this whole discussion about micro not being a good endpoint is a nice intellectual discussion but I don't think any of us at this table doubt that a micro endpoint works.

We all have subtle concerns that there may be situations in which it might not work, inflammatory mediators, this sort of rapidity of sterilization. But none of us feel that micro is not going to be the appropriate indicator, so using micro as the primary endpoint and then putting whatever little qualifications you want to say, "This may not be the end-all and be-all," I am happy with.

But I don't want to get away from the fact that we all feel that the micro endpoint is valid.

DR. EDWARDS: Mike, I would like to ask you to contribute to the issue of the hard clinical endpoint since we have really got a golden opportunity to discuss that here.

DR. SCHELD: I am not familiar with all of

the subtleties of the Glasgow Outcome Score that was described in the paper last week in the New England Journal, but what attracts me about it is that they define a group that clearly did very well, could return to work, return to school, was functioning, had no definable neurologic sequelae, and were obviously alive.

That was one group. Everybody else was in the other group which is one hard outpoint that you could use. I know it is in there. I haven't looked at it in a couple of days. They gave us all of seven days to write the editorial, by the way, and they took out part of the good stuff.

So I think these things can be measured better than they have been in the past. I think it is a little bit easier in adults than it is in children because they have a lot of the developmental milestones that they have to meet. I would not wish to speak to that. Maybe John could say a word about it.

But I think it should be blinded. I support going to a PO in phase IV type of environment, although I want to ask Roger one quick question. The numbers you presented for trova, did that include the meningococcal experience in

Nigeria?

DR. ECHOLS: No. This was their single trial which did get published.

DR. SCHELD: They did do a separate trial which you may or may not know about.

DR. ECHOLS: Yes. You can read about it in The New York Times.

DR. SCHELD: It has gotten some flack in the lay press; yes. Nevertheless, what they found in Nigeria, which was the response rate between trovafloxacin and ceftriaxone was roughly identical. 75 percent of those children received all of their trovafloxacin by the oral route.

To have an oral drug that would be inexpensive and in a resource-limited setting where you don't have a cold chain for injectable antibiotics would be a major advance. I think that would be nice to have down the road, but I would not encourage you to incorporate that into a phase III trial now.

DR. EDWARDS: Stan?

DR. DERESINSKI: Roger, I would like to take what--you discussed the issue of changing therapy being counted as a failure, et cetera. I would like to take it a step further than you did

and that is I think if you demonstrated that the spinal fluid had, in fact, been sterilized at the point when the antibiotics were changed, that that ought to be counted a success for the assigned therapy, certainly a microbiological success. Maybe we can talk about that.

The other is it was brought up the issue of the noncomparative study and how that influences clinicians' management of patients. It is certainly a valid point, but what it speaks to is the same sort of thing that we deal with when we develop guidelines and that is the strength of the evidence.

If the alternative to having some noncomparative data is to have no data at all, then I think everybody would agree to the fact that having the non-comparative data, perhaps with an appropriate historical control, as was done with the Caspofungin work, would be better.

DR. EDWARDS: Stan, those comments really bring the opportunity for us to discuss this noncomparative issue. Before we do that, George, go ahead.

DR. TALBOT: That is exactly what I want to comment on because I think that is a very

important consideration. To preface that, I would say that the conversation has flowed despite the comments from Dr. Bradley and Dr. Gilbert again towards the clinical endpoint, the delta for clinical endpoint and so forth.

I am not convinced at all that, with the sample size of 300, any companies are going to study acute bacterial meningitis. I am just not convinced of that so correct me if I am wrong. But, given though we are hearing about people exiting this business, I am just afraid that people are going to feel good in leaving the meeting that we have gotten it down to 300 from 700. But I am not convinced that is going to make any difference at all.

So what about the noncomparative design? I think that there are some merits there to consider. I would add one little tweak to that which is I would do two things. I would have an endpoint that is microbiologic with a sample size that allows a fairly narrow confidence interval around that and pick that by using historical data, as, say, 95 percent is your target or what have you.

But I would include a control group, not

for the purposes of performing a statistical comparison but to allow two things. One is blinding to address all the potential errors of ascertainment, of adverse events, treatment decisions that could be biased because of the standard therapy versus not issue.

Second of all would be to provide some internal anchor for the study which tells you whether the study has somehow gone grossly wrong, that, for some reason, the study was not conducted according to the standards you would think.

Your power to detect that with a small--not one-to-one, but, say, a three-to-one randomization--your power to detect it with a small comparative group is, admittedly, low but all I would be looking for would be some gross difference in the point estimate of those results, microbiologically and clinically.

So, with that variation, I would come back to I would really like to make it possible to have a microbiologic endpoint. I would pick it a priori, as has been done for some other indications. But I would include a small comparative group as an internal anchor.

DR. ECHOLS: One of the figures I showed,

again, just to reiterate some of those numbers, if you have a microbiologic response of 95 percent, and if you are comfortable with a plus-or-minus 5 percent around that, sample size, then, for a single arm, is only about 100 enrolled. Evaluable, is only about 75.

The problem is, then, your experience with Strep pneumo is small, estimate of around fifteen cases of Strep pnuemo. If you throw in another 25 percent for some sort of gauge for clinical response, again, obviously, or confidence intervals would then sort of go pretty wide but you could do it for 150 subjects.

Just to come back to your question, George, about what other companies might want to do. This is a study we have talked about doing within our company for some time, with the agency for some time. I know it is in our budget and we are ready to roll with this 300-patient study. We were not willing to undertake a 700-patient study, not so much the resources but we just didn't think we could do it.

So I still think we can do a 300-patient study. It is not going to be easy, but whether that same hurdle would be something other companies

would accept I think is a reasonable question.

Doing meningitis trials, pediatric meningitis or meningitis, period, it is not for a market that anyone wants to go after. It is very much of a secondary gain and it may be different for different programs. But it is never because there is money to be made in the treatment of meningitis. So it is a difficult question for companies to answer. There are motivations for doing the trial that are not directly necessarily obvious in terms of what the market size is.

DR. EDWARDS: Could I ask for comment from others regarding Roger's comments?

DR. GESSER: I guess the question is whether we would consider that feasible or whether Merck would consider that feasible. I think there are just too many factors to consider to give blanket statement what is feasible and not feasible. But I think Roger has expressed the difficulties and the salient features and the hesitancy and issues that will come up going forward.

So it is really hard to give you a flat answer. It depends on the agent. It depends on the program. It depends on the status of vaccine,

so many things. Possibly, it depends on Roger's experience if he is the first one going forward.

DR. TALBOT: Everybody else is going to wait two or three years to see how Roger does?

DR. GESSER: It takes a while to--it sounds like Roger is in a position to make a decision.

DR. TALBOT: I guess I am sort of putting you on the spot because what IDSA is saying is we need more data. I don't sense that there is unbridled enthusiasm here about the feasibility of even a 300-patient trial.

DR. COCCHETTO: Although, George, my common sense tells me I would probably be better off to remain silent, I think your statement is more correct than incorrect. Certainly, if we looked at this with a drug in hand, I can say, and I suspect Richard would agree, inside the company, it would be a very energetic and animated discussion.

This is a tough one. The study that Roger is talking about conducting gives me chills, frankly. I think, from a regulatory perspective, you have got a pretty substantial probability of losing on that study--I think. If I were your

regulatory affairs professional, we would have some tough one-on-one discussions about whether to undertake that trial.

I think those outcomes are very demanding on your drug and, obviously, it is going to depend on the drug. So I tend to agree with you, George. I think it is a tough one to persuade an organization to undertake. I would want to be focused on, really, exactly the right drug and have very tight agreement on the clinical definitions particularly

DR. GOLDBERGER: Could I make a comment?

DR. EDWARDS: Yes, Mark

DR. GOLDBERGER: A couple of things. First, about a noncomparative trial; I think that one concern which I thank came up in some of the discussion is that, from situation to situation and over time and at different clinical study sites, people do things differently. So, when you try to figure out what is the target I am looking for, you take into assumptions of what has been in the literature.

One of the problems is the literature doesn't always completely report, well, certain patients dropped out, certain patients were

nonevaluable, how were they really counted. You make your assumptions about how you want to see performance. You don't really know everything that was necessarily done.

As a result, when you do the noncomparative trial, you may end up with something different than what you anticipated which really wasn't bad but, based on what your plan was going in, it leaves you with a problem.

One example that comes up is when we were involved, for instance, with Adventis a few years ago with the development of rifapentine for pulmonary tuberculosis, one of the interesting things that came out of it was if you looked at the rifampin arm, and, again, these studies were done largely in rural South African farm workers--the rifampin arm, which was better than rifapentine, but the rifampin arm's failure rate was higher than what most people would have expected.

If you were using some kind of historical control, you might have been fooled. The fact is that some of the data in the literature either didn't take into account all of what we knew about failures, et cetera. It didn't take into account the kind of severity of patients that you might be

enrolling in a contemporary trial. It was probably somewhere between 50 and 100 percent higher than what you would have expected.

As a result, the rifapentine was higher than that. But you might have been misled if you ended up doing a noncomparative trial. That is my first comment.

My other comment is, and I don't know whether Roger--I don't want to put him on the spot about this, but, in truth, when we talk about, well, what is the incentive for a company to be doing something like this. There are a lot of reasons for doing it. It can project a very favorable image for the company. It makes their product overall look better.

But, remember one thing with regards, for instance, to the meningitis indication, depending on the molecule you have one hand, one of the things is, it is a lot easier to justify this if you have got a product out there already that is doing fairly well as opposed to something that you are in early phases of development because then you have the option, is the indication in question, et cetera, going to be something that doing a study like this might, for instance, qualify for six

months of additional pediatric exclusivity.

Keep in mind that that is a pretty significant financial payback. If you have got a product earning hundreds of millions of dollars, six months of extra exclusivity does give you a more meaningful financial return and can be an incentive where, for a company who is developing the product doesn't have it out there yet, that calculation may be very different.

The other thing to keep in mind, that for pediatric exclusivity, you need to perform the study. The fact that the product, for instance, does not work as well as performed may mean you don't get it in the label--you get some statement in the label about how it performed, if there is a concern. But you also get the exclusivity.

You do not have to be successful in how the product performed. You have to be successful in performing the study. So there is that incentive.

Now, that doesn't apply, obviously, for indications that are going to be used exclusively in adults, et cetera. But meningitis is a little different. For the right product, that currently does exist. We do not require any additional

legislation. So you might keep that in mind; in some circumstances, that is a useful tool.

The last comment I make is people are familiar with what products, for instance, Roger's company, may have available. But one thing no one actually has talked about--everyone has talked about additional trials to look at new products in meningitis. Actually, I don't think anybody has mentioned to date what products they want studied in those new trials. We would certainly be interested in hearing that, what people would like to see in terms of, say, a larger trial to assess efficacy, what other products there are that people are interested in, particularly products that are a little further along.

But we haven't heard any product named, I don't think, at all in this discussion.

DR. EDWARDS: I think we are going to take a break now. Let me just, if I may, briefly summarize this discussion by saying that, with the introduction of a balance, there is at least one major pharmaceutical company strongly considering embarking on a trial within the confines of a balance analysis strategy and others who are noncommittal at this point.

One can look at that either positively or negatively. For some of us, that is very optimistic, realizing the difficulties studying this particular entity. For others, it might drive even a stronger interest in trying to do some of the fine tuning, on the balance, to entice others.

So, let me leave it at that. If we could come back at just a little after 11:15, that would be great so we can move on. Thank you.

[Break.]

DR. EDWARDS: We are now going to turn to the issue of acute exacerbation of chronic bronchitis. We are sort of leaving one extremely difficult topic and moving to one of, perhaps, even greater complexity.

We will use the same format and have three speakers and then begin moving through the questions. I would like to ask Jan Hirschmann to begin. Jan?

Issues in Clinical Trials of Acute Exacerbations of Acute Bronchitis

IDSA Speaker

DR. HIRSCHMANN: Thank you very much.

[Slide.]

Most people in the United States who have

acute exacerbations of chronic bronchitis receive antibiotics. But, do they, in fact, work?

[Slide.]

To answer that question, we have to address two different definitions. First of all, what do we mean by chronic bronchitis? This is a disease that occurs in current or previous smokers with a long history of tobacco use. These patients have chronic sputum production without any other explanation.

Acute exacerbations are defined as acute attacks in which there is one or more of the following symptoms; increased cough, increased dyspnea, increased sputum or a change in sputum color.

[Slide.]

On average, a patient with chronic bronchitis has one to two episodes of these per year. We know that there are certain noninfectious causes that are convincingly demonstrated. Air pollution, changes in barometric pressure, exposure to fumes, dust and smoke, exposure to cold air can all bring about these symptoms.

[Slide.]

In addition, however, we also know that

there are certain infections that are causes. Viruses are responsible for somewhere between 20 and 65 percent of the cases of exacerbation, probably closer to the higher number using the most recent data with the most sophisticated techniques.

Two organisms which might be responsible and might be usefully treated by antibiotics turn out to be present in very small numbers. Mycoplasma pneumoniae is represented in less than 1 percent of the cases of acute exacerbations and Chlamydia pneumoniae probably less than 5 percent. In fact, there are probably no cases in which it has actually been isolated from the sputum. These are all on the basis of serological studies.

So the information about acute exacerbations of chronic bronchitis relate primarily to three respiratory organisms; Hemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. These organisms, whether the sputum is taken by expectoration or whether it is taken by protected bronchoscopic specimens are present in about 20 to 50 percent of cases of acute exacerbations.

That means, of course, that 50 to 80 percent of exacerbations have no demonstrable

bacterial cause. In these 20 to 50 percent in which Hemophilus influenzae, Streptococcus pneumoniae or Moraxella catarrhalis are present, does that mean that these organisms are, indeed, responsible for the exacerbation?

The answer is, not necessarily because these very same organisms are present in the sputum of patients with chronic bronchitis even between acute exacerbations. What we need to know is whether these are innocent bystanders who are colonizing or whether they are actually responsible for the exacerbations.

How are you going to answer this question and how are we going to answer the original question that I asked; that is, are antibiotics useful in exacerbations.

[Slide.]

We have to do this by doing controlled trials. The ideal trial, in this particular respect, would be randomized, double-blind and placebo-controlled and it would have to have a large number, not only for statistical reasons but some people believe that this is a heterogeneous disease in which there are several subgroups which are different from others.

So we have to have a trial that includes these various subgroups in adequate numbers to make sure that we know which, if any, of these groups actually respond to antibiotic therapy. We have to have microbiology to determine what the actual cause of these things are and we have to have chest films to exclude pneumonia.

Now, pneumonia is not a very common complication of acute exacerbations, but it is clear that even a small number in any group would make a major difference in terms of the outcome of antibiotics versus placebo. Very importantly, we have to have standardized therapy. Everybody has to be treated the same and that means bronchodilators, both beta-adrenergic agents and anticholinergic agents and systemic corticosteroids, a point I will return to in a moment.

[Slide.]

We have to stratify patients by severity, not only of the exacerbation, itself, but also of the underlying disease. Because some people believe that the advanced patients with chronic bronchitis have a different microbiology from those who have mild to moderate disease; that is, they

believe that Gram-negative rods are more important in these patients than they are in patients with less severe disease.

We have to use outcome criteria that are assessed early. We know, on the basis of almost every acute bacterial infection, that there should be some response in the first few days. It doesn't make sense, then, to look at the evaluation three weeks after the particular problem occurs. We should be looking at it three to five days, seven days, and so forth, not looking, as so many studies have done at 21 days after the event started.

What symptoms should we be looking at? Patients come in to their doctors not because there are sputum changes from white to green or yellow. That, after all, is an aesthetic question like the difference between a Hogarth and a Matisse, say.

They come in because they are short of breath. They can't do as much as they want to do. So the outcome criterion which we should look at is dyspnea. The other symptoms that might be important are cough, but the difference between white and yellow sputum isn't really an important outcome criterion.

People like to have numbers, to have some

evidence of objective evaluation as well in terms of exercise capacity. This may be something as simple as six-minute walk. How far can the patient walk in six minutes, a very easy criterion to use or it could be more elaborate.

We also should have pulmonary-function tests, not because these are necessarily so good in evaluating dyspnea, but because they do provide us with an objective criterion which we can measure from time to time and have been used in previous studies.

The other criterion that would be important is a return to usual activities.

[Slide.]

There should be long-term follow up because we want to know if we can eradicate the organisms that are present in the airway, does that, in fact, reduce the incidence of recurrent attacks. Can there be some benefit beyond just reducing the problem of the acute exacerbation and having some benefit over a longer period of time.

There are some people that have argued that these organisms that are present during periods of remission such as Hemophilus influenzae and Pneumococcus might, in fact, have some

long-term deleterious effect, that they are not innocent bystanders, they are actually pathogenic even at a time in which the patient seems to be at his baseline.

We also have to have a careful record of adverse drug effects. We tend to look upon studies as are they effective or not. But we have to weigh what the problems are with the drugs, themselves.

If we were able to show that an antibiotic reduced the acute exacerbation by one day, and yet the risk to the patient was 20 percent of diarrhea, nausea and vomiting, very few patients would say, "I would want to take that antibiotic." They would prefer to have the extra day without the new symptoms.

We have to have appropriate analysis. It has to be statistical analysis for significance but we have to look at the numbers that come out of that; are these, in fact, clinically significant in addition to being statistically significant.

[Slide.]

There are eleven placebo-controlled trials. Eight show no benefit and three favor antibiotics. The three that favor antibiotics include two from a British hospital in the 1960s

that describe a group of patients that almost certainly had bronchiectasis and these two studies are not relevant to current standards.

The eight that show no benefit have in common among other things that they are not satisfactory in terms of numbers. Moreover, none of these trials meet all the criteria that I mentioned and, in fact, none of the trials meet even most of the criteria that I mentioned.

So, in fact, what we have to conclude almost immediately is that we can't answer the question I originally asked because the data are, in fact, inadequate. That hasn't prevented people from trying, however.

[Slide.]

There was a meta-analysis that was published in 1995 that looked the six placebo-controlled trials. It had the similar outcome criterion of peak expiratory-flow rate. The advantage to antibiotics was a peak expiratory-flow rate 10 liters per minute greater than in the placebo group.

Every person who is a proponent of antibiotics has quoted this trial as being supportive of antibiotics. It must be some kind of

decerebrate reflex because if you look at what those numbers mean, they are meaningless. The peak expiratory-flow rate, on average, in these patients was 200 liters per minute. This represents a 5 percent change, a change that cannot be reproducibly done between one setting and another within moments.

Moreover, there is not a person in the world who can tell the difference of a peak expiratory-flow rate of 10 liters per minute in terms of improving the symptom of dyspnea or increasing his exercise tolerance. So this difference is absolutely physiologically and clinically meaningless.

What we can conclude from this meta-analysis is whatever else antibiotics do, they are not good bronchodilators.

[Slide.]

