

Optimizing the Use of Antimicrobial Therapy

Resistance and the Induction of Second Mutations

Dr. Bishai: Ms. Brueggemann, you mentioned the *parC* and gyrase mutations and how they can combine to make a higher minimum inhibitory concentration [MIC]. Is there any microbiologic evidence that the different fluoroquinolones have differing rates of second mutation induction? This issue has been raised in marketing presentations with the newer fluoroquinolones.

Ms. Brueggemann: Clearly, all fluoroquinolones are not created equal. There are differences in *in vitro* activity, pharmacokinetics and pharmacodynamics, etc. With respect to fluoroquinolone resistance and *S pneumoniae*, the most common pattern of resistance is a mutation in the *parC* gene, with a possible subsequent mutation in the *gyrA* gene. Double mutations result in decreased activity to the entire class of fluoroquinolones. However, isolates are being recovered that do not fit the usual pattern of resistance mutations, for example, isolates with a single mutation in the *gyrA* region and no *parC* mutation. There are reports in the literature suggesting that differences may exist among the newer fluoroquinolones with respect to the induction of resistance mutations. It is possible that this is true, but more data are necessary. The major advantage is that the newer agents have much greater activity versus the pneumococcus than the older agents.

Appropriateness of New Breakpoints

Dr. Nicolau: How does what you found in your most recent survey relate to the proposed new breakpoints for amoxicillin and the cephalosporins?

Ms. Brueggemann: The National Committee for Clinical Laboratory Standards [NCCLS] breakpoint changes for the β -lactams are entirely appropriate with respect to predicting outcome in patients with lower respiratory tract infections due to the pneumococcus. However, without a corresponding change to the penicillin breakpoints, there exists a fundamental disconnect among β -lactam antimicrobial interpretive criteria. For example, as it stands now, using the new amoxicillin breakpoints of ≤ 2 , 4, and ≥ 8 $\mu\text{g/mL}$ [susceptible, intermediate, and resistant, respectively], an organism could be categorized as amoxicillin susceptible, but penicillin resistant. Given the mechanism of β -lactam resistance—altered penicillin-binding proteins—this does not make sense. If, however, the penicillin breakpoints are also shifted to the recommended ≤ 1 , 2, ≥ 4 $\mu\text{g/mL}$ [susceptible, intermediate, and resistant, respectively], then concordance among the β -lactam agents is achieved. Importantly, a shift in the penicillin breakpoints to ≤ 1 , 2, ≥ 4 $\mu\text{g/mL}$ is only appropriate for pneumococci causing lower respiratory tract infections, not for pneumococci causing meningitis. Experience indi-

cates that the current penicillin breakpoints [≤ 0.06 , 0.12 to 1 , ≥ 2 $\mu\text{g/mL}$] are entirely relevant to predicting outcome in patients with pneumococcal meningitis. Therefore, it appears that we need infection-specific interpretive criteria for the β -lactams versus *pneumoniae*.

Dr. Nicolau: Given that the Centers for Disease Control and Prevention [CDC] guideline susceptibility is up to 2 and the high level is 4 or more, what is the rate of pneumococcal resistance to penicillin in the most recent surveillance study?

Ms. Brueggemann: Six percent of the *S pneumoniae* in our most recent national surveillance study had a penicillin MIC of 4 $\mu\text{g/mL}$ and would therefore be considered resistant using the proposed breakpoint of ≥ 4 $\mu\text{g/mL}$. This rate of resistance coincides with the 6% amoxicillin-resistant *S pneumoniae* in this study, defined using the new amoxicillin breakpoints. There were no *S pneumoniae* isolates in this study with a penicillin MIC > 4 $\mu\text{g/mL}$.

Dr. Steinberg: I think part of the problem lies in there having been more emphasis upon oral antibiotic agents than upon parenteral agents. If you look at the application of oral antibiotic agents in the at-risk population, particularly among children in daycare centers, you will find the fewest tested isolates, yet these are the isolates that have been the most antibiotic selected. To illustrate this point, patients who require a tympanocentesis or a sinus puncture have been recalcitrant to multiple antibiotic exposures. And it seems to me that the NCCLS has sort of driven the wagon toward the area where there is less clinical and microbiologic eradication data in assigning breakpoints for oral antibiotics for sinus and ear infections, but making decisions about these breakpoints

based on where the most data, for instance blood and cerebrospinal fluid isolates, exists. For instance,

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—William Bishai, MD, PhD

shifting the breakpoint of loracarbef up 4-fold to be the same as amoxicillin is ludicrous, considering this drug’s MIC₅₀ of 16 $\mu\text{g/mL}$ and MIC₉₀ of 128 $\mu\text{g/mL}$ on penicillin-intermediate strains; yet giving an appearance that it is similarly active.