I want to look at three studies particularly that have often been quoted and I think tell us a lot about what the studies can say.

This Canadian study is the shrine at which the antibiotic proponents worship. It contains 173 patients. It has looked at 362 attacks over four years from 1981 to 1984. It analyzed the attacks

in terms of three different groups, whether they had one, two or three of all the symptoms of increased dyspnea, increased sputum volume or increased sputum purulence.

If the patients had only one or two, there was no statistical significance between the placebo and the antibiotic group. If they had all three, which is 40 percent of all the patients, then there was some benefit for antibiotics in terms of increased success and decreased deterioration. Now, this was seem to be strong argument in favor of antibiotics.

[Slide.]

But the trial has several problems. In the first place, there was no microbiology performed. This doesn't invalidate the results but it would be much more scientifically rigorous if they could show that there was a correlation between the clinical benefits and the microbiologic findings.

Secondly, there were no chest films done. This was particularly important in this study because 30 percent of the patients were reported to be having fever. So even a few patients who had pneumonia who were undiagnosed would make a real

difference.

But, to me, the mortal wound for this study is that there was no stratification for corticosteroids. 40 percent of patients received them but there was no systematic assignment. There was no standardized dose and there was no standardized duration.

So this study fails to meet the absolute minimum criterion for a placebo-controlled trial; that is to say, the confidence that the two groups were identical in every important respect except the intervention being analyzed. We don't know whether the groups who received corticosteroids are, in fact, the same in terms of those who received antibiotics.

[Slide.]

One study that avoided this problem was done in Denmark from 1986 to 1988 and had 270 patients. It eliminated all corticosteroid use from these patients and made sure that the patients didn't have pneumonia. When the patients were evaluated by peak expiratory-flow rate or by the physician evaluation at eight days, there was no difference.

[Slide.]

But this doesn't really answer the kind of clinical question that I would like to know and that is what benefit, if any, is there in patients who are receiving corticosteroids because what we know now, from various studies, is that corticosteroids make a major difference in acute exacerbations, whether the patients are in-patients or out-patients. These controlled trials have all shown that corticosteroids will improve these patients faster and there will be fewer failures.

Some have suggested that the duration between the time in which the patient is treated and the time in which the next exacerbation occurs is lengthened by those patients who receive corticosteroids. So any trial, I think, should have patients have systemic corticosteroids as part of their standardized therapy.

[Slide.]

When you do that, do antibiotics have any additional benefit? This was looked at in a Dutch study that looked at 71 patients from 1988 to 1991. Everybody received corticosteroids and they were randomized to receive amoxicillin, sulfatrimethaprim or placebo. They could find no difference among these groups in symptoms, peak

expiratory-flow rate or future relapse.

The problem with the study is the numbers are small. The patients were not particularly ill and there were a few patients with asthma.

[Slide.]

If we look back at the Canadian study for this particular question, in those patients who received corticosteroids, was there any additional benefit to the antibiotics, the answer is no. There are 73 in the placebo group and 72 in the antibiotic group, and those patients had no difference in outcome.

[Slide.]

So what conclusion can we draw from this particular information. The available studies are inadequate to answer the question I originally posed. We do not have the information that antibiotics are effective overall for any defined subgroup and particularly with the current kind of therapy we use which includes bronchodilators and corticosteroids.

We need an appropriate study now to answer the question, is this study safe?

I want to end on a personal note. When I was a pulmonary fellow in the 1970s, I looked at

the information that was available then on antibiotics and I didn't find it very compelling. On the other hand, on the basis of my own clinical experience, I thought corticosteroids were. So ever since then, I have treated acute exacerbations with corticosteroids without antibiotics.

I have treated over a thousand exacerbations and I have never regretted it.

DR. EDWARDS: Thank you very much.

Our next speaker is Roger Echols.

PhRMA Speaker

DR. ECHOLS: Thank you.

[Slide.]

You might expect some fireworks. I don't want to line up the number of patients, obviously, that I haven't treated personally but, in clinical trials, in many thousands over the last twelve years, with antibiotics, but actually I have to agree with--I don't have to; I do agree with Dr. Hirschmann that the evidence for delta 1, the evidence that there is a benefit of any antibiotic therapy over placebo is woefully not only inadequate but missing.

So I may surprise some of you with some of the conclusions.

[Slide.]

But I do want to address, based on a very recent study, how we have tried to address some of the criticisms of previous clinical-trial design and so the study I am about to explain to you really focused on what was considered to be true exacerbation of chronic bronchitis. The word "true" is really meaningless, but we did have very strict criteria in terms of people having underlying chronic bronchitis.

Smoking history was--not only history was identified in the vast majority of patients but about 40 percent of them were still current smokers. What we are talking about has nothing to do with secondary bacterial infection of acute bronchitis. I just want to make sure that people understand that.

But even when you try to select an appropriate population to study in a noninferiority design, and where we have been going from how to tighten the confidence interval that we are not having biocreep, the numbers here sort of illustrate that when you have an expected success and the guidelines that we have following for many years look at one to two weeks following the end of

antibiotic therapy, the resolution of clinical signs and symptoms has been the outcome.

With a two-sided 95 percent confidence interval, with a well-powered study, 90 percent, where about 85 percent of the subjects are evaluable, with a 15 percent delta which is what has been the standard, you need to enroll about 350 patients. By tightening that confidence interval to delta of 10 percent, you see a substantial increase in the patient population.

Now, in AECB, finding patients is really not the issue. I would say doing a study with a delta of 10 percent certainly is doable. That is the study I would like to present to you.

[Slide.]

This was a study of a quinolone versus a macrolide. I think to try to show differences within class is much less likely than between classes, particularly given the differences in the microbiologic spectrum of the two classes of drugs. This was a study powered for 10 percent delta, hence a nearly 800-patient enrollment with an average age of 53. We required, or tried to require, all three cardinal symptoms in addition to cough, for all the cases and so the description

that Dr. Hirschmann mentioned about the Canadian study, that is the Anthonisen study, the type 1 where the benefit of antibiotics over placebo had been shown.

In fact, in this study, 90 percent of the patients were type 1 and the other 10 percent were slipped into type 2. As I say, over 80 percent had a history, or at least admitted to a history, of smoking which is always going to be somewhat an underestimate, but 46 percent were still current smokers.

Over half the patients had had symptoms, acute symptoms that had persisted for more than seven days. But only 10 percent of the patients had been receiving chronic steroids or receiving concomitant steroids, systemic steroids, at the time of enrolling in the study.

This is an important point, I think, when we get into the discussion of standardizing for steroid use. Yes; we did stratify to assure that there were equal numbers of patients receiving systemic steroids but with subjects meeting all the other criteria for a type 1 exacerbation, only 10 percent were getting steroids.

So, to me, it would be easier to not allow

any steroids than it would be to put everybody on steroids in a clinical trial.

[Slide.]

The subjects with pathogens--in other words, a positive culture from a valid sputum showing inflammatory cells and not contaminated with epithelial cells, was a nearly two-thirds, or was two-thirds, of the overall population with the vast majority of these being a single pathogen.

As expected, the big three, pneumococci, Hemophilus and M. cat were about equally distributed in 40 percent, but there were a significant number of other possible pathogens, again with AECB, whether it is colonization or whether it is pathogens, I think, is very much a question that is very difficult to answer.

Staph aureus; is that a nonpathogen in AECB? Again, the Gram negatives, about the most common Gram-negative organisms we saw were Klebsiella pneumoniae, which is certainly a respiratory pathogen, and then Pseudomonas aeruginosa, which can be a pathogen in respiratory-tract infections.

So this, again, to me is a typical distribution of organisms in a large clinical trial

using a central laboratory. These patients were pretty much all from North America, but the point I want to make here is when we did susceptibility to all the organisms, 99-plus percent were susceptible to the quinolone. Only 70 percent were susceptible to the macrolide.

So one might expect, if there were an effect of antibiotics, that you would be able to demonstrate a clinical difference and, perhaps, even a microbiologic difference. However, we did not.

[Slide.]

It is not relevant here for purposes of which drug had the slightly higher or the slightly lower success rate, just to show you that when you do a large enough study and the success rate is, the point estimate difference, is small, it is easy to satisfy the lower boundary of 10 percent. So that is not a problem.

From a noninferiority point of view, doing a large study in AECB to show that your equivalent is doable, but then to try to make sense out of it and say, really, what is the benefit of your antibiotic, it is more difficult.

I point out, particularly, the

microbiologically evaluable subjects. These are patients that had positive sputum cultures at entry. There is absolutely no difference in the clinical outcome in this subpopulation. Even when we look at patients that had Gram-negative organisms, there was no difference in the clinical outcome between the quinolone treatment and the macrolide treatment.

There was a slight difference but, again, it was not significant when you looked at the eradication of individual organisms, but, as I think many of you know, now in every case do we get a follow-up sputum so, sometimes, that eradication rate is driven by the clinical response.

[Slide.]

So from, I am going to say, my personal perspective, and some of what I am proposing here is not necessarily something that is endorsed, I think, by--and I don't want to claim that I am representing all of PhRMA or even my own company--I think there are real issues with noninferiority studies in AECB.

As I said, you can tighten the delta and get confident that you are not different from your active control but what questions have you really

answered even when you try to select the patient population in the most stringent way possible.

Is the positive culture reflective of infection or colonization? Again, we used the so-called Anthonisen scoring system to identify those patients with type 1, but using objective measures of response, other than the clinical response, whether--the pulmonary-function studies have been mentioned. It is important to note that, to get a baseline--the way these studies have been done is a stable of patients generally within one or two centers and they have baseline--in other words, not when they are having an acute exacerbation, pulmonary-function studies, you sort of need that kind of background information to do that assessment, to do your first pulmonary-function study in the face of an acute exacerbation, the data, I think, are much more variable and difficult to control.

I will come back to that in a second.

[Slide.]

The flip side of--antibiotics are not helpful or you can't correlate the microbiologic response with the clinical response. We still have to consider, I think, these exacerbations to be

somewhat--to be a clinically significant illness, even though the placebo response measured at about three weeks is about 50 percent, even in the Anthonisen type 1.

As Jan pointed out, should we be measuring this at three weeks or should we be measuring the differences at a much closer, much more proximally to the acute exacerbation. But, of those patients that fail, about half of them end up being hospitalized. Again, chronic pulmonary disease remains a leading cause of death.

Nevertheless, I have to admit that, based on our own studies and I think most other studies that I have seen, that trying to get a strict correlation or validating, say, the microbiologic evidence with the clinical evidence, they don't correlate well.

[Slide.]

I am not going to re-review the placebo-controlled trials. Dr. Hirschmann has done that and I think Dr. Thompson will as well, there haven't really been, with the exception, I think, of a recent Italian study, anything that has been conducted in recent years, which is a placebo-controlled study. There were lots of

problem with the design and even the Anthonisen study, the Canadian study, was of a crossover design, which the FDA would never allow us to do.

So when you look at the acute exacerbation, first episode, among the Anthonisen type 1, the numbers really get small. I agree that the outcome measures that we have been looking at certainly have not been consistent and I am not even sure they are useful.

Dr. Hirschmann, with his experience, has based that, I think, somewhat what I would say on older antibiotics but also his personal experience. I don't want to begin to contest that, but I do think that we have not tested in placebo-controlled trials more contemporary antibiotics.

It is not that that is a radical idea. It is a risky idea from a sponsor's point of view. There have been several--actually, more than one company I have worked for, but, in addition to that, where the idea of doing placebo-controlled trials in the last decade have been advanced only to be basically not consented to by other--the more sort of commercial side of our organizations, particularly for a product that is already on the market, that the risk is so high, from what we know

from the literature and placebo-controlled trials, that you wouldn't be able to show a definite benefit or you wouldn't change anybody's mind, that the risk is just too high to conduct a placebo-controlled trial.

I mention that because I think this forum, and maybe follow up, obviously, with an advisory committee forum, is really what we have to begin to create the need, or the requirement, really, for placebo-controlled trials in the future.

[Slide.]

That is why I am calling this, really, a way out for my dilemma even though I think the outcome--my prejudice about the outcome and being able to show a benefit of antibiotics contrasts with Dr. Hirschmann who is confident that antibiotics won't be able to show a benefit.

But I think we are together in many respects in the need for doing additional placebo-controlled trials. What I am suggesting is that that need needs to be not just tacit but explicit. It needs to be something that becomes part of regulatory and clinical requirements; in other words, guideline committees, et cetera, need to insist on placebo-controlled trials.

The question, I think, and where I would like to have some of the discussion is what are some of the clinically meaningful benefits that we might define, whether it is time to clinical response, not looking at are you better or not at three weeks, I would suggest, also, that you might design a clinical symptoms scoring system.

I have looked at our own databases, looking at what are so-called the cardinal symptoms of dyspnea, sputum production, sputum purulence and, if you wanted to add cough or not. You can create a scoring system of worse, improved and look at the composite score rather than sort of a total summary or, "Are you back to baseline?"

I have difficulty with some of the objective measures. Again the pulmonary-function studies, as I mentioned, I think you would really have to have a stable baseline before people got an exacerbation. There are other tricks of the trade which I reviewed recently. I am not necessarily supporting them, but people have really gotten into sputum examination and really developing quantitative measures of sputum purulence that might be something that people might consider of value. I don't necessarily share that.

Then there is quantitative microbiology which has just its technical problems but that is something that I think might be considered. The one point I failed to mention in terms of clinically meaningful benefits might be time-to-next-exacerbation.

So I do think the time has come to do additional clinical trials. I would suggest that, without some arm twisting or persuasion, either from the clinical community or the regulatory community, that the sponsors of antibiotics are not likely to volunteer to do placebo-controlled trials because of the risk.

But I think we would all benefit in the future if we could answer what the role of antibiotics is in AECB.

DR. EDWARDS: Thank you very much.

Now I will call on Susan Thompson from FDA.

FDA Speaker

DR. THOMPSON: Good morning.

[Slide.]:

I am going to covering today issues in drug development relevant to the indication of acute exacerbation of chronic bronchitis.

[Slide.]

I am going to attempt to not be repetitive. What I would like to focus essentially are on study-design issues that are specific to the regulatory and review process in the hopes that that is expediting the discussion that will follow.

We will quickly cover some issues in diagnosis, study design considerations, relevant inclusion and exclusion criteria, outcome assessment and timing, statistical issues and then some conclusions from our standpoint.

[Slide.]

Very briefly, I will mention, again, we contrast this disease with acute bronchitis which is a viral etiology in healthy adults and we are not talking about that today. AECB, as you all know, occurs in patients with chronic bronchitis which is a subset of patients with COPD. I think it is important to always recall that this is a common disease and an important public-health problem and it accounts for 5 to 10 percent of all the antibiotic prescriptions in the United States.

Again, I think a point that is self-evident but is worthy of emphasis is that a positive sputum culture is not diagnostic of AECB

nor does the bacterial isolate necessarily document the etiology of a particular exacerbation.

[Slide.]

Study-design considerations you have already heard mentioned but we think it is important to reiterate that concomitant medications and therapies have been shown to have independent therapeutic efficacy in the treatment of AECB, specifically steroids and bronchodilator use needs to be controlled in clinical trials of AECB.

[Slide.]

Study-design considerations lead us to a consideration, again of placebo-controlled trials. Certainly, in our context, we had initially conducted a review of available placebo-controlled trials in an effort to define the benefit of active control over placebo.

I am not going to review specific trials, but I would like to bring up the specific conclusions that we have made from that review. It is important, I think, to know that, in the past forty years, only 1100 patients have been enrolled in randomized, placebo-controlled trials of antibiotic treatment of AECB. None of these trials have been of identical design.

Clearly, there have been differences in the definition of what constitutes an acute exacerbation and, importantly, there has been a lack of standard outcome measures. I have listed here some of those that have been used.

[Slide.]

It is very important, I think, to realize that there has been a lack of reproducible rating system for severity in these clinical trials. The Anthonisen trial, you have already heard described. The Winnipeg criteria have been used most frequently in discussions and other clinical trials have attempted to look at their relevance.

I think you are all aware they constitute cough, sputum production and sputum purulence with type 1 being all three of those and being the most severe. I think it is important to realize that those criteria, at least in one other study, were not validated and what was found to actually be more predictive of severity were historical parameters; that is, the patient's cardiopulmonary status and the occurrence of more than four exacerbations per year.

[Slide.]

Other study-design considerations relevant

to placebo-controlled trials include, again you have already heard the patient populations in these studies have not been uniform. Very importantly, the outcomes have varied from showing no effect to showing some effect of antibiotics in other studies. You have heard that discussed.

Most of these trials are old and were performed more than ten or fifteen years ago. I have included here a conclusion that a number of the metaanalyses as well as a number of the professional societies that have evaluated this point have reached, patients with more severe illness may benefit most from antibiotics but this has not been conclusively demonstrated.

In most cases, narrow-spectrum antibiotics are preferred. I present that to you in the context of the discussion today and I think that the evidence for this--well, I will leave you to evaluate that.

[Slide.]

Relevant inclusion and exclusion criteria, I just wanted to bring up that, in our current guidance, we suggest pulmonary functions and/or arterial blood gases be done, but they are not required. It is required that the patient have a

history of chronic bronchitis and a sputum culture.

Items that I presume will be discussed a little bit later today include the fact that a definition of chronic bronchitis and of an exacerbation is critical. Relevant items that may be helpful to define those patients with some precision include the patient's smoking history or age as well as the presence of FEV1. We have already mentioned control for concomitant interventions and cigarette smoking.

[Slide.]

Just very briefly to present this to make a point, this is a comparison of an NDA that came to our division in the last couple of years with some items that were extracted from the Anthonisen study. What you can see is that a typical NDA that comes to us had a significantly younger age range as well as fewer patients with a smoking history than we are seeing in the Anthonisen study.

We actually didn't receive information to look at FEV1, sputum or to define with precision the presence of type 1 or type 2 symptoms.

[Slide.]

I would just like to throw out a few points regarding evaluation, timing of assessment

and outcome which is obviously critical for design of these trials. What we currently ask for at FDA is that the test of cure for acute exacerbation of chronic bronchitis is the clinical response to find is return to baseline at one to two weeks after the completion of therapy.

Clearly, there are other outcome variables that may be more relevant. Some that have already been mentioned but, again, I think are worthy of discussion are the time to resolution of symptoms, some use of a validated symptom or severity score or the presence of deterioration.

Just, again, to mention that a microbiological endpoint as the primary endpoint is not appropriate for this disease entity.

[Slide.]

To refer back, just briefly, to the statistical issues that are relevant in AECB, clearly AECB has a low attributable mortality and morbidity and thus we would allow a loss of efficacy with respect to control of a relatively large degree, and, certainly, greater than 20 percent. The relative entity in AECB is delta 1; that is, the estimation of the benefit, if any, of active control over placebo, thus the review of the

available placebo-controlled trials.

Our conclusion, from a review of those trials, is that a metaanalysis with determination of delta 1 and, thus, delta is not a valid approach for AECB due to the limitations of the currently existing placebo-controlled trials. We have mentioned them already but, specifically, differences in study design, in outcome, in the patient population and in endpoints would not allow a definitive estimation of the benefit of the active control over placebo.

[Slide.]

What are some alternatives? I would just like to throw these out for discussion. First of all, we have already heard mention the possibility of placebo-controlled trials in its simplest form being drug versus placebo. At the advisory committee earlier this year where this issue was discussed, early escape was mentioned as one possibility to insure safety of those patients who might experience deterioration in either arm of the study.

It was felt that if this is included in a study design that relatively rigid discontinuation criteria at a specific time point should be

prespecified and specifically objective criteria for a deterioration or a progression should be given.

Mention was made of doing only high-risk patients to presumably include those that might have microbiologic cause of their illness or low-risk patients to minimize the risk to patients. But, in both cases, I think you will recall from the earlier discussions that we are still not quite clear how to define those patients.

[Slide.]

Other options for future trials include a superiority trial, the standard of care versus an experimental drug. We could continue to do noninferiority trials for all or for a subset of AECB. I have already pointed out, I think the difficulty in choosing an appropriate delta for this indication.

Suggestions have been made that that sort of a trial be conducted only in those who are severely ill that, perhaps, different deltas could be assigned to different strata of illness in a three-arm trial is another suggestion along those lines.

[Slide.]

The conclusions that we have reached, from our review of this topic, are that, first of all, selection of appropriate study design is critical for future trials in AECB. That includes choice of patient population, definition of concurrent therapies and how they are handled in the trials as well as the choice of endpoints.

We have also concluded that placebo-controlled or superiority trial design should be conducted for antibiotic trials in patients with AECB.

That is the end of my remarks. Thank you.

DR. EDWARDS: Thank you very much.

Discussions

Again, our bulleted points are brief enough that I would like to read them before we begin the discussion.

Are there methods to select a patient population more likely to benefit from antimicrobial therapy? Is it more appropriate to look at patients with exacerbations of chronic obstructive lung disease as defined by PFTs in all patients with chronic bronchitis and what other criteria should be evaluated such as patient age?

Please discuss the effects of potential

confounders of the measurement of antimicrobial effects in the trials. Should concomitant medications, beta agonists, anticholinergic agents, steroids, be standardized in the protocols? Does the use of these agents differ across geographic regions, current smoking status, the patient's prior history of exacerbations; example, are patients with more exacerbations per year more likely to fail in a therapy?

What is the benefit of antimicrobial therapy over placebo, delta 1, in the absence of adequate data to determine the magnitude of such a benefit? Are there alternative trial designs which could address this question? We have just touched on that, superiority design and placebo controls. What is the appropriate patient population for placebo-controlled and what are appropriate endpoints for trials of AECB?

Please discuss the utility of time to resolution of symptoms in superiority or placebo-controlled trials.

Dave?

DR. GILBERT: Follow-up question for Susan's nice presentation. I wanted to be sure that I was clear. Is the agency suggesting that,

from this point forward, that they will only accept for licensure protocols that are placebo-controlled? If that is true, then what happens to the products that are already out there that are licensed? Do you take away approvals once you show that placebo works just fine with steroids, et cetera?

Then, the corollary that comes to my mind is, to industry colleagues, of placebo-controlled trial is the rule of the land, which we would all love to see, of course, who is going to do it? Industry, as Roger pointed out--it is high risk for industry to do it. Do we have to work on some federally funded consortium, et cetera, or do we have to wait for maybe an antiviral drug to come along and then we get the answer with a different class of anti-infective.

I'm sorry; that was several questions.

DR. EDWARDS: Let me turn it back to Susan first.

DR. THOMPSON: I will start by saying that our clear requirement for what sort of trial should come in for acute exacerbation of chronic bronchitis is that that is justified by the data. We would accept and welcome placebo-controlled

trials. To accept, I think, a noninferiority trial at this stage of the game would require a justification of what delta 1 should be.

I think you have heard from our discussion, we just don't think that is doable at this point. But if somebody has better information from the literature, then they could justify that under certain circumstances.

As to what would happen should that become the standard from now on, my understanding is that we don't actually remove indications from a product label--I am ready to be corrected if that is incorrect--but that we would, in the future, grant appropriate indications based on the studies that are submitted.

DR. POWERS: This kind of gets back to what Mark said earlier about we are so glad that people practice medicine according to our labels and nothing else. If one would do a placebo-controlled trial showing that there is no benefit of antibiotics, you could ask the question of why would clinicians even worry about what is in the label for those older drugs.

DR. THOMPSON: Maybe just a last example to point out is you may all be aware that we no

longer accept acute exacerbations of secondary bacterial infection of acute bronchitis as a label which we used to do. It remains in the label of several drugs today, although we feel that most people would no longer use it for that purpose.

DR. SORETH: To go back a little bit more in history, a number of years ago, antibiotics that were coming to market for respiratory infections were labeled under an umbrella, "lower respiratory-tract infections." If you take it back again further to a drug like amoxicillin, it basically gives a list of organisms.

The same with doxycycline, et cetera. If you go back to those original NDAs, it could be very hard to tease out precisely who was studies under an umbrella like LRTI, pneumonia, bronchitis, acute exacerbations of chronic bronchitis, et cetera. We have typically not gone back and changed those labels because it is very difficult to do so.

One other thing to add to the types of trials that we might pose for further study for acute exacerbation is also one that would look at a dose response. If the feeling is that there is not proper ethical handling of patients and that, if

you were studying the most severe patients in a trial who may have the greatest likelihood for benefit of therapy, we would also entertain that kind of a trial.

DR. BRITTAIN: With the question of who would do the trials, I don't know if I can answer that but I do just want to put out on the table, probably these placebo-controlled trials, especially with the time-to-resolution endpoint, would be a major sample-size advantage over the current noninferiority design, so that might be a factor here in making them attractive.

DR. EDWARDS: Roger?

DR. ECHOLS: If I might just respond for a second, industry--I am thinking of it as an organism. It is a large organism but it still responds to sort of normal stimuli of the carrot and the stick. You have mentioned the label. I think AECB is a large enough market where--if there is a motivation to have market share in that arena.

So I think the fundamental motivation to try to do it in a way that will satisfy regulatory agencies is there. I think that could be facilitated if, in the label, a company that did a placebo-controlled trial were allowed to

distinguish themselves from a routine label, that could somehow differentiate their product from others which would then allow promotion to differentiate, on the basis of the evidence, their study.

So I think there are, again, because of the size of the market, potential rewards to having performed a placebo-controlled trial. The opposite is that, if there is a stick, if you don't get labeling at all for AECB because you haven't conducted a trial, and I am thinking of the future, of course, you are at such a disadvantage that that is an incentive, too.

So I am just saying that I think companies would respond if both rewards and penalties were in place.

DR. GILBERT: But, Roger, there is 10 percent of the use of antimicobics is for the acute exacerbation of chronic bronchitis. We are facing another crisis with the emerging resistance of the target organisms, if you will. So, if the likelihood is that industry, and I can understand it, didn't want to take on this challenge for fear of failure of the drug to show anything better than placebo, then the IDSA and the American Thoracic

Society and other professional organisms should lobby very hard with the National Institutes of Allergy and Infectious Disease or the like to put together a consortium to federally fund the study to answer the question.

That is why the industry stance is so terribly important.

DR. ECHOLS: No; I think that is another way of at least establishing delta 1, and then people could go back--I suppose, could go back to doing a strict noninferiority study against a drug that has been established to show benefit over placebo.

DR. GESSER: I would support both of those comments. I would suspect that the IDSA members are interested in the results of such a study. Certainly, a placebo study from the perspective of a sponsor puts that sponsor at a potential risk compared to agents that are already licensed. Certainly, some aspect of an active control would probably be desirable in any study that a sponsor took. But I think I would love to see a non-sponsor-driven study.

DR. GILBERT: Roughly, how much would it cost?

DR. ECHOLS: It all depends how greedy the investigators are.

DR. GESSER: You tell us.

DR. HIRSCHMANN: If I may make on comment. There actually is an ongoing randomized double-blind trial that meets all the criteria that I just delineated that is going on in The Netherlands. It started in June. It is looking to have about 250 patients, total and it is expected to be completed in two years.

DR. GESSER: How sick are--

DR. HIRSCHMANN: All of them had all three criteria that we mentioned from the Winnipeg--the idea was, and this can address one of the issues that had been brought up before. From the studies that were done in Canada, the type 1 study clearly had no benefit for antibiotics. The Danish study that I mentioned also showed no benefit for antibiotics. Those patients had pretty mild disease so I think you can argue, very forcefully, on the basis of the information we have now, that there is no reason to study mild disease again.

The patients we want to look at are the patients who are severely ill. That is the group that they are studying in The Netherlands and that

is the group that I think ought to be studied here. That is the group that also needs to have corticosteroids. We know that from these studies that have been done, that corticosteroids have a major impact on acute exacerbations.

So I think these trials have to include everybody getting corticosteroids. That is what The Netherlands study does. That particular study is in hospitalized patients rather than outpatients, but they wanted to take the most severe group and, I think, appropriately so figuring that, if you can't show a benefit for antibiotics in the most severely affected group, and we have the information that the milder exacerbations are not benefitted, that one could reasonably conclude that nobody is going to benefit.

DR. EDWARDS: Stan?

DR. DERESINSKI: In that regard, perhaps you could comment on the Tunisian study that was published in the Lancet earlier this year.

DR. HIRSCHMANN: The Tunisian study was a study in which they took very severely affected patients with acute exacerbations of COPD, most of whom got intubated. The problems with the study

were severe. Patients did not receive adequate treatment. Nobody got corticosteroids. Nobody got anticholinergic agents. Only about 65 percent got beta adrenergic agents.

They gave them theophylline which is thought to be ineffective in this situation. The outcome criterion really was what is the incidence of pneumonia on patients who were ventilated for acute exacerbations of chronic bronchitis. It doesn't answer any clinically relevant point and it is a very poorly done study.

DR. DERESINSKI: There were a lot of problems with the study but I think you could also make the counterargument, is that it was a pure study of antibiotic therapy in those patients. It was placebo-controlled, so I think there is some relevance and some information to be taken from that study.

DR. HIRSCHMANN: But, as a clinician, we don't want to know what it is, in isolation, that an antibiotic does. We want to know what does it do in the context of the way in which we treat patients ordinarily. A patient we treat ordinarily with acute exacerbation of chronic bronchitis who is severely ill, nobody treats them with

antibiotics alone. They treat him with a whole conglomeration of things which are standardized.

They get beta-adrenergic agents. They get anticholinergic agents and they get corticosteroids. That is the group we want to find out about.

DR. ECHOLS: When you talk about patients that are hospitalized, to me, that is a whole other patient population. That clearly is the most severely ill patients both from their degree of pulmonary function, baseline pulmonary function, perhaps, as well as the severity of their exacerbation.

I would like to ask the agency whether they would be satisfied with studies that just dealt with hospitalized AECB or whether there is really a need, because virtually all the other previous studies, all the previous labelings, have been based on ambulatory patients with AECB, whether a hospitalized patient population would be what you would want.

DR. POWERS: I think that gets to a couple of questions, though. One is, you were talking about advantageous things that might be put in the label. I could see where that might be very

advantageous to a company to say, "We studied the sickest of the sick and our drug actually works in that patient population."

I think one of the other questions that comes up is you could ask the question another way around. If we were to look at this study from The Netherlands and it shows some benefit of antibiotics over placebo in the sickest group, what happens when somebody comes to us and then wants to study the non-sick group again. We can't really use that data to apply to the non-severely ill.

The third question comes up about the Tunisian study. It is just what we were talking about meningitis this morning, asking the right question when you come to the endpoints. The Tunisian study shows that ofloxacin prevents hospital-acquired pneumonia. That is the answer that it came up with. It didn't say, does the person get better from that episode of exacerbation.

DR. DERESINSKI: Actually, probably it was more complex than that because most of the pneumonias appeared within the first three days.

DR. POWERS: They had pneumonia when they came in.

DR. DERESINSKI: So they had pneumonia when they came in which brings up another point relative to screening for pneumonia because it is clear, based on studies doing CTs and people suspected of pneumonia is that a chest X-ray is quite insensitive in detecting pneumonia.

DR. HIRSCHMANN: I don't agree with the last point. I think the vast majority of people with acute exacerbations of chronic bronchitis don't have pneumonia. I think there are clinical circumstances that allow us to suspect it. I don't think everybody needs to have a chest X-ray. But, from the point of view of a trial like this, as opposed to clinical practice, I think it would be important to have that as part of it but, in clinical practice, I treat the overwhelming majority of patients with chronic bronchitis without getting a chest X-ray because I feel quite confident, on clinical grounds, that they don't have pneumonia.

DR. ECHOLS: The clinical trials that I discussed and I think all of the recent ones have had--one of the criteria that are in the guidelines is a chest X-ray that demonstrates the absence of pneumonia. So that is part of the standard trial

design currently.

DR. EDWARDS: I would like to ask the IDSA folks if they agree that a trial in hospitalized patients would need to be followed by a trial in outpatients.

DR. SCHELD: Listening to Dr. Powers, I think that is correct.

DR. HIRSCHMANN: I agree, as well. My point wasn't to tell you that that was going to be the definitive trial. I think it is a very useful trial and I wanted to tell you that people there feel it is ethical and they are doing it. I think there ought to be a trial in patients who are outpatients as well. That is actually the much larger group of patients that we see.

But I think, as I say, if you can conclude that the antibiotics don't work in the most severely ill patients, then you can certainly have no problem in treating the patients--or doing a trial in patients who are less severely ill.

Let me make one other clinical point. When I said I treated over a thousand exacerbations without antibiotics, I am including the patients who have the mildest to the most severe patients including patients on ventilators. I do not use

antibiotics in acute exacerbations of chronic bronchitis in the absence of pneumonia no matter what the severity of patients is. And I have never been wrong in the sense that I think the patients have suffered from that decision.

DR. POWERS: Before we get too far away from that, because we have mentioned several times now severely ill patients versus not-severely ill--although we quickly say that, that is actually problematic when we come to this disease. The Anthonisen criteria doesn't look like it holds up, at least in the one trial that actually tried to look at it.

When you are defining, Dr. Hirschmann, severe versus nonsevere, what kind of criteria were you talking about?

DR. HIRSCHMANN: The severity of dyspnea, I think, is probably the most important, how severely limited are they in their ability to do the functions that they ordinarily do. You can see a patient who comes in and says, "I am mildly ill in the sense that I can walk ten blocks instead of a mile." But you see patients who come in who are short of breath at rest, and that is not their usual state.

You can demonstrate that by objective criteria, if you want, pulmonary-function test, oxygen saturation and so forth. But, on a clinical grounds, I think you can pretty clearly delineate patients who are sick enough to require hospitalization versus those that can be managed as outpatients.

The basic issue is dyspnea because that is the major reason we put patients into the hospital, not because they have yellow sputum or not because they are coughing a lot. It is because they are really short of breath and they can't walk to the bathroom. So we can't send them home. We have to admit them to the hospital until they get better so they can do those functions.

That is why dyspnea is the most important criterion in any of these studies. That is the limiting factor. That is why patients come seeking medical attention.

DR. POWERS: So would you say, then, that the presence of dyspnea would be severe, the absence of dyspnea qualifies as mild, or is there some way to grade the dyspnea to separate those?

DR. HIRSCHMANN: It would be grading dyspnea. My way of looking at the study, if I were

to design the study, everybody would have dyspnea and then they would have either increased sputum volume and increased--or increased sputum purulence so you would have those groups. But everybody would have dyspnea because I think the problem with Anthonisen's study type 2 is you could have increased sputum volume and purulence, but what difference does that make in most patients, really. They don't care. Most of them know that they have colds and this is going to happen and they are going to get better.

So, unless they are told to come in and this is important that they get antibiotics, a good number of them just stay at home and do quite all right. It is the dyspnea that, I think, is what is really critical to the evaluation of these patients and I think has to be in every--every patient has to have that as a symptom, in my mind, to make the study meaningful.

DR. EDWARDS: Could you just elaborate a bit more for us on your definition of dyspnea? Let me say a definition that would be optimal for study.

DR. HIRSCHMANN: Dyspnea is a sensation of breathlessness that means either at rest or

exertion so that the patient is unable to do the kinds of activities that they normally do and it is a significant difference from with their baseline is.

Now, a good percentage of patients with obstructive lung disease are dyspneic anyway. But they will tell you that it is substantially worse. You can look at this by various scales that have been developed. There is a scale that you just say, "Is it the worst you have ever had, versus normal?" that kind of thing, or you can look at it in a more functional way.

One of the ways to do it is the six-minute walk. That is one of several ways to do it, but how far can you walk in six minutes. In the clinic, you take the patient and you walk him around for six minutes and you see how far they go. Those are the ways we look at it in a basic practical manner.

DR. ECHOLS: Jan, doing pulmonary-function studies is not going to be a direct correlation, or is it, for dyspnea?

DR. HIRSCHMANN: The correlation between pulmonary-function tests and dyspnea is approximate but not, by any means, perfect. It is a numerical

value that you can then compare one to the next. But you can see a patient with an FEV1 of 1 who can walk ten miles and the next guy with an FEV1 who can't get across the room.

We know that that particular criterion isn't, by itself, an adequate substitute for dyspnea but it does give you some numerical support. So I think it is useful to have those measurements because people like to look at numbers in these kinds of trials.

But, in my mind, the most important issue is the subjective sensation of dyspnea supported by the ability to do things. So, rather than a number of FEV1, I would rather see how far the patient can walk as the criterion that I would find most useful in determining how helpful these different interventions are.

DR. CRAVEN: I think that the question up about doing a study for acute exacerbations of chronic bronchitis in mild patients is extremely important because if you look at the antibiotic use up there, the 5 to 10 percent of prescriptions, almost all those are for people that are being prescribed on an outpatient basis.

So not only does it increase the problems

of resistance and the development of multidrug-resistant organisms which is a major problem we are trying to face, which would have a gigantic impact, but also, if you look at patients that have risk factors for pneumonia, particularly a patient who has been hospitalized, one of the major risk factors is antibiotic use, in the outpatient setting, in particular, so that it increases a patient's risk of having pneumonia and pneumonia by a multidrug-resistant organism.

So there is a whole series of things that I think are going to play out to be very important and a study like this that was funded would, I think, have dramatic or very important implications for antibiotic resistance in the country.

DR. EDWARDS: Bill?

DR. CRAIG: I just want to say that there are also marked differences in the pharmacodynamics of the different antimicrobials. Clearly, the fluoroquinolones eliminate the organism very quickly from respiratory secretions so that, if the organism was at all important, one would expect to be able to see a difference in time-to-improvement.

So I think any placebo-controlled trial needs to know what the antibiotic is that they are

using for their therapy and design it in such a way that you try and maximize the chance to show different. So, to me, a quinolone versus placebo would be the more logical type of study to see if adding the drug which eliminates the organism very quickly adds anything to the overall efficacy.

On the other hand, macrolides are drugs which are antiinflammatory. Inflammation, we know, can also affect airway resistance and contribute to dyspnea so that some of the improvement that could occur with a macrolide may not be related at all to its antimicrobial effect. It could be related to its antiinflammatory effect.

So you could run into problems in assessing overall activity based on, I think, the type of drug that is used as well.

DR. HIRSCHMANN: One other point. I think if I were to design the ideal trial, I think it would include a fluoroquinolone, but would also include one of the more basic older medications as well, and then placebo because I think if there is, in fact--I don't believe it will happen, but if there is some benefit for antibiotics, I think it would be important to determine whether the newer antibiotics really have any benefit over the older

antibiotics.

So that would be ideal trial. That may be more complex than we want, but I think that would be the most useful clinical trial you could do.

DR. EDWARDS: A three-armed trial.

Roger, you listed several things for consideration regarding evaluation of benefit of the drug, and they included time to response, clinical systems, scoring system, clinical symptoms, scoring system, possibly pulmonary-function test, sputum exam, quantitative microbiology and time-to-next-exacerbation.

Could you just tell us what you think would be the optimal benefit analysis that would be attractive to you for study?

DR. ECHOLS: I am thinking quantitation in a sort of a trial design. In other words, the more points you have to measure, sort of the greater the sensitivity or the ability to differentiate treatment arms from each other. So a treatment scoring system that looked at not just dyspnea but also sputum production, sputum purulence, would provide, I think, a more enriched material to evaluate, particularly if it was done more as a continuous scale rather than a yes/ no at a certain

point in time.

I think the problem with that is what is clinically meaningful. If I have agreement with Dr. Hirschmann, certainly, that dyspnea is the most important symptom, but it is not the only symptom. People that are coughing up quantities of purulent phlegm don't necessarily like that and I would suspect you wouldn't like to be sitting next to them on a plane.

I am not saying that the other symptoms are without benefit. I would like to look at more of a composite clinical score but I think there are things--if dyspnea is the most important one, I think you can, if there is a way to--when I say "easily," I mean the six-minute walk sounds to me like something that is very doable in a clinical trial whereas standardizing PFTs and stuff is much more problematic.

So I certainly would not be against trying to quantitate dyspnea. My other concern, though, with dyspnea and it is based a bit on some personal family experience is that dyspnea, even though they get better, can take a long time to get back to baseline. It can take, literally, weeks in your severely ill patients. On occasion, they never

really do get back to where they were before.

But I am hoping that, from what you are saying, is that you can show at least some gradation, some improvement in a relatively shorter period of time.

DR. HIRSCHMANN: What is different in your experience from mine is that corticosteroids make a tremendous difference and they make a tremendous difference quite rapidly. So patients are markedly better after a few days in terms of dyspnea.

So I think that you will not see these patients lingering for three weeks and still not better. It is unusual not to be substantially better after three to five days of corticosteroid use.

DR. ECHOLS: That gets into, I think, the big issue of whether steroids--you want to not use steroids to look at the effect of antibiotic or to use steroids in everyone. The really severely ill patients that are either close to being hospitalized or close to be being put in a ventilator, you certainly are not going to withhold steroids.

I don't know how the agency feels about requiring steroids in everyone and then looking at

clinical symptoms which, again, you can't necessarily discern are due to the steroids or due to antibiotic.

DR. HIRSCHMANN: I think the clinical question we want to know is how can we best get patients better. If we are going to be using these things anyway, what benefit is it to us to know what antibiotics would do in isolation because we are going to be treating these patients with these other things as well.

What we want to know is is there an incremental benefit for antibiotics in patients who are receiving the optimal medical therapy. I think that is the kind of question that we should be asking all the time; what is the optimal medical therapy and then what does your particular drug have to offer in addition to that.

DR. POWERS: Could I ask the question, since we have got Marissa Miller from NIH and we have heard several times about the public-health importance of this, if maybe you could address for us some of the issues about publicly funded trials, and then, Todd, maybe you could weigh in on the CDC's version of how this would help in controlling antimicrobial resistance.

DR. M. MILLER: The question has come up several times whether there might be federal sponsorship for a trial in this area. I would say that there is interest on the part of a number of agencies. For NIAID, I mean the fundamental issue about antimicrobial use for this indication, its implications to resistance development, is becoming more critical all of the time.

There are a number of options that exist. One is that investigators from IDSA or elsewhere could come in with a grant proposal to do such a trial and there would be support on the part of the agency. Obviously, you have to get through the peer-review process.

The other option would be--and I was interested in the discussion with severely ill versus outpatients. We do have a clinical-trials network which is the Bacteriology and Mycology Study Group which has, as part of it, looking at highly ill or multidrug-resistant bacterial infections in the ICU environment. So that might be able to answer one end of the spectrum in working--and Don Goldman is our PI for that risk group.

So we certainly would entertain

discussions with that group in terms of doing such a trial. The other idea that came to mind, the Agency for Healthcare Research and Quality, AHRQ, is very interested in clinical practice, clinical-practice guidelines and also antimicrobial resistance as well.

They have CERTs, the Center for Excellence in Research and Training, where they conduct clinical trials. They also accept grant applications in this area. I think that they would have a fundamental interest to use antibiotics or not.

So I would encourage you all to continue with this discussion and even to come in and speak with us at NIAID at a later time.

DR. EDWARDS: Marissa, what sort of a number would be on a grant proposal that would go into to NIH. It wouldn't be an RO1; correct?

DR. M. MILLER: Perhaps UO1, research projects that could come in a group. You might be able to do an RO1. For more than $500,000 direct cost per year, you have to come and request a waiver. That is considered a large grant. The problem is, in doing such a trial, if you came in as an RO1, all of the collaborating institutions,

their direct costs--their costs are accrued to the direct costs of the primary investigator. So you tend to get very high numbers going.

But I think that we can discuss these things together and, perhaps, the Institute would be willing to accept a large grant because of the significance.

DR. EDWARDS: Am I correct, then, in understanding that there is not an RFP out at the present time of any format for this particular study?

DR. M. MILLER: There is no RFP. Hence, having dicussions with the BAMSID Group and also we have other contracts within NIAID; for example, the Vaccine Treatment and Evaluation Units which also look at drugs, therapeutic trials. And there are a number of contracts through the VTUs that are in the outpatient setting. So that is another possibility.

But we do accept unsolicited RO1s. The UO1 would be more problematic at this time.

DR. EDWARDS: Let me just ask one other question in this area and that is do you think it is feasible that an RFP could--that would make a tremendous difference, of course, if an RFP went

out from NIH. Would it be feasible for one to be developed?

DR. M. MILLER: It is certainly feasible. What would be helpful would be perhaps an outcome from this meeting or the establishment of further discussions so that the Institute kind of hears back both from industry and from the scientific community and clinicians that there is a need.

Some of you were involved in a summit that we held, now I guess it is three years ago, looking at what the needs are on the part of both large PhRMA and small pharma and biotech companies in terms of developing new products for public-health needs.

We are still in an exploratory mode in that end. We have had a challenge-grant initiative which attempted to entice industry into the development of products that may not have a large market share and may not have a lot of incentive on their own part.

Follow up to the challenge-grant initiatives, we have had partnership initiatives which also tried to link industry with people in academia that have good ideas, novel targets, novel approaches. So we are very open to having these

discussions but I think it would take considerable feedback from the community coming in to come up with a RFA.

DR. EDWARDS: Thank you.

Alan?

DR. GOLDHAMMER: I just want to add to that. I am glad I can make at least a minor contribution to this meeting at this point in time. We are actually doing that same thing in the area of hepatotoxicity. We cosponsored a major workshop just about two years ago with the American Association for the study of liver diseases in the FDA.

One of the outcomes of that was a series of follow ups and a letter that we are getting the final sign-off right now that will be cosigned by the Association, FDA and PhRMA that will go to Jay Hoofnagle over in, I forget which institute he is in--your institute-proposing some research activities on the part of the NIH in the area of hepatotoxicity.

So I would not be quick to dismiss that. If one of the conclusions of today is that the three groups think there are some resources that only NIH is in the best position to donate towards

this cause, maybe we should think about that.

DR. GESSER: Is this within the purview of the Interagency Task Force on Resistant Issues? It sounds as if it--

DR. POWERS: The Interagency Task Force is not a clinical-trials network.

DR. GESSER: I know--not necessarily to conduct the trial but to stimulate interest in funding, requesting, submissions.

DR. EDWARDS: Can anyone speak to that? Todd, can you comment?

DR. WEBER: Marissa can answer it, too. Purview, yes, in the most general terms that if there are issues surrounding antimicrobial resistance. But, clearly, the different agencies involved with the task force have different responsibilities for this. I think NIH probably has more than others, possible AHRQ and others, depending on the type of question posed.

But stimulating interest, we have tried to--I don't know if we have picked out specific diseases so much but as a group tried to pick out somewhat more general topics where funding needs to be done in terms of trials, generally, et cetera but I am not sure what the mechanism would be for

picking this particular syndrome and such.

DR. GESSER: Conceivably, as identified, it is an area where a lot of antibiotic use is. It is an area where there is concern that the potential for overuse and confounding by viral pathogens, for example. And it is an area where not only could you determine whether there was a benefit of antibiotics, but you could also determine whether was a downside in terms of some of the things that the task force is--

DR. WEBER: That is an extremely good point. I didn't really think I had much to add to what Marissa had to say but, in response to that and John's question about antimicrobial resistance, I am somewhat anxious over the discussion in that I think it can quickly put us on a slippery slope towards actually encouraging antimicrobial use where it may not be needed.

Suppose trials are done and antimicrobial use in this syndrome shows no benefit but it doesn't show harm either. Given the way physicians work, faced with mild or severe disease, they may say, "I am going to use it anyway."

Now, we are trying very hard to dissuade physicians from that attitude in both pediatric and

adult populations for various syndromes. And big trials that show maybe marginal benefit or no benefit may have the perverse effect of actually encouraging use where there shouldn't be. I am not saying that would happen but that concerns me. I certainly wouldn't want to dissuade folks from doing appropriate trials to see if there is an effect. I just throw that out as sort of note of caution because we have worked very hard--it is very hard to change physician behavior when they have gotten in the habit of certain prescribing patterns.

We have invested a lot of time and money in education and other sorts of campaigns with state health departments, medical societies, et cetera, and it is quite difficult to do. I wouldn't want to sort of add fuel to the fire of antimicrobial overuse.

DR. GILBERT: Can we talk about that over lunch, Todd? I would like to do it privately because I might get emotional. Lack of confidence in the physician intellect is disturbing.

DR. EDWARDS: Dave, now I am going to put you on the spot because I really think we need a response to that issue, if you both could.

DR. SCHELD: We applaud the CDC for the educational efforts they put into changing physician behavior. There is evidence that, in fact, that has changed in some regards especially with the treatment of acute bronchitis in otherwise healthy adults.

What we don't agree with is that physicians are uneducatable and, therefore, we think that this trial should be done. I think our society is extremely interested in approaching the NIH with regard to a placebo-controlled trial in acute exacerbations of chronic bronchitis, perhaps three arms like Jan has said.

They should be getting state-of-the-art care and then antibiotics should be added on top and we will eventually find out whether it is really beneficial or not.

I would be interested if the IDSA, in concert with the American Thoracic Society, were to approach NIH about such a trial, whether FDA would consider this to be a good idea and would they give us some support, at least in terms of the concept.

DR. POWERS: I think we would think it would be a great idea, actually. I guess the issue as to how we could help in the trial-design issue

is we assume this will probably be with an older drug versus placebo where somebody probably wouldn't be coming in for labeling for this anyway so we could actually help out in the design issues up front.

DR. SCHELD: We will take you up on it. While we are at it, maybe we should do acute bacterial sinusitis as well.

DR. POWERS: And if you want to check otitis in there, we can get all three for one deal.

DR. ECHOLS: I think I have to go back to a point that Bill Craig made. If someone does a study with amoxicillin and shows no effect, I don't think that is going to answer the question. To have a three-arm study, I think, would be fine. But I think to use a drug like a quinolone, and, thinking about this, I would say, please don't--I mean the best thing that could happen is you just call it a quinolone. You don't even identify what the drug is.

Don't ask for any sponsorship. Don't have any affiliation. Keep it as clean and pristine as possible. But use a drug that at least has the microbiologic spectrum and that the PK/PD characteristics, if an antibiotic is going to work,

it has got the characteristics I think you want.

DR. SCHELD: If it works, then do you break the code later and say what the quinolone was?

DR. ECHOLS: No; don't. As I said, really, identify it as a quinolone.

DR. SCHELD: A respiratory quinolone.

DR. BRITTAIN: I guess I have a little bit different perspective on that. Ideally, from our point of view, we would like to see the comparison against placebo be a drug that would be likely to be used as an active control, as a comparator, because that is the information we need to set the delta 1. So we would like to know what that drug is and it would be a drug that would be a common, a likely comparator.

DR. EDWARDS: Is there any chance, from this side of the table, that someone might step forward with a likely comparator?

DR. ECHOLS: I'm sure you could find someone to donate some drug. There are drugs out there, but I guess my concern, just to restate it, is you use a drug that has holes in it from the point of view of what an antibiotic might be doing, people will question the study design.

I guess the only other question is if you do a study and a benefit is demonstrated--in other words, a delta 1 is demonstrated--would the agency then go back to, if I can use that term--would they then, in the future, accept noninferiority studies?

DR. POWERS: That is what we would use that information for. Now, the question is are you going to do a noninferiority study with a delta of 0.03 for the next trial based on what that number comes out to be. That might be the tricky part is that, as Mark said, you are talking the size of trials for thrombolytics with 10,000 patients per arm.

But if that is what it shows, that is where the utility of these trials would be for us is how to use them for future noninferiority trials.

DR. BRITTAIN: But, if it did show that, if it showed it was only 0.03, then you would probably want to use placebo-controlled trials in your regulatory trials because the sample size would be much smaller.

DR. GESSER: The other value of requesting this type of trial and having a funding body critically evaluate the study design, et cetera, is

that there are many questions regarding intermediate time points, graded endpoints, the correlation between the micro information and the clinical information that it seems like could be gleaned from this.

So, regardless of what agent you choose, really, I think those things should be considered when you are choosing what agents you are going to use and the endpoints you are looking for in this trial. It sounds like there is a lot to be gained in terms of basic information.

DR. CRAIG: The reason, clearly, that I think fluoroquinolone is there is there is some data in some other respiratory infections, even community-acquired pneumonia, that suggests that time to event occurs quicker with fluoroquinolones than with some of the other comparative agents.

So, for that reason, I think, if there is going to be an advantage, you want to try and use something that is going to maximize your chance of showing something in the clinical trial.

DR. POWERS: Could I just ask a question about this. Mike, you mentioned ATS and IDSA, but are there any existing clinical trials networks that would already be set up to address a question

like this?

DR. ECHOLS: Do you know of any through the ATS?

DR. HIRSCHMANN: I don't know of any.

DR. SCHELD: I don't know either, John. I know, with the Critical Care Medicine Society, there is a trial network set up to investigate things like adjunctive therapy in sepsis or septic shock. I know quite a few of the investigators, but that is a little bit different category than we are talking about. I think we probably have to create this.

DR. EDWARDS: Other comments? I think we are going to conclude this discussion unless, John, there is anything else from FDA.

A summary point I would make is that the notion of developing an approach to NIH that might result in some sort of an RFP may be a very valuable thing coming out of this discussion today. I don't think any of us have really thought about that issue in the kind of depth that we probably will after this meeting. So I think that is a very positive notion.

What I would like to do is go to lunch a little bit early and come back a little bit early

with the notion that we might be able to end a little bit earlier this afternoon. I thought that might be popular.

So would it be possible for us to come back at--it is five of 1:00 now. If we came back at 2:00, that gives us a fifteen-minute lead on the afternoon. There might be a vote for even coming back earlier. I hate to have a vote. Would 1:45 be workable?

All right. We will return at 1:45.

[Whereupon, at 12:05 p.m., the proceedings were recessed to be resumed at 1:45 p.m.]

A F T E R N O O N S E S S I O N

[1:50 p.m.]

DR. EDWARDS: At this point, we are going to move on into the issues related to hospital-acquired pneumonia. We will start right out with Don Craven who will do the first of the three presentations.

Issues in Clinical Trials of Hospital-Acquired Pneumonia - IDSA Speaker

DR. CRAVEN: I wanted to thank David Gilbert for the invitation to participate in this conference. It has a been very enjoyable experience.

[Slide.]

This is the first of three presentations. We actually shared slides to try to minimize overlap between the different topics. So my charge is to give an overview of hospital-acquired pneumonia but I am going to primarily focus on ventilator-associated pneumonia as one subset of this group.

On the slide, you see that it says healthcare-associated pneumonia. This is a term that has now been incorporated to look at patients that are not only in the hospital but people who

are in the community, particularly in chronic-care facilities like nursing homes or people that have been in the hospital that are discharged that come back with pneumonia.

The idea is to try to lump these because the pathogenesis and the microorganisms are, oftentimes, very similar so that the idea would be to try to look at this entity. But, today, I am going to focus primarily on hospital-acquired pneumonia and VAP.

[Slide.]

I think one of the issues, when you talk about clinical trials, is definitions. We have talked a lot about definitions and there are a lot of definitions that are used for--we use a very simple definition that basically hospital-acquired pneumonia is one that occurs 48 hours after admission to the hospital and is not incubating on admission.

For VAP, it is a pneumonia that occurs 48 hours after intubation and mechanical ventilation. There are a lot of terms that are used in the studies that make it very hard to interpret this literature. You would think that people would understand mortality, but when you look at

mortality, it is defined as mortality within seven days, mortality within 14 days, 30 days, in the ICU or 30 days after discharge from the hospital. So you have to look very carefully at the definitions that are used.

We have a problem now with epidemiology particularly with the involvement of multidrug-resistant strains and also one of the complications of VAP is superinfections or secondary episodes of pneumonia after they have been extubated.

For HAP and VAP, one of the problems that we have is that this site, in comparison to the CSF, is not a sterile site. The lower tracheal-bronchial tree is not sterile. It is colonized. One of the problems with diagnosis is trying to discriminate colonization from infection.

There are different methods. I am going to talk briefly about clinical diagnosis in some quantitative cultures, talk a little bit about therapy and our approach to therapy. There is a guideline that is being written by IDSA and ATS to try to get guidelines for managing patients. This, hopefully, will be completed in September of 2003.

[Slide.]

Just some basic facts about HAP. When you put an endotracheal tube into a patient, you increase the risk of pneumonia 6- to 21-fold. More than half the antibiotics that are used in the intensive-care unit are used to treat lower-respiratory-tract infections.

We have a concept that has emerged between early and late onset because the pathogens for early onset are different than late onset. Crude mortality in different studies goes from about 20 to 50 percent depending on the population studied. The attributable mortality, or mortality attributed to the pneumonia, itself, in studies range considerably but probably, in most studies, it is in the range of about 30 percent that can be directly attributed to the pneumonia. Cost, as you know, is in millions.

[Slide.]

Looking at risk, and this is medical ICUs, nosocomial infections, urinary-tract infections are most common but pneumonia has the highest morbidity and mortality. The same, blood-stream infections, also. So, of the nosocomial infections, pneumonia is important because of the consequences.

You basically look at the definition of

early-onset. HAP is usually within five to seven days of intubation or five to seven days of coming in the hospital. That is early-onset disease. Late-onset disease would be after that time. If you look at early-onset, hospital-acquired pneumonia with no risk factors, you can see the pathogens, Pneumococcus, Hemophilus, anaerobes, Staph aureus, and some of these are mixed, are very similar to what you see for community-acquired pneumonia.

There are not as many MDR strains and, when you look at early-onset HAP, the outcomes are much better and the mortality is lower.

[Slide.]

When you look at the late-onset players--these are after seven days--many of these people have many risk factors. I call this the dark side because the organisms here are quite different. MRSA and possibly, in the future, VRSA. KES strains, Klebsiella, Enterobacter, Serratia, Pseudomonas, Acinetobacter, et cetera, Legionella and some of the other pathogens.

So you have a group of pathogens that are more multidrug resistant.

[Slide.]

Looking at this study that came from France, what are the risk factors for multidrug-resistant organisms? They looked at 135 patients with VAP. 57 percent had multidrug-resistant pathogens. The risk factors were late-onset disease which we already know, prior antibiotic use within the previous 16 days, and particularly quinolones, third-generation cephalosporins or imipenem had significant odds ratios.

The point of the study was that if you had these risk factors for MDR pathogens, the initial coverage should be broader spectrum to cover these pathogens.

[Slide.]

Also, if you look at the spectrum of these pathogens in different ICUs, this is a study that was comparing pathogens in Paris, Barcelona, Seville and Montevideo. You can see that the variation in pathogens in these units, most of them did have Acinetobacter. Pseudomonas was a player in some units, but wasn't a player in other units. MRSA was very low, whereas certain units in the United States and other ICUs, MRSA is very important.

MSSA had very low results. But even within the same hospital, the spectrum of pathogens can vary between a medical and a surgical ICU.

[Slide.]

You know what? This is the wrong--oops. That is the first set. I sent a first set and then--this is going to be a little interesting. This diagram looks at--basically, when you put an endotracheal tube into a person's trachea, you have secretions that pool. There is heavy contamination in the oral pharynx with pathogens.

Also, the stomach can be a major reservoir for organisms. The bacteria can go up and back and they pool above the endotracheal tube cuff which is not a good cuff and there is continual leakage into the lower respiratory tract resulting in colonization in virtually every patient and tracheal bronchitis.

What we want to know is what is going out here in the alveolar spaces. So we have to look at measurements here to try to identify what is going on in the alveolar spaces.

[Slide.]

I want to talk a little bit about clinical diagnosis of VAP and the use of quantitative

bacteriology. We look at different methods. There is a clinical spectrum of disease which I will talk about in a second, a new scoring system which is called CPIS which I will also go over.

A lot of this, you can look at sputum examinations crudely looking at the Gram stain in the cultures from endotracheal aspirates. Urine antigens are helpful for identifying some pathogens. Then, more recently, a variety of specific quantitative techniques have looked at quantitating the bacterial that is in the endotracheal tube using blind bronchial-alveolar lavage or protected specimen brush or bronchoscopy, putting a bronchoscope down doing BAL or PSB.

A lot of the studies have looked at sensitivity and specificity, and quantitative bacteriologic techniques have greater specificity. I also am pretty old-fashioned. Gram stains, to me, are very helpful because, if you can see organisms on Gram stain, you have a pretty good idea about what is going on and it correlates with about 105 to 106 organisms per ml using quantitative techniques.

[Slide.]

So, for clinical diagnosis, we use fever,

white count, and usually sputum. If it is purulent looking, a Gram-stain is cultured. We want a new and persistent infiltrate on chest X-ray. If you have blood cultures in pleural fluid, that is great but many of these patients don't have either of these and, more recently, as we will talk about in a second, there has been a scoring system that looks at these criteria to give a score that tells you about the probability of a clinical diagnosis.

The problem with clinical diagnosis is that the specificity is very poor.

[Slide.]

Quantitative techniques are used for urinary-tract infections. We basically manage patients by whether they have 105 organisms per ml. For catheter-related infections and bacteremia, we have quantitative techniques for culturing the catheter that help us decide. For wounds, there are even criteria looking at wound infections. Quantitative criteria are available for these.

For VAP, there have been a lot of problems. Using PSB, it is usually 103 per ml, BAL, 104 per ml, or quantitative endotracheal aspirates, 105 per ml. These techniques, I think, are not that difficult and should be used but very

few centers in the United States use these techniques because microbiologic labs are under a lot of stress.

[Slide.]

Basically, here, we have an intubated patient. You put a catheter down blindly. It usually goes into the right main-stem bronchus. You pull back fluid and you do quantitative analysis of that fluid. If it is over 104, that is consistent with a diagnosis of pneumonia.

This is a pretty easy technique to do and the quantitative bacteriology isn't that hard.

[Slide.]

When we look at outcomes from different studies, I have shown on the left here what I consider sort of traditional outcomes. We look at mortality, which we have the problem of attributable mortality. We look at morbidity and we look at cost.

But I think there are other outcomes that are very important. If they don't have pneumonia, stopping antibiotics is an important thing to do. We want to try to decrease antibiotic resistance, particularly of intensive-care units which are a haven for resistance organisms.

We want to try to reduce other nosocomial infections, superinfections and, most importantly, we want to reduce device days because if we get the endotracheal tube out, we have a decreased risk of getting pneumonia. The longer that endotracheal tube is in place, the greater the risk of pneumonia.

[Slide.]

This is a nice study, I think, the only comparison study looking at a clinical diagnosis which is used most commonly in the United States versus invasive diagnosis. Invasive is bronchoscopy with BAL and PSB. It is a fairly large study, 31 ICUs in France, 413 patients. Clinical diagnosis was in 204 and invasive diagnosis was in 209. They looked at microbiology in outcomes.

[Slide.]

As you can see on this slide here, you can see that the microbiology, there were more people in the clinical group shown in green here that had a positive culture in their endotracheal tube, which you would expect. Much lower, if you used invasive diagnostic techniques in that criteria.

Also, we always talk about polymicrobial

pneumonias, ventilator-associated pneumonias. You can see that polymicrobial pneumonia was significantly more common in the group that used clinical diagnosis.

[Slide.]

They also were able to demonstrate a decrease in mortality. For people that had a clinical diagnosis, it was 26 percent versus 16 percent. Also, sepsis and organ failure was decreased in the group that had invasive diagnosis and the number of antibiotic-free days, which I think is an important variable in the ICU, was significantly less, was significantly less in the people that had--or significantly more in the people that had invasive diagnosis.

So, looking at traditional outcomes, some of these other outcomes and, particularly, some of these lesser outcomes, we can see that there seem to be some advantages, at least in this study. Obviously, it would be nice to have this study reproduced in the United States.

[Slide.]

Why would VAP, stopping the antibiotics help? Because people that had negative cultures basically had their antibiotics stopped and

basically there was a look for other sources of infection that could be giving the clinical syndrome that was suggestive of pneumonia.

So, basically, by reducing antibiotic use, we can, perhaps, reduce multidrug-resistant superinfections and, perhaps, improve outcome, at least in this study.

[Slide.]

I want to mention just a few points about treating VAP. HAP or VAP, hospital-acquired pneumonia or VAP, is a very dynamic disease. There are a lot of variables that go into determining what happens to a patient.

Most important is, I think, to try to assess the severity. The severity is whether they have severe or mild disease. People with severe disease, more prompt attention, more broad-spectrum antibiotic therapy and the CPI score, which I will show you in a second, will help to do this.

We also look at certain risk factors for certain pathogens that may be present. We always want to retain blood and sputum cultures as a basis of the microbiology which will be available in 48, 24 to 48, hours to help adjust therapy.

We want to begin appropriate antibiotics

and then basically look at the clinical response for those antibiotics over a 24- to 48-hour period and then adjust the antibiotic regimen based on the microbiology that is available.

[Slide.]

It is important that we have initial therapy looking at inadequate therapy, shown here in yellow, versus adequate therapy and generally looking at the mortality. Most of these studies, in almost all of them, the mortality was reduced but only in two studies was the mortality significantly reduced by the use of adequate therapy.

[Slide.]

I want to talk a little bit about these studies. Sorry; things were a little out of order here compared to the old style. This is the CPIS scoring system. It was originally described in 1991 and modified in 2000. You get a fever for either having a very high fever or very low fever--you get points. White count, if it is low or very high, you get points. If there are bands, you get points.

If the endotracheal aspirate is purulent, you get points. If the Gram stain is positive, you

get points. They looked at oxygenation here and the oxygenation, you would get points based on the PaO2-FiO2 ratios and whether the chest X-ray had diffuse or localized infiltrates.

This later study, the Singh study, actually did a subsequent CPIS scoring system at Day 3 to help define therapy at Day 3. A study that is in progress now, or a study that is in press now, is going to look at CPIS scoring to monitor the impact of therapy and outcomes of patients that are on different antimicrobial agents.

I think this will be a very important study because it showed that the CPIS scoring, particularly the oxygenation, was a good monitor for people who were responding and people that did not respond and would go on to die.

[Slide.]

Looking at the Singh study--this is a very nice st because the question was do we really need short-course or long-course therapy for absolutely every patient. What they did is they took patients with suspected nosocomial pneumonia or ventilator-associated pneumonia who had the CPIS score less than 6--would be a low probability of

pneumonia.

They randomized to ciprofloxacin for three days versus standard antimicrobial therapy and then basically, at three days, the group that got cipro alone as a single agent had a CPIS score. If it was greater than 6, additional treatment was added. If the CPIS score was less than 6, they stopped antibiotics after three days and they looked at outcomes in the standard-treated group, the standard of care group, versus the group that had short-course cipro therapy based on the CPIS score.

[Slide.]

You can see here that basically the short-course group had fewer costs of antibiotics and hospital stay. There were less multidrug-resistant organisms and superinfections, lower mortality and the ICU days were decreased in the people that got short-course therapy.

[Slide.]

This is another approach that has been looked at by Ibrahim and coworkers. They looked at the pathogens that were in the intensive-care unit before they started an intervention study. Basically, appropriate antibiotic therapy was actually very poor in the group before they did

their intervention.

What they did is they looked at the pathogens that were in their unit and they basically made a drug cocktail to cover all the pathogens that were in their units; Pseudomonas, methicillin-resistant Staph aureus and Acinetobacter. So they made a regimen that would cover all those pathogens and actually improved appropriate antimicrobial therapy after the initiation of this study.

[Slide.]

I think what this points to is the fact that it you know what you are treating and you can get an appropriate cocktail, you should start broad-spectrum therapy and try to reduce it when more antibiotic information is available.

When we have HAP, we have what is called the liberal approach. That is the failure to recognize the entity, HAP. Lack of antibiotic efficacy due to resistance results in increased mortality due to ineffective antibiotics. So the liberal approach would be to use more antibiotics.

The conservative view says we have increasingly ill patients, more MDR pathogens. We have loss of effective antibiotics secondary to

overuse of antibiotics, therefore we should use fewer antibiotics.

What the consensus seems to be emerging is that, up front, if we don't know what we are doing, we try to use liberal antibiotics to cover all the potential pathogens. So early appropriate therapy appears to improve outcome. Then, based on the results of the microbiology, the antibiotic regimen can be streamlined or therapy can be stopped if there is no evidence of VAP and, basically, for responders or nonresponders, if a person is not responding to therapy, I think you need help assessing the diagnosis and therapy.

So the antibiotics we are talking about for Gram-negative rods and Pseudomonas would be, basically, third- and fourth-generation cephalosporins, aminoglycosides or imipenem. For MRSA, it is vancomycin and linezolid which is data that are in press suggesting that linezolid would be a good alternative for MRSA.

For atypicals like Legionella, if you have a hospital that has Legionella, you need to cover for these. Anaerobes play a very, very low role in VAP except early onset VAP.

[Slide.]

A study that has recently been done looked at clinical response to antibiotic therapy. I think this is an important study.

[Slide.]

They basically looked at the response, looking at white count. You can see by the arrows here that basically most of the people had a white count that was back approaching normal at about eight days. Basically, the log decrease in organisms was present by Day 6. Looking at the FiO2, the maximum improvement in FiO2 was about Day 8.

So, one of the questions now is how long do we treat patients with VAP or HAP. There is a large multicenter, double-blind study looking at short versus long course therapy. But it suggests here that a lot of the clinical parameters suggestive of pneumonia appear to be improving on about Day 7 to 8.

[Slide.]

So here is sort of the approach that is being worked on at the present time. HAP suspected, check a CPIS score, obtain cultures, begin early in appropriate antibiotics based on the severity of disease and risk factors at 24 to 48

hours, look at culture data, CPIS score, and try to make a decision about management at that time.

If they are improved, you might want to de-escalate antibiotic therapy. If patients are not approved, look at alternative antibiotics, check out the diagnosis and consider getting a consult to help.

[Slide.]

So what we want to do, I think, for this particular avenue, is to look at traditional outcomes but also to look at some of these other outcomes that may be important in looking at mortality, morbidity and some of the other outcomes that may be important in measuring things such as device days in clinical trials.

[Slide.]

This is a quote from Oliver Wendell Holmes. "One man's mind, once stretched by a new idea, never regains its original dimension." I think this is true. We have learned about HAP, particularly in the last four or five years. I would say, for myself, I started this conference in this position right here and, after two days of hearing some of the data discussed, I feel that my mind has been stretched.

Thank you very much.

DR. EDWARDS: Thank you very much, Don.

We will move on now to Dr. Gesser from PhRMA.

PhRMA Speaker

DR. GESSER: Thank you, Dr. Edwards.

[Slide.]

I would like to thank my codiscussants for sharing their slides with me. One of the things I noticed last night, as I was looking at my slides, is that I looked at the title slides for each one of our talks and we each have a different name for this disease entity.

As Dr. Craven pointed out, he had the title, Healthcare Associated Pneumonia. I have got Nosocomial Pneumonia. Dr. Beidas has Hospital Acquired Pneumonia. I think the good news is that we are all talking about the same thing but, perhaps, we will need to revisit that during the discussion session.

[Slide.]

This is the overview of my slides. I thank Dr. Craven for giving such a great background for the disease process such that I can summarize what I want to say in one slide. I will review

briefly some of the recent data from the two most recent double-blind comparative pivotal trials resulting in approvals for drugs for nosocomial pneumonia and will focus on some issues that came up during the course of those trials, and then specifically go through a number of issues that make trial design particularly challenging for this indication.

Then, I think, in quite a few slides, I will pose a number of questions that, hopefully, we can get into further during the discussion.

[Slide.]

First, just to add to what Dr. Craven said, I think what is really important to keep in mind is that every patient in these trials has another active illness. They have an existing comorbidity that they are being hospitalized for and being treated for or are in a nursing home and being cared for.

So this adds to the possibility to obscure to diagnosis. It limits enrollment in the trial, confounds assessments of efficacy, safety and is important to keep in mind. If we can sort out the patients who don't have pneumonia in the population that do, we are really talking about a very

heterogeneous population that includes ventilated patients as well as nonventilated patients.

An important component, as Dr. Craven mentioned, and becoming increasingly important as we get older, is the population of patients who are in long-term-care facilities where pneumonia is the second leading cause of infectious morbidity.

As Dr. Craven mentioned, patients can be separated as to early onset and late onset. That is true of both patients who are ventilated and patients who are not ventilated. Additionally, the literature has assessed a number of risk factors for severity and poor prognosis in this disease.

Delta 1, I think, needless to say, it is difficult to quantify. I don't think we will be able to quantify delta 1, but I do believe that the group would agree that there is clearly substantial benefit of antibacterial therapy for documented pneumonia in these patients.

Mortality is high in these patients. As Dr. Craven already mentioned, attributed mortality is really what we would like to get a perspective on and, depending on what literature you read, 30 to 50 percent of the crude mortality can be attributed to pneumonia in these patients. This,

again, reflects the complicating underlying illnesses and also the pathogens identified and responsible for pneumonia.

[Slide.]

This is a schematic, not meant to be very scientific or overly inclusive, but basically lays out the pathogens we are talking about and it gets at some of the issues in the clinical-trial design and, also, it is a focus for discussing the types of agents that one might consider in trials of antibacterial agents. That includes both approved agents and potential agents.

As Dr. Craven points out, the spectrum of pathogens is really broad. It is influenced by the duration that the patient has been hospitalized and/or on ventilation and also influenced by the prior antibiotic experience that the patient has had.

Anaerobes, generally a small part of the illness, early onset, particularly in patients who are at risk for aspiration. Gram-positives, a significant important population, and increasingly important is the population of patients with resistant Gram-positives which would include penicillin-resistant Streptococcus pneumoniae and

also methicillin-resistant Staph aureus and, in the future, likely glycopeptide-resistant Staph aureus as well.

Enterics play a big role in the disease, particularly resistant enterics. This is including ESBL-producing enterics and other mechanisms of resistance in the enterics including AMC production, both constituitive and derepressed and other forms of enteric resistance.

Important pathogens, particularly in late-onset disease, are the nonfermenting Gram-negatives and of particular concern is the small population for now but increasing population of resistant nonfermenting Gram-negative pathogens.

In terms of the types of agents that are approved and might be studied in this indication, we have agents that have been studied that are specifically focused on the Gram-positive area. There are agents that cover the traditional enterics and with varying degree of efficacy against resistant enterics but limited activity against positives.

This would include beta lactams and some beta-lactam/beta-lactamase inhibitor combinations, agents with increasing Gram-negative coverage such

that we are now into the nonfermenting group. This would include, again, beta-lactam/beta-lactamase inhibitor agents, some fluoroquinolones, less activity, Gram-positives. Some agents can expand in that direction and also cover; for example, penicillin-resistant Strep pneumoniae.

Of particular interest is new agents, and specifically new agents that can really stretch the Gram-negative spectrum of things to include resistant nonfermenting. These are potential agents, as listed here, and certainly agents that there is quite a lot of clinical interest in.

Additionally, one could theoretically come up with an agent to cover all pathogens. I think that target is yet to be discovered.

[Slide.]

Just want to now focus on the two most recent double-blind comparative pivotal trials for these indications. I am not going to talk about delta so much here, or outcome here, as just the logistics of study design and some of the components of the studies that I think are important.

Study A was a broad-spectrum agent. It was studied versus a licensed comparator for

nosocomial pneumonia and Study B is a more select Gram-positive agent. It was studied versus vancomycin which isn't approved for the indication but was considered a standard of care in the treatment of patients with nosocomial pneumonia, particularly evidently those at risk for Gram-positive agents.

If you can recall, Roger gave you data from meningitis trials. Sixty centers were included in those trials. Upwards toward ninety centers were included in these trials. 264 patients were studied in the first trial, approximately 400 in the second trial. These patients, basically, are coming from throughout the world, primarily the U.S., North America, Europe, Costa Rica, in this study, a significant component from South Africa in this study as well as Australia, Israel and, again, Latin America.

The enrollment for these trials is shown here. I think enrollment is influenced, to a certain degree, by the proportion of patients with ventilator-associated pneumonia here. One thing to point out here, the number of patients with VAP--this is the clinically evaluable number of patients with VAP. This is the total patients

treated. Likewise, 110 clinically evaluable patients with VAP in Study B.

[Slide.]

Just to look at the study populations. What you see here, the percentages refer to the percentage of the treated patients that fit each one of these study populations. The asterisk here is the primary efficacy population; that is, the clinical evaluable population in these two studies. As you can see, approximately 55 to 60 percent of the total patients treated in these two trials were considered clinically evaluable. I think it is interesting to see the consistency in these two trials.

In terms of micro evaluability, something that Dr. Craven focused on quite a bit in his talk, this includes a population of patients with at least one identified pathogen without regard to quantification. Again, it is interesting to see that the proportion of treated patients in these two trials is similar, the proportion of treated patients with a pathogen who are considered micro Eval are similar, 24 to 28 percent.

This micro Eval-2 population is actually a population for whom quantitative culture results

were available. This was only done in the second study. The initial study requested quantitative cultures from all patients including those without VAP. According to the information available through the Freedom of Information, the protocol was amended to then just request that of patients who were ventilated.

I think the important thing to see here is that, of the total treated patients, only 11 percent met the criteria--that is, 103 or 104. It is not clear from reading this information whether endotracheal quantification was used, but, certainly, a low proportion of the total treated patients.

In terms of the proportion of patients who had mechanical-ventilation-associated pneumoniae, it differed in the two trials. Basically, 50 percent of the clinically Eval population were ventilated in this study and approximately 20-odd percent in this.

Interestingly, the proportion of ventilation-associated pneumonia patients who were micro eval, the proportions are not that significantly different than those did not require mechanical ventilation. I think that gets to the

specificity and sensitivity of endotracheal cultures versus deeper cultures as well.

[Slide.]

I just want to focus in on some of the issues that we encounter in these clinical trials. They are quite complicated. These patients are ill, as you can imagine. Issues of consent, in some circumstances, assent, are really quite important. These are patients who were receiving quite a lot of adjunctive therapy and, as I have mentioned already, are being managed for some other primary illness prior to the onset of their pneumonia.

For ventilator-associated patients, a particularly definitive diagnostic criteria, as Dr. Craven points out, really have not been agreed upon. I think there are a number of studies. The general criteria used, in addition to the radiographic requirements of a new or worsening, hopefully alveolar density or a bronchogram.

The classic triad is fever, leukocytosis and purulent tracheal secretions. For patients who are nonventilated, this is more important. I think the CPIS score gets at this for patients who are ventilated--i.e., looks at measurements of

oxygenation.

The studies that address the specificity and sensitivity of the clinical criteria I think are important although most people agree that the specificity of clinical criteria along with radiographic criteria are low, that specificity increases the more signs and symptoms that you include. For example, if you include fever, leukocytosis, purulent tracheal secretions, most people would agree and most studies agree that the specificity is greater.

This gets at, I think, some of the issues brought up by the CPIS score in which it is a composite of all these signs and symptoms and I think it will be interesting points for discussion during the discussion section.

Regarding micro criteria, I don't think I have anything really new here. The issue is, again, we are culturing a nonsterile space. We are going through a particularly nonsterile space to get to those cultures and it is not clear that the microbiological results are that reliable nor is it clear that they correlate that extensively with the clinical results.

Additionally, many of these patients

receive prior antibiotics and these cultural results, particularly the quantitative results, are extremely influence by whether or not patients have received prior antimicrobial therapy.

[Slide.]

Treatment issues, now, which impact on clinical-trial design. This is a real tough issue especially since there are broad initial empiric antibacterial coverage guidelines and, more and more, this is being considered the standard of care.

Another issue is that, in general, cultures are not available, as Dr. Craven has already pointed out, to guide the management of these patients to at least two to three days into the initial course of therapy. What is important, though, it appears, in numerous studies, is that patients who are sick in whom you suspect the diagnosis, you really want to cover broadly initially because, if you don't, there is greater morbidity and mortality.

However, as pointed out in that schematic diagram, it is difficult or possibly impossible to cover all potential pathogens, so there has to be some way to look at that. Empiric coverage

generally takes into consideration things like duration of hospitalization, ventilation, as we mentioned earlier, versus late-onset disease, the duration and the spectrum of prior antibacterial therapy and also, as Dr. Craven pointed out, I believe, in a Spanish study, the local microbiological and susceptibility data.

[Slide.]

Then we get on to the issue of outcome determination. Traditionally, the outcome assessment in these studies has been the clinical response. Traditionally, it has been in the clinically defined population of patients. I suspect we are going to discuss that during the discussion period. I think it is important because it is a clinical assessment. There is some subjectivity involved and, obviously, if at all possible, a blinded assessment is the preferred assessment, although, I must say, with all kinds of concomitant therapies and contingencies based on the treatment guidelines, this may be challenging in some circumstances.

I think the good news about the subjective clinical assessment that there is a finite and objective nature to this in that patients should no

longer require antibacterials once this clinical assessment is being made and, if they do and they are required to receive them for the disease under study, they are generally considered to be failures.

In terms of the clinical measures looked at, perhaps the CPIS score can get at this in a more succinct way which generally has been looked for as a complete resolution or return to baseline with resolution of acute signs of the infection, for example, fever, leukocytosis and purulence in the sputum.

Micro assessments; as endpoint assessments, these are difficult. As primary assessments, as you can see from the way the populations broke out in the two studies that I showed you, Study A and B, these populations are smaller. In addition, it is not clear that the micro results correlate completely with the clinical response.

Additionally, for patients who are judged to be cures, often, usually, the microbiological response is that of a presumed response and I guess we can get into a discussion of the ethics and practicality of getting follow-up cultures,

different types of follow-up cultures, in patients who are otherwise judged to be cured.

[Slide.]

I just want to focus on logistics again. We are talking about ninety centers, multicentered, multinational, clinical trials. Whatever we design into our clinical trial has to have broad acceptability across many institutions if we are going to maintain the same sorts of sample sizes that we have in the past.

Additionally, the study design, whatever it is, must be acceptable to investigators, patients and to local ERCs and IRBs. We must also take into account regional differences in susceptibilities, diagnosis, management of the disease. Whatever procedures we decide on, they should be standardized procedures, things that can be done reasonably with reasonable proficiency, done by qualified personnel throughout the study sites.

Any invasive procedure, I think as Dr. Craven points out, needs to be justified as a standard of care or something really clearly identifies an improved outcome for patients.

[Slide.]

I think a lot of these questions are going to be addressed by Dr. Beidas during his talk, but I will quickly go through these questions that still remain. Can the diagnostic specificity be increased for this disease and still maintain a broad applicability both in terms of the applicability of the study results to a broad population of patients and also the broad applicability of the study procedure such that we can solicit the help of clinical investigators basically throughout the world?

Do culture results improve diagnostic specificity or sensitivity and, if we believe that they do, what is the preferred approach? Is one method truly better than another? I think we can talk about, hopefully, during the discussion section, the relative merits of endotracheal cultures versus more invasive cultures and, again, some of the practical issues of a culture obtained.

[Slide.]

One important issue, and it has always struck me as particularly different, is I think there is an opportunity in HAP. This is where we see highly resistant pathogens. These are hospitalized patients. They receive many

antibiotics. The issue, in general, for these antiinfective, antibacterial clinical trials, we tend to exclude patients who have received greater than 24 hours of antibiotic therapy in the 72 hours prior to enrollment unless they have a pathogen identified at baseline.

The problem, as we already pointed out, we don't know that until two or three days into the study. The question I ask is how can these studies be designed to include these patients? For a number of reasons. One is to capture more of the resistant pathogens. The other is it strikes me--one thing I forgot to mention when I mentioned the study design, Study A and B; all those patients received concomitant therapy during the course of the treatment for hospital-acquired pneumonia.

In the Gram-positive study, obviously, those patients received azetreonam unless it was perfectly clear that they had nothing but a resistant Gram-positive or a Gram-positive agent. Additionally, those patients also had the possibility of receiving aminoglycosides if Pseudomonas was identified. In the broad-spectrum agent, likewise, double coverage was offered for Pseudomonal coverage.

The irony is that we allow a disconcomitant therapy but yet we exclude it is prior therapy. I think we need to revisit this. It is not easy. It is a problem. It is a problem for me as a sponsor designing a trial. I am sure it is a huge problem for a regulatory agency to get at, to dig through the data to try to get a handle on the contribution of the study drug to the overall response.

But I think it is something that is important and that we need to discuss.

[Slide.]

Therapy; again, I have mentioned how there are a lot of antibiotics tossed around here. How do we do these studies in the light of published guidelines for empiric treatment? How do we incorporate those guidelines? I think I am going to rely a lot on some stimulating conversation by the IDSA colleagues.

Do we need to cover empirically--in the initial coverage, does it have to be double coverage for Pseudomonas? In what circumstances is empiric MRSA coverage required? I think these are all things we need to visit and probably revisit as time goes by.

If you do have a new anti-Pseudomonal agent, can you study it as monotherapy in HAP? What do people have to think about that? In terms of avoiding biocreep, you saw treatment is a wide spectrum of agents that could be used in this disease entity. What are the key properties of licensed agents or standard regimens that could be considered as appropriate comparators?

I think, obviously, we could have an interesting discussion in that regard as well

[Slide.]

Regarding outcome, again, what is the most appropriate primary outcome variable, clinical or micro? Should follow-up cultures be obtained in patients other than those who are clinical failures? Are there reliable culture methods such that follow-up eradication could be used as a primary measure of effectiveness?

Can invasive follow-up cultures--I touched on this already--be justified in cures? How should missing results be dealt with; i.e., if you are cured, you are not going to get an invasive culture and yet your study design calls for it. Missing information sometimes is dealt with in a negative way. How do you deal with that in the setting of

this type of clinical trial?

How do you deal with concomitant therapy, particularly when the concomitant therapy overlaps the spectrum of investigational agent and, finally, the delta. What criterion should be met to demonstrate noninferiority of investigational antibacterial?

I will stop there.

DR. EDWARDS: Thank you very much.

Dr. Beidas from FDA.

FDA Speaker

DR. BEIDAS: Thank you, Dr. Gesser, for pointing out our different definitions as we started.

[Slide.]

For the last two days, I have thought I was the only one who is confused about HAP and nosocomial pneumonia or healthcare-associated pneumonia.

[Slide.]

This slide summarizes the time line of hospital-acquired pneumonia in relation to clinical-trial issues and identifies some of the issues for discussion this afternoon. The text in blue reflects the three areas in which we would

appreciate the committee's discussion.

These three areas are definition and diagnosis, test-drug issues, adjunctive therapy and comparator agents, and then the outcomes.

[Slide.]

The regulatory history for the indication of hospital-acquired pneumonia is brief. Prior to 1990, respiratory infections were all lumped together under the heading of lower-respiratory-tract infections. This included entities like acute exacerbation of chronic bronchitis. It included pneumonia and it included empyema, among others.

In 1992, the IDSA published guidelines for the evaluation of antimicrobials and the FDA published the Points to Consider Document in which lower-respiratory-tract infections were divided into community-acquired pneumonia and into healthcare or hospital-acquired pneumonia.

In 1992, the reason to separate community-acquired pneumonia from hospital-acquired pneumonia was necessary in clinical practice and as well in trials due to differences in epidemiology such as the population that was affected, the infecting organisms, the cure rates and other

factors as well. Beyond that, the ATS and the IDSA, as well as others, described other subcategories of hospital-acquired pneumonia such as nursing-home patients, immunocompromised patients and surgical patients.

[Slide.]

Recognizing the large amount of literature that is available recently, or that has recently become available on hospital-acquired pneumonia, the agency really raises the question, are patients with ventilator-associated pneumonia sufficiently different from other patients with hospital-acquired pneumonia to warrant studying them separately and does efficacy in patients with ventilator-associated pneumonia predict efficacy in other patient groups with hospital-acquired pneumonia?

[Slide.]

The multiplicity of diagnostic methods suggests a lack of agreement among clinical investigators and clinicians on how to best diagnose ventilator-associated pneumonia. Maybe that is so.

You have heard this afternoon from Dr. Craven about the study by Singh using the Clinical

Pulmonary Infection Score to treat patients with suspected ventilator-associated pneumonia early. Therefore, one may ask, could the CPI score serve as a useful tool in enrollment strategy and should we look at all patients or only patients who are culture positive?

If we cannot identify the organism that is causing the infection, how do we then figure out if the test drug is treating what it is supposed to treat?

[Slide.]

Another question related to inclusion/exclusion criteria is should patients already on antibiotics be excluded from enrollment? It is well-recognized that antibiotic therapy alters microbial flora and increases rates of resistance and colonization.

Also consider what effect does prior antibiotic therapy have on the yield of microorganisms in a diagnostic study.

[Slide.]

Among comparator issues and adjunctive therapy; what is an appropriate comparator in ventilator-associated pneumonia? From what has been described here by Dr. Craven today, clinicians

may be more inclined to use early empathic and broad antimicrobial therapy in patients with suspected hospital-acquired pneumonia. So when you study drugs in combination that have overlapping antimicrobial coverage, how do you know which one is really exerting the effect that you are looking for?

I have listed here two examples. The first one is really the easy example. Linezolid was compared to vancomycin. Both of them have Gram-positive coverage. The adjunctive therapy in both cases was azetreonam. It covers Gram-negative organisms.

When we go to the recently approved levafloxacin for the indication of hospital-acquired pneumonia, it becomes more dicey and it becomes more complex. The comparator was imipenem with step-down therapy using ciprofoxacin and, in both arms, ceftazidine and aminoglycosides were used as adjunctive therapy in more than 50 percent of cases.

[Slide.]

If we believe that the survival of patients in ventilator-associated pneumonia is linked to early empiric therapy, as has been

described this afternoon, should we be testing drugs that have no Pseudomonas or Staphylococcus coverage? Also, a related issue is the local resistance and susceptibility at each center which may play a significant role in determining what is appropriate therapy.

I think it is also important to recognize that appropriate early antibiotics have desirable effects on antibiotic use, on resistance, on cost, on ICU stay and on mortality and, from the standpoint of clinical trials, how could we structure trial design in order to take into account those factors.

[Slide.]

What endpoints should we be looking at; bacterial eradication, clinical cure, radiologic resolution, or maybe a combination of those, and how do we define a failure or a cure?

[Slide.]

Then my last slide, I come back to delta. Do we believe that the effect of drug over placebo is more than 20 percent and, if we do, then we are implying that the test drug is superior to placebo. Such as claim is built on the assumption that the active control used in the trial is similar to its

effect in earlier historical trials.

That assumption may be undermined by information bias, selection bias and secular trends in diagnosis and treatment at the historical time frame.

For delta 2, recognizing that there are potential deaths in hospital-acquired-pneumonia trials in either the test drug or the comparator arm, what is an acceptable loss of efficacy relative to a control for a serious illness like hospital-acquired pneumonia?

[Slide.]

Mr. Chairman, and committee members, I would like to leave you with a list of questions for discussion in the next two slides.

DR. EDWARDS: Thank you very much.

Discussions

DR. EDWARDS: Obviously, this topic could involve an at least two-day workshop all unto itself. But let's try to accomplish as much as we can here. Who would like to start? David?

DR. GILBERT: Don, Dr. Craven, isn't it true that there was recently a consensus conference that you chaired, or moderated, I am not sure which, that dealt with the subject of

ventilator-associated pneumonia and, specifically, I want to throw out a couple of rather dramatic statistics and see if they are true or not, that if you use, as a gold standard for the diagnosis--and I am only talking about ventilator-associated pneumonia for the moment--that either a positive culture directly from the lung or quantitative microbiologic by protected specimen brush and so forth, that even if the clinical pharmacology infection score is positive, that only one-third of the patients have microbiologic evidence of pneumoniae.

Is that true?

DR. CRAVEN: I don't know about the last point. I think that we have to start with some assumptions. This is an incredibly difficult disease because it is difficult to make a diagnosis of pneumonia. But I would suggest that we should start with ventilator-associated pneumonia because I think the microbiology is absolutely key to understanding t. If you don't have any microbiology, I don't know what you are treating because there are so many syndromes that mimic pneumonia that you have to have something to start with.

To me, the place you start is with bacteriology. I think the quantitative bacteriology would be, in my opinion, imperative for a clinical trial because I think it at least gives you something to start with where there is a criteria. You have organisms that are there. There are obviously a lot of other caveats. But also, it might be a very good marker to look at response, looking at the response.

If you look at the Dennesen study, you start out with a pathogen and you look at log reductions like we do in a lot of other infectious diseases. So, to me, for clinical trials, although people will argue about a clinical diagnosis in a center, that we definitely should start with quantitative bacteriology.

You can use quantitative endotracheal aspirates. You could use a blind. You don't necessarily have to put a bronchoscope down and do PSB and BAL on everyone because there has been nice comparison studies between quantitative techniques that suggest that they are relatively comparable.

So I can't say about the CPIS score because the CPIS scores really had pretty limited use except that this article coming out in press

where they looked at serial CPIS scores after the initiation of therapy. As I mentioned, it looks like it is a good parameter.

What is the CPIS score? The CPIS score is what you do as a clinician when you start an antibiotic. You look for a clinical response. You look that the white count goes down, the temperature goes down, that the oxygenation improves, that the sputum becomes less and that you can't culture the organism or see the organism in Gram stain. The CPIS score is kind of a collection of things that we would do in a clinical management of a patient, but it hasn't been really shown--at the conference--the ATS put on a consensus conference about VAP. The whole two days was on ventilator-associated pneumonia, and there was a lot of controversy.

But I think it has to start--for a clinical trial, we have to really be sure the person has pneumonia and it should start with microbiology. I would say I would prefer to have quantitative bacteriology performed in one of the methods that can quantitate the organism. Then there are some other criteria that you would use.

DR. GILBERT: So the consensus conference

is going to be published, I assume. I just want to be clear; the statements you just made, were those a consensus of the conference or your personal opinion about the role of quantitative microbiology?

DR. CRAVEN: I haven't seen the final productions. Actually, the consensus conference that I chaired was really on management, looking at antibiotic therapy. A lot of the concepts that I kind of went over briefly today were the concepts that were emerging from the experts who were talking about management.

But the CPIS score has very, very limited use. Personally, I think it is going to be valuable, but I think the data are still very slim on that. I think there was a consensus that, for clinical trials and for diagnosis of pneumonia, that we need quantitative techniques and the quantitative techniques are preferable to clinical techniques because of the increased specificity.

But this is going to be quite a change because there are very few--the numbers of centers that are doing quantitative bacteriology in the United States are actually quite few.

DR. GILBERT: We set it up at our center

some seven or eight years ago and it has quickly become the standard of care. Everybody is very comfortable with it. But the most exciting thing you said, just for emphasis, is that the blind protected-specimen-brush results can be as valuable as the directed bronchoscopic collection because that means that the resident can do it or even the critical-care nurse can do it or the emergency-room nurse can do it. So you get around a lot of the problems of waiting too long to do it. You can get the specimen before the first dose of antibiotic is given.

DR. CRAVEN: If you don't want to do BAL, there is very nice work that has come out of Barcelona. They have two or three papers out where they take the regular endotracheal aspirate and do quantitative estimates on that. It is a higher cutoff. It is 105. But that correlates very well. They looked at patients that had bronchoscopy with BAL and then they looked at quantitative endotracheal aspirates. The microbiology is virtually identical.

Some people find that, with the endotracheal aspirates, it is harder to work with sputum because the sputum is very tenacious and

trying to break it up for quantitative techniques--so it would probably be easier for a laboratory to use BAL. But, even respiratory therapists could do a BAL, a blind BAL. And brush is easy, too.

DR. DERESINSKI: But if you have a quantitative threshold for diagnosis, then you would probably answer another question because you will probably will be excluding patients whose pneumonia develop while they are on antibiotic therapy because those thresholds don't hold for patients on antibiotics; is that correct?

DR. CRAVEN: It is a complicated issue. If the person has had prior antibiotics, personally, although there is data suggesting this is not true, I think that the antibiotics have a profound effect on the quantitative bacteriology. I can look at Gram stains and start antibiotics and see that, within hours, those organisms have disappeared.

So I think that concurrent antibiotics or antibiotics within a certain period of time, 24 or 48 hours, should be obviously some kind of cutoff. But, if a person develops pneumonia on antibiotics, many times, these people have a resistant--most

people can have a superinfection with a multidrug-resistant organism.

I think that the points that were raised by Sary and Richard are, obviously, very important issues. These are extremely difficult studies to do and to recruit and enroll, get informed consent. The issues, I think, that were outlined are formidable.

DR. SCHELD: I just would like to add my endorsement to the quantitative culture issue. This is not just based on the review of the literature but it is also, like David, based on personal experience which is now in our hospital. We just recently rewrote our criteria for both diagnosis as well as management of ventilator-associated pneumonia.

It is very clear, it is just VAP that we addressed, but we used the CPIS score as well as quantitative microbiology and, at Day 3, you reassess where you are. The same as Singh. If you are less than 6, then you stop therapy. Again, it is not a randomized trial but the amount of antibiotics that have been used in our ICU has dropped. The resistance pattern in some of our nonfermented Gram-negatives has dropped and I think

those are outcomes that we need to track as well.

DR. CRAVEN: Just one comment on that. I think you have to be careful extrapolating the Singh data to patients in an ICU with pneumonia because what they did was select out a very low--a population that had a very low probability of pneumonia. When you have a CPIS score less than 6, do those people really have pneumonia?

DR. SCHELD: I don't think they need to be on therapy at all.

DR. CRAVEN: That's right. So the question comes up, do you need ciprofloxacin or do you need a placebo? I think that is obviously a question that comes up. So I think we have to be careful about extrapolating the Singh data to patients with pneumonia because I personally think three days, if a patient has nosocomial pneumonia, particularly due to Pseudomonas or MRSA or Acinetobacter, three days is not going to do it.

If you just look at the Dennesen data looking at time, you need time. What the time is, I think, is open to question and hopefully there is a multicenter French study looking at short-course versus long-course therapy, a randomized study. That will help, will give us the types of

information we want.

But I think your point about doing a serial CPIS score is important and when these other data are published, I think this may become an important standard for monitoring response and that it will be very helpful.

DR. GESSER: I just want to make a comment about the CPIS score relative to the clinical criteria that are usually--that have been used to enroll patients in the clinical trials. They are pretty close. Based on the criteria it takes to get into a trial, you would need a score of 5 or 6. You would get a score of 5 or 6.

So they are pretty close. As you point out, I think the importance of the Singh data is to decide, just for that patient, who really you have significant doubts about, or who purely just have an infiltrate without a lot of symptomatology who you are debating whether to treat or not.

I think there is value from the study in that although it is only about 30 to 40 patients in each arm. But, clearly, for the types of patients that have been enrolled in these clinical trials, they basically are Singh-6-type patients, just based on an inclusion criteria that is usually

required.

DR. EDWARDS: John?

DR. POWERS: I guess the question would then come up, as far as clinical trials go--it doesn't seem like CPIS is a good way to diagnose pneumonia, in particular, but could it be used as an inclusion/exclusion criteria to more likely select patients who have hospital-acquired pneumonia?

DR. GESSER: I think there is value in that. I think one concern, in terms of enrollment, certainly for VAP patients or ICU patients, it requires a blood-gas. I guess, for nursing-home patients, or for patients who are non-ICU, how standard is that? I suspect maybe we could incorporate an oxygenation criteria that is less invasive for those types of patients.

DR. POWERS: I guess the other question I would have is are we ready to accept that data. I mean, this Pugin trial from '89 had 28 patients in it. The Singh trial is actually not that large either. Is this something that we feel is at the point that we are ready to use it?

DR. GESSER: The nice thing about actually--I guess it was Pugin who was the original

author. Actually, it was originally used as a validation for invasive cultures, 6, to measure the predictive value.

DR. POWERS: Right. It is almost circular reasoning. They compared CPIS to this bacterial index, but how does that actually relate to who has pneumonia or not. But that is a separate question, again, of using it for diagnosis versus using it as an inclusion/exclusion criteria.

DR. GESSER: The thing I find reassuring using it as an inclusion/exclusion is it probably tightens up a little bit of the criteria that exist already in the guidelines, particular for VAP patients. It doesn't look as if it would negatively impact on enrollment and participation in study centers, that kind of thing with the one exclusion of blood-gas in non-ICU-type patients which I would ask my IDSA colleagues to--

DR. SCHELD: Pulse-ox.

DR. GESSER: I think that is a reasonable--

DR. GILBERT: I am still a little nervous here. I am not sure what you are asking, John, but you are going to overtreat a half to two-thirds of the patients if you don't have the microbiologic.

If you are talking about initial screening, then the CPIS probably is fine.

DR. POWERS: That is why I was mentioning it. I guess the idea for these folks is you can screen loads of patients and then these people end up being microbiologically unevaluable. Does the CPIS score help you select out patients who would then get randomized into the trial who are more likely to have a microbiologic diagnosis. That would then be helpful

DR. GILBERT: In order to answer that, you would have to do a trial where you correlated the CPIS score with the quantitative microbiologic and we don't have that.

DR. POWERS: So I am asking whether that is ready for prime-time at this point or not.

DR. GESSER: The concern I have over the quantitative cultures--I think they improve the specificity. I am not sure they are the gold standards and they are fully sensitive. The problem is what do you compare them--what is the gold standard, what do you compare them to.

I guess I get back to how are patients being managed. I still think the clinical criteria are the prime--at least for the initial therapy,

clinical criteria are really the mainstay of making the initial decisions on therapy. The downside of cultures, in general, is that that information is not available for a few days.

Certainly, people have looked at initial Gram stain, but I think that requires even more expertise, looking at 5 percent of the infected inflammatory cells. Actually, the French study, the Fagon study, that showed an outcome, used that as the criteria to decide whether patients needed initial antibiotics or not.

So that is interesting but I really think to broadly apply those results is problematic. I am not sure I am convinced that the mortality difference that was shown there really has anything to do with bronchoscopy or other diagnoses.

Actually, I read that paper quite carefully because it is the only study that shows an outcome difference, the sensitivity-specificity issues, as you point out. One issue that really struck me is in that study, there were twenty-five patients judged to have received inappropriate initial therapy. Twenty-four of those were in the standard-treatment group. One of them was in the invasive group.

Now, you could say that is obvious because you are more likely to get a pathogen from the tracheal culture in those patients. But the pathogens they got, ten MRSAs, eight resistant Pseudomonads, I believe it was six resistant Acinetobacters and two resistant enterics. So there were clearly significant pathogens in that setting.

The other thing is the mortality difference in that invasive study was all within the first four days, again suggesting a concern about inappropriate therapy. The office postulated because patients didn't get antibiotics during that early period, they were more likely to pick up other things like line infections and that sort of thing.

The data seem to support that, but I am not sure that mortality was really attributable to that. I would like to know where the mortality was attributable in that study. The other issue, too, is even if they did have line infections, the patients in the standard clinical arm were receiving basically the ATS guidelines, pretty broad-spectrum drugs.

So I think, as you point out, the

reproducibility of that study is really in question and, again, there was a significant proportion of the inappropriately treated patients in the standard arm. I think the mortality wasn't looked at as a variable. Actually, the mortality was greater in patients who were inappropriately treated. It was 33 percent versus 20 percent overall, 20-odd percent, in that group.

So I think it is an important factor that may cloud the enthusiasm we have in terms of an outcome from those types of studies.

DR. CRAVEN: Just two points on what you just made. I think that what the clinical suspicion of pneumonia--one of the criticisms for the study is what was really the clinical suspicion of pneumonia that put them in. I think some of us feel that maybe those criteria were not tight enough and that we really should try to reduce that.

The second thing is delaying therapy is a bit risky and I think, at least among current concepts, delaying therapy unless you are absolutely certain the person doesn't have pneumonia, I think is problematic and can lead to poor outcomes.

DR. GESSER: One last point on that study. The clinical specificity was in question. As I pointed out in my talk, the cardinal three signs, fever, leukocytosis and purulence, to get the clinical criteria required for that study was one of those three signs. There are numerous studies. I think it is well substantiated that the more of those signs you have, the more specific the diagnosis is going to be.

So if those patients were dying, again, you ask the question is attributable mortality. So I think that is another good point.

DR. EDWARDS: George?

DR. TALBOT: I am not sure that we are ready to get to a discussion of delta 2 yet, but I do want to articulate what I see as the relationship between this discussion of sensitivity and specificity and then what we will get to in terms of what delta 2 should be.

Sensitivity is certainly desirable in terms of maximizing enrollment but, in the context of a noninferiority trial design, specificity is really crucial because, in a noninferiority trial design, to the extent that you don't have specificity, and you therefore dilute your study

population with lots of patients who don't have the disease in question, you are increasing your chance of reaching a conclusion of noninferiority.

But the reason you reach that conclusion, potentially, is that, for example, only half your patients have the disease in question. So it really is very, very critical to use validated criteria for diagnosis of VAP or HAP and to separate what might be a clinical goal of not missing a patient who has VAP or HAP--in other words, delaying treatment--from the goal in a clinical trial, I think, which to make sure that that patient really does have that disease because, if you don't, your conclusion of noninferiority may be tremendously flawed.

DR. GILBERT: I don't know if I agree or disagree, Richard, but if you go back to Shastray's original data, it is very convincing that these quantitative cultures are the gold standard. People that were not on antibiotics did protected-specimen-brush cultures and, Don, correct me if I am wrong here, and then immediately, post mortem--we could never do this study in the United States--he opened their chest and cultured the lung.

That is where these criteria come from. That is about as gold standard as you can get.

DR. GESSER: Then the question is what is the reproducibility of that result and then you look at the literature, similar types and maybe not as well-designed studies, you see variable rates of the sensitivity and specificity.

So I think it is a problematic--conceptually, I can see it as a problematic area. It is not as clean-cut as urine. I think there is only one--we would like to think of it that way. The bladder is normally sterile. There is flushing. We don't have the benefit of that. I think as soon as the endotracheal tube is in, there are bacteria being showered in the airway.

I think the question is how specific are those cutoffs.

DR. SCHELD: They are not very specific.

DR. GESSER: I think there is clearly value to it. What I am concerned about is it will be extremely difficult to do a clinical trial that is driven by quantitative, for all the logistic issues. I think it is important to get that information because it builds on the body of

knowledge that exists, but I look at everything as what is the tradeoff.

If you drive the study in that way and you just can't get it done, how do you deal with that? Is it truly better? I think treatment and diagnostic guidelines would go a long way to get us there. If it becomes a standard that people are applying routinely, then that is a different story, I think. But it is not the standard. I think the result--maybe things have changed.

I will confess the second study was a linezolid study, Study B. Basically--I am not sure of the details. They are not all available through the Freedom of Information, but 11 percent is not a great yield in terms of the treated population. I would be concerned if you set out to do something like that.

Again, I don't imagine the study is going to get smaller after we are done talking about this so I suspect we are still dealing with something on the order of 90 sites and these sites are basically throughout the world.

So I have a concern with the quantitative issue as the primary population for study although I do think it is important to get that information.

DR. CRAVEN: I would sort of disagree. I think if you are going to do a clinical trial, I think you have to be really sure that the person has pneumonia. Clinical criteria are very vague. I think, if you look, there have been a hundred studies comparing quantitative techniques to clinical diagnosis. They all say the same thing, the specificity is much better using quantitative techniques.

In an intubated patient that has bacteria in the trachea that is colonized and that may have tracheal bronchitis, et cetera, there are a lot of variables. So I think we have to start somewhere. It is not perfect, but we don't have an answer. We really don't have a gold standard so we sort of have to define a gold standard that we will start with.

To me, for a clinical trial, I think you have to start with the microbiology and that would be, I think, an important delta to see eradication. Now, eradication is also going go be a problem because certain pathogens are not easily eradicated, even with good antibiotic therapy. Particularly Pseudomonas and MRSA tend to stay around for a while. Then you have to decide what

is the definition of eradication; Day 3, 48 hours after therapy ends? A lot of these organisms are suppressed, but they are there again or they are colonizing the oropharynx and they will go back in and cause tracheal colonization.

But I still think eradication is a parameter that we have to study for delta 2. I think basically microbial eradication is still a criteria although we have to be able to interpret it and understand what it means and what its limitations are. I think you also need clinical endpoints of which there is a variety of clinical endpoints which are combined in the CPIS score and there may be some other endpoints that can look.

The other thing that would be very interesting for a clinical trial, for a comparison trial, is to look at the response to therapy between the two groups because the response to therapy in terms of oxygenation return, looking at the Dennesen study as a profile or a model, might be a very nice way to compare studies as far as the ability--the rate at which an organism is eliminated, the response time for all the inflammatory markers because this is basically the story of a war between bugs, the number and the

virulence of the bugs, that are in that lower airway and the host response, the inflammatory cells, the humoral responses, the cytokines and all these things that are mediating.

So I think that clinical outcome parameters that measure those things, and looking at the changes between the two group, looking almost like a Kaplan-Meier, comparing the two groups, may provide very important data because mortality has its problems because mortality--the underlying disease, you have an attributable mortality of 30 percent or less. So, if you are using mortality as your endpoint, you really have to power up your study because a lot of studies, there aren't a lot differences in mortality, particularly as you enroll patients with more severe underlying disease.

So you have to look, I think, at a variety of parameters. I think if we did a study like this, there would be a lot to be learned by analyzing and thinking about the data in a different way than we had with the trials that you discussed which I don't even know how to interpret. I mean, I don't know what it means. I am completely lost at the outcome in those studies

because there are so many things that I think are really not addressed.

I think a trial is available, but it is difficult and I think it will take a lot of discussion and much more than we have probably this afternoon.

DR. EDWARDS: John?

DR. BRADLEY: In validating these clinical scores and correlating microbiology, I would like to make a pitch for validating these scores in pediatrics all the way down to the neonatal intensive-care unit where nosocomial ventilator-associated pneumonia is a huge problem.

The number of studies we have for community-acquired pneumonia is vast. The numbers for ventilator-associated pneumonia is almost nonexistent. With respect to the Pediatric Rule incentives, I wonder if you can get an extra six months exclusivity for each indication that you might treat.

The other thing that is unique about ventilator-associated pneumonia, at least in pediatrics, is that it is the interface of critical-care, pulmonary and ID. Each organism is moving forward with initiatives, I think, to study

this. We all have the same goal in mind and I think integrating the three disciplines is very important.

In terms of funding, since there are so many unknowns in this as there were with acute exacerbation of chronic bronchitis, maybe forming funding through the NIH may be another format to standardize things.

DR. EDWARDS: Mike, let me ask you and then Roger.

DR. SCHELD: I think a lot of us are saying very similar things here in terms of how the trials should be done. One of the things I was impressed by in the Dennesen paper is that I think it helps us define appropriate treatment durations which are all over the place and usually made up either of five or ten, because we have five fingers, or seven or fourteen because they are days of the week and they have no rationale whatsoever.

The other thing is, in the Dennesen, just as you said, Don, the Pseudomonas always persisted and so did MRSA. DR. GESSER: And enterics, as well.

DR. SCHELD: What we see clinically is in the surgical intensive-care unit, the house staff

chase these cultures continuously and they keep the patient on antibiotics for weeks or months. You are off for two days. You are back on imipenem. It is a nightmare, clinically.

I would like to know how many of the people in this room use any of the regimens that were shown in the slide in the recent clinical trials for the treatment of hospital-acquired pneumonia? The answer for me is zero. They haven't told me much and I am not going to change what I do. So we need better trials, John.

DR. TALBOT: Just to ask; does that speak for not using a microbiologic endpoint here? In other words, use clinical criteria as inclusion-exclusion to increase, if you will, your pretest probability of disease, confirm the diagnosis microbiologically, treat but use clinically relevant outcome criteria such as resolution as infiltrate, improvement in oxygenation but not look at whether the bugs go away.

DR. SCHELD: I don't know how hard it would be to do, but I see Don shaking his head because I know what he would say, is he wants quantitative microbiology--

DR. GESSER: He said no to resolution of infiltrate, I think.

DR. CRAVEN: No. Resolution of infiltrate, I think, is not a good parameter.

DR. SCHELD: No; that is not a good parameter.

DR. CRAVEN: But, for Pseudomonas and MRSA, you look at quantitative decreases because they are going to be there colonizing. But the colonization, the numbers of organisms colonizing are, actually, very, very small. The trachea is colonized with an intubated patient. There is chronic colonization, so eradication may or may not be a parameter.

I think it is a parameter I think we need to look at, but if you have Pseudomonas or MRSA, we would probably want to look at log decreases, like in the Dennesen study, they still had colonization of some of those pathogens and it may be important. The persistent colonization at a certain level.

DR. TALBOT: I think that makes good sense. I remember an HAP study I was involved in, one of the outcome criteria that actually came from Jean Yves Fagon, his work, was satisfactory reduction which wasn't actually a satisfactory

outcome parameter for some of our colleagues in the room.

But I think that makes more sense. As long as you don't require eradication as dichotomous yes/no variable, then that makes sense, if you can define the satisfactory reduction by a certain number of logs or to a certain absolute level.

DR. GESSER: My read on the literature on eradication is you can get rid of Strep pneumo, you can get rid of Hemophilus and everything else hangs around. There really are no data consistently to show log drop, although intuitively, you suspect it is so because you have criteria to get in.

So I think that is information that is interesting, but I am not sure we would know how to deal with that in a dichotomous way. Even substantial drop or satisfactory drop, I am not sure which term we would use there, but--

DR. TALBOT: So are you saying you would or you wouldn't--

DR. GESSER: I think it is information worth getting. I think there is a certain amount of risk, especially in a patient who is off antibiotics, has stopped antibiotics, has had a

clinical response. I am just not sure what--has that patient failed because they have only dropped a log? I don't know.

DR. TALBOT: That is really what I was asking as to whether you use just clinical criteria without regard to bacteriologic and Don is saying, well, you need to use bacteriologic. But, clearly, there are flaws to bacteriologic in terms of--just persistence growth or not can be misleading at best and irrelevant at worst. So you need to find a balance.

DR. GESSER: Do people consider stopping--I think there are two separate issues. One is to define the population to study. I am hearing that microbiology is good for that. But don't people feel that, in terms of an objective criteria for success, there is no further need for antibiotics to treat whatever it was that caused you to treat it in the first place.

DR. TALBOT: Right. But that is not necessarily the same as no bugs left.

DR. GESSER: I think they are two different things. Both are interesting questions but the pertinent treatment question, really, is the fact that investigator had made a decision not

to treat any further.

DR. GILBERT: The doctor at the bedside observes decreasing purulence in the tracheobronchial secretions, a fall in the white count, a fall in the temperature to normal and improved oxygenation and you quit.

DR. CRAVEN: Just one other variable to throw into the foray. The endotracheal tube, when you put it in, become colonized very rapidly and the bacteria get enmeshed in biofilm. So one of the variables is why you may not be able to eradicate is that you have got biofilm formation that is enmeshed with bacteria and, basically, the biofilm, when you put a catheter in or put a bronchoscope in, you break off pieces of the biofilm.

That gets embolized into the alveolar spaces. With the biofilm, the polys can't destroy it. Antibiotic and complement can't actually take a hold and destroy the bacteria so that some people feel that this biofilm phenomenon is very important in the pathogenesis of pneumonia.

I actually had a slide of the biofilm coming out that I thought was interesting. But there is work being done now looking at trying to

reduce biofilm formation on the endotracheal tube which may also be important for clinical studies in the future.

DR. ECHOLS: I haven't done a nosocomial pneumonia study in a while, although I have had some experience. It seems that, and I think some of the data that Richard presented was that we might end up with an evaluable population after you have screened for clinical but confirmed by quantitative microbiology. You end up with an evaluable population, assuming everything else goes in an unconfounded way, that is less than 50 percent of the population you are enrolling.

What do our statisticians have to say and what is the regulatory perspective on a study where the evaluable population is really a subset of the patients that are being enrolled?

DR. BRITTAIN: As long as we are talking about baseline characteristics, like the microbiologic assessment at baseline, I don't think any of us would be concerned about the patient population being dropped due to baseline characteristics. So it is more the exclusion for things that happen after baseline that are worrisome to statisticians.

DR. ECHOLS: In the intent-to-treat, if you have got a heterogenous population, your primary endpoint, you are only looking at, say, 40 percent. The likelihood of having a somewhat different result if you look at the intent-to-treat population is going to be, I would think, greater than if the populations were more closely matched numerically.

DR. BRITTAIN: Again, I think the intent-to-treat population you would be interested in in this case would be the micro intent-to-treat. Is that what--

DR. ECHOLS: I am thinking, intent-to-treat is everybody that is enrolled in the study.

DR. POWERS: But just to put it into perspective, that is what we have to deal with right now. When Richard showed those last two trials for hospital-acquired pneumonia, what we are seeing is 50 percent of the people that go into the trial--who is evaluable at the end?

DR. ECHOLS: Were you comfortable with that or uncomfortable with that?

DR. POWERS: When you read some of these ICH guidelines, it says that if you have less than

70 percent evaluable, you have got to think about what is going on there. The problem is can we come up with something to improve on that because that is what we are seeing.

If you go through the last couple of drugs that we have looked at, even back to, say, the early '90's, for hospital-acquired pneumonia, that is the kind of evaluability rates you see.

DR. ECHOLS: I am just concerned that--again, we do studies that are global. The FDA is certainly in a leadership role, but if ICH Guidelines say you have a failed study, if your evaluable population is less than 70 percent--

DR. POWERS: I don't think it puts it that strongly. It just says that you need to think about what is going on in that trial if you see that kind of nonevaluable rates.

DR. EDWARDS: I am going to need to make a logistical interruption here. I have gotten the secret sign from the IDSA that their time for departure is coming very soon. Actually, both Dave and Mike have to be out of the room at a quarter of 4:00.

So, John, I need to get your guidance here. One of the things that I was hoping to do is

to be able to try to put together some sort of summary of the meeting but to still have a few moments for discussion of the summary because I think there are some important points that may come out of the summary that have to do with where we go from here.

If we are going to do that, I might have to sort of start that about now. But, otherwise, we could just plan to do that later and continue this discussion. I would like to have your thoughts.

DR. POWERS: I think we can go ahead with the summary. I guess what I am not hearing out of this is what I felt we heard in the earlier discussions today about reaching some kind of--I hate to use the word "consensus" but I guess that is what we are getting to.

And I sort of want to ask this of the PhRMA folks. It sounds like there is, from the IDSA side, kind of an agreement on using quantitative microbiology. But the question that then would come up to us is if it is hard to do it for meningitis, why is it any easier to do it for this and does it impose too onerous a burden on you guys to do these trials.

DR. GESSER: There was a recent approval on this indication. I am not privy to those data. I think it will be very challenging to do quantitative and get a population and get a delta around that. What experience we have is, again, it is not likely we are going to be able to do these trials with less than eighty or ninety sites, or certainly no less then seventy, I would think.

DR. POWERS: I think there are two separate questions, though. One is using quantitative microbiology as a diagnostic criteria. The second thing, which would be the delta issue, is using this decrease in log CFUs as an outcome. There are two separate questions.

DR. GESSER: I think that second is an exploratory analysis and I think I agree it could aid to the specificity of the diagnosis going in and I agree that it is problematic. I am concerned that it would be universally applied in a consistent way for the same issues that we mentioned for meningitis.

Also keep in mind, these are even bigger studies in terms of the centers in controlling that sort of information. That is why I am concerned that something like that would drive the primary

population.

To be honest with you, I would prefer, in terms of the feasibility of getting it done, is if we could agree to tighten the clinical perhaps along the lines of the CPI score and evaluate that I think is a step in right direction. I think the Dennesen information is interesting. It is correlated with quantitative information on the fact that oxygenation and acute response generally occurs in the six to nine-day time frame.

I think those are interesting supportive pieces of information that would lead one to believe the antibiotics are working on something that involved bacteria. So I think that is an important addition.

I think it would be really difficult to do the quantitative in such a broad way. Again, I don't know what the recent experience is with Levaquin. They recently filed--they had 43 percent, I believe, overall patients who were micro evaluable, so I suspect they had a higher VAT population than some of the other studies.

But I don't know those data. I don't know whether they did quantitative. I don't know whether you can talk about that. I would be

curious. I suspect their experience was similar to the experience of the linezolid group ran into a few years back.

I am concerned, in terms of the feasibility of getting it done and the quality in a way that would be broadly applicable.

DR. GILBERT: John, I think you ought to ask the clinicians the same question because, even though there was a recent approval for a fluoroquinolone for nosocomial pneumonia, I think most of the academicians are saying, where did this come from? All we are getting is generalized promotional material, no hard data. Unless there is microbiologic data there, I don't think that we are going to believe the result.

DR. POWERS: Again, let me ask that question the same way. Micro data for diagnosis? Micro data for outcome? Or both?

DR. GILBERT: Mainly for diagnosis because that is where the garbage-in starts is with diagnosis.

DR. DERESINSKI: I am still concerned, though, that using quantitative cultures with current thresholds for diagnosis is going to exclude a huge number of patients. A one-day

prevalence survey some years ago showed that 62 percent of patients in ICUs in the U.S. were receiving antibiotics on that one day.

So you have immediately eliminated 62 percent of the patients in the ICU and about 10 percent of the patients, 8.2 percent actually, had nosocomial pneumonia in those ICUs.

DR. GILBERT: Jack is getting very nervous. The Spanish data--I think it is the Spanish data--shows that if the patient has a bump in their white count, new pulmonary infiltrate and then the new microbiologic data at the time of that clinical appearance correlates with disease, we can still use it.

DR. EDWARDS: Thank you for the last comment, Dave.

John, I really have mixed emotions about this because this discussion is just getting going here.

DR. POWERS: I don't think we are going to answer all the questions about hospital-acquired pneumonia today.

DR. EDWARDS: I don't think so either.

DR. POWERS: So I think stopping at this point is probably legitimate.

Summary of Meeting

DR. EDWARDS: I am now going to have to really try to abbreviate a summary, so forgive me for that. I really do want to have just a couple of minutes for discussion.

It will be impossible for me to not reiterate why we are here which is the circumstance that, at this time, where infectious diseases are still the third most common cause of death in the United States. We have widespread emergence of resistant organisms. We have new and reemerging pathogens and we also have bioterrorisim.

The pipeline for new antibiotics has come down to a trickle, both in terms of the numbers approved and the numbers being submitted for approval. So, from an IDSA perspective, the issue is critical and would be viewed as not only acutely critical but also is going to be a chronic problem.

I think that we are all very appreciative of being able to have this forum to address what needs to be brought into clear focus as an extremely important problem that has solutions. This is one that would could solve if we are creative enough.

Yesterday, we explored, without developing

a formal consensus, without developing a consensus method. We developed some general agreement and I am going to interpret what I heard and we might need to readjust that interpretation somewhat.

But what I heard from PhRMA is that clarity related to analysis standards, labeling issues and priorities was a highly desirable entity within the FDA. Whatever decree of clarity could be developed would be an incentive, of itself, to PhRMA, not only clarity in analysis evaluation but also in labeling issues.

I heard that there was a strong feeling that a list of resistant organisms would be contributory to that clarity. The mechanism for the derivation of such a list would be something that would need to be developed because it really isn't the responsibility of the FDA to do that and would need to be derived from a variety of sources.

Comments were made--some of the interpretation I am going to give you has come not only from the discussion within the meeting but also outside of the meeting. There were comments made about the desirability of completion of the Draft Guidance Document, both the primary document and the one that is being developed regarding

resistance.

Those comments were about completion of those documents made within the context of understanding how difficult it is to come to a consensus, not only, I'm sure, internally but we, at least, in IDSA, have difficulty coming to consensus on treatment guidelines so the complexities are clearly recognized but the notion that some form of completed document that might be, then, considered a working document, available by some mechanism for continued development and adjustment would be a very constructive idea as far as the guidances.

Earlier, Mark asked me whether there was any discussion about whether the primary antimicrobial guidance or the resistance document should be prioritized, which one would be most desirable go to a more formal development stage. We haven't discussed that so I am going to have to leave that hanging at the moment.

We continue to explore the use of the PK/PD data to facilitate analysis of available clinical data and possibly expedite final evaluation and approval. We did not come to any crystal-clear guidelines there but definitely

explored the entity, and we are going to come back to that in a moment.

We have come to the notion that the delta will not be fixed and will be individualized for individual studies. We also discussed extensively surrogate markers and constantly brought up the issue that the term "surrogate" may be the wrong term for these other markers and discussed how they might help us, again, in reducing sample size in facilitating development.

With regard to developing incentives beyond those that already exist, the comment was made that most companies are using all the currently available incentives. However, there has been a bit of an amendment during the discussions that it is possible that the companies might even be able to leverage the existing incentives even further.

The notion was put forth that the existing incentives are not fully adequate for incentivizing. So there is a critical need for the development of incentives not currently available. We discussed that, perhaps, the IDSA should take the lead in increasing the awareness of the public and political leaders regarding the severity of

this problem as it exists now and is likely to exist and discuss the issue of a IOM study which would be focused on the unmet need and that this study should take into account the circumstances which have led to the problem.

I am going to take some liberties here and say that the problem exists because we have a society that is evolving into a demographic shift to an older population so that, while we still have acute, rapidly lethal infectious diseases, we also have a competing need for the development of drugs for chronic illness.

So we are in a very interesting and unique situation in terms of the evolution of needs here. I think that we all fully understand that there is a great deal of competition for the development of antimicrobials that is coming from the need to develop drugs for chronic infections and also the competition that exists within industry for the development of those drugs that would be applicable to chronic diseases.

I think there is no question at all that we understand that our system is based on competition. In this area, again I am interpreting a bit here, I think I can comfortably say that the

IDSA is willing to explore internally whatever mechanisms we might have to bring the severity of the problem into as clear a focus as possible. Whether that is the organization of a national antimicrobial use committee similar to NVAC, whether it is involving other disciplines similar to ours, the issue is we need to discover what the severity of the problem is and then bring it into clear focus if it is very severe. However, we really think we know the answer to that question right now.

With regard to the individual issues, entities, rather, that we have discussed today, I am going to be very brief and say that we seem to have come to a balance situation in the trial design for antimicrobial agents for acute meningitis. I won't go into the details right now, but with strategies taken into consideration, we discussed trials of approximately 300 patients and came to the notion that there are some companies that might be attracted to a trial of that size, others not.

The incentive for pediatric exclusivity was pointed out as a possible driver to encourage companies to go into that direction.

With regard to acute exacerbations of chronic bronchitis, major study-design issues still remain. A very valuable discussion ensued regarding approaching federally funded studies, specifically NIH and, again, IDSA may be able to take a lead here in exploring the mechanisms through which we might approach NIH and other agencies to develop the very much-needed studies on this public-health problem.

With regards to hospital-acquired pneumonia, I will use that term, we clearly identified the fact that this is a big subject that is going to require extensive discussion and evaluation and is almost beyond the scope of this particular meeting. But we got a start on it.

I now am concluding this extemporaneous summary and, in the remaining three minutes, want to ask the question, where do we go from here. Let me start with a subquestion there and that is do we have general agreement that this forum is of value. Maybe we should raise our hands on this one. Let's do it.

[Show of hands.]

I think we do have general agreement there. The question is how do we proceed from

here. A notion that I have been incubating through the day today is that it seems to me it would be very valuable if, in a subsequent meeting--I am making the presumption that that will happen--we try very hard to ascertain what were the tangible effects of this meeting.

Did we get an RFP from NIH? Did we finish the draft documents? Have we addressed the issues of PK/PD in any examples that might have come forward? Have we started a study on meningitis under the desirable constructs that we have discussed and assess the quality of these discussions?

How we evaluate the effectiveness of this meeting is something I don't think we are quite prepared to decide on in the next minute or two. However, Mark, in a discussion during the break, suggested the possibility of a conference phone call to further discuss the idea of how we assess the quality of this meeting.

Now I am speaking a bit personally on behalf of the IDSA and, in your remaining 30 seconds, you can help me if I am wrong, but I believe this meeting has stimulated a great deal of momentum from our perspective, from the IDSA

perspective, and I think we are ready, as soon as we can get together, to talk about some of the concrete notions which have arisen during these discussions.

So if you could comment briefly right before you go regarding what you feel would be the next direction for us, I think we would appreciate that very much. Then we will let you go.

DR. GILBERT: Mike and I thought we would both briefly comment. First of all, I was privileged to be in on the conference-call group that organized this meeting. Some of you were not, so let me point out that there was a long "to do" list, a whole bunch of problems, and the topics that were presented over the last two days were the prioritized top of the problem list.

But there are a lot more problems and I hope the IDSA's participation has been constructive and helpful. That was the intent because we feel strongly that there is a crisis, as Dr. Edwards outlined. I think the delegation to Dr. Edwards, who is doing such a great job of pulling together the work group that organized this meeting, to plot our next move, would be the salutary outcome.

DR. SCHELD: I couldn't agree more. I

feel very fortunate to be able to participate in the meeting, maybe even more fortunate that I didn't have to plan it. So I am really expressing my appreciation to the FDA and PhRMA colleagues that worked so hard in putting this meeting together.

Personally, what I plan on doing upon leaving here is sending out a message to our membership by blast e-mail that this meeting took place and then alerting them to be on the alert, to look at the website and to CID and other venues to try and see some summaries of what came out of the meeting.

I would be very enthusiastic about planning for meetings in the future and including members of our membership if we can be of any service. It is clear to me, we have several action items, Jack, and many of these are going to come through the Public Policy Committee and we need to talk pretty soon so we don't lose the momentum.

DR. EDWARDS: In respect to your needs to get out there, I really appreciate your comments and your attendance not only right now but through the whole meeting and thank you very much for organizing the IDSA for this meeting.

Before we completely break up, I want to express my gratitude to PhRMA and FDA who were principal drivers for this meeting. As someone who has to actually treat patients from time to time, I really deeply appreciate the fact that this meeting was able to go forward and I do believe that we are faced with a problem here that does have a solution. This is within our control if we can be creative enough.

So, John, with that, I would like to turn it over to you to dismiss the meeting.

DR. POWERS: I just wanted to point out that, for people that were not around the table, or who may want to look at the results of what came out of this meeting, that all of the slides that were presented in the last two days plus a transcript of everything we have said will go onto the FDA website at this site right here. I guess I should say it for the transcript. Of course, you wouldn't be able to get to the transcript if you don't know that, but it is www.fda.gov/cder-present/idsaphrma so that you will be able to find that there.

The docket number, also, to submit comments about what occurred at this meeting is

02N-0461. We will be on the lookout for those things as well.

I just wanted to thank everybody for actually coming. This was months in planning. I want to thank Dr. Goldhammer who actually sent the original invitation about this thing to try to get us all together to do this and then the months of planning that came into it.

I wanted to thank Dr. Edwards for actually agreeing to be the Chairperson for this thing. I don't know how he said yes. When he said yes, I asked him what he was smoking at the time. With those California guys, you never know.

And I wanted to thank all the PhRMA participants. I also wanted to thank all the FDA folks that helped put this together as well. Leo Chan is going to take a six-month vacation after this, I think, after all this work. [Applause.] Plus all the other support staff that have helped us out with that.

Again, thanks everyone for their participation. I think we all have our homework assignments so we can go work on this and, hopefully, we can do this again in the future.

DR. EDWARDS: We are adjourned. Thank you

all very much.

[Whereupon, at 3:50 p.m., the meeting was adjourned.]

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