Multiple Contributors to Guidelines and Breakpoints

Dr. Bishai: I think the stage is being set for considerable confusion in the management of respiratory tract infections. We have the NCCLS setting breakpoints, the American Thoracic Society [ATS], and the Infectious Diseases Society of America [IDSA] setting clinical practice guidelines that are incongruent. Until recently at least the breakpoint and treatment guideline producers were separate. Now, however, with the CDC treatment guidelines also giving recommendations on clinically relevant breakpoints for the pneumococcus, we have divergent recommendations on what constitutes resistance. With multiple guidelines and the experts in some disagreement, I think busy practitioners are confused and may begin to lose confidence in the process.

Dr. Steinberg: You didn’t mention that there are microbiologists who are

talking about pharmacodynamics and pharmacodynamically relevant breakpoints. In the case of the macrolides, they are basing their discussions purely on serum levels. Dr. Jacobs' article from last year [*Antimicrob Agents Chemother* 1999;43:1901-1908] estimated the activity of these agents for *Haemophilus influenzae* to be 0%. Well, that begs the question: Why then would the drugs work? The preponderance of data suggests that something about these drugs is working.

Dr. Bishai: Yes, and while you might think that animal models could help resolve this issue by sampling other tissue compartments, so far the emphasis on serum concentration has prevailed.

Consistency and the Breakpoints

Ms. Brueggemann: It is confusing to have to consider one set of interpretive criteria for one disease process and a different set of criteria for another disease process. When penicillin breakpoints were initially developed, they were intended to predict outcome in patients with pneumococcal meningitis. Since then, we have learned that these same breakpoints [≤ 0.06 , 0.12 to 1 , ≥ 2 $\mu\text{g/mL}$] are too conservative for predicting outcome in patients with pneumococcal lower respiratory tract infections. This emphasizes the importance of reevaluating existing breakpoints as more laboratory and clinical data are obtained.

Dr. Steinberg: Consider the paradox of our being encouraged to increase amoxicillin dosing in pediatrics from 40 mg/kg/day to 80 mg/kg/day at a time when the organisms have suddenly become more sensitive, with the breakpoints increased 4-fold. You should be able to use less drug if the bug is more susceptible.

Clinical Exceptions and the Epidemiologic Perspective

Dr. Bishai: Because we have CDC-recommended breakpoints for sputum isolates of *S pneumoniae* from community-acquired pneumonia [CAP] patients and different NCCLS breakpoints for blood or meningeal isolates, it's possible for a patient to have a pneumococcal blood isolate that is resistant and a sputum isolate that is susceptible when, in fact, it is the exact same isolate of the pneumococcus. Ms. Brueggemann, how do we present the paradox to the actual caregivers? Has your institution begun to address that kind of problem?

Ms. Brueggemann: Not to my knowledge. You raise an important issue. It would seem prudent to err on the side of being conservative and treat the most serious infection. If a patient has a penicillin-resistant pneumococcus in the cerebrospinal fluid, aggressive therapy is warranted, regardless of the susceptibility of isolates from other specimen sources. It would be important then for the microbiology laboratory to report the actual penicillin MIC value for each pneumococcal isolate, along with each set of interpretive criteria. The physician would then have to make a decision regarding therapy using his or her best clinical judgment.

Dr. Spiritus: Yes, but although we can talk about these issues in an abstract way, the reality is different. With the average length of stay for CAP of less than 4 days, most doctors never see an MIC unless they obtain a blood culture.

Dr. Nicolau: Everyone has seen cases such as occurs when emergency department physicians find that the organism they are treating with an oral agent is a resistant pneumococcus. And the doctor may leave the patient who has a bloodstream infec-

tion on an agent whose *in vitro* susceptibility is not the best when the patient appears to be doing well. However, the real key is to be aware of change and maintain an epidemiologic perspective.

Dr. Tanigawa: Are those clinicians really calling for advice when clinically the member is improving and the *in vitro* susceptibility is low?

Dr. Nicolau: They call the division, and we tell them to follow the patient closely. But while a change in susceptibility may not cause clinical failure in a patient in 1 day, there is a point in the development of antimicrobial resistance at which it's impossible to get enough drug into the patient to overwhelm the organism. The NCCLS is addressing these kinds of changes and asking what is being done about them. In January, the NCCLS also discussed for the first time the issue of site-specific breakpoints. That caused a tremendous amount of confusion among the experts.

Dr. Tanigawa: Would you leave the patients on the oral agent?

Dr. Nicolau: Yes, and you may get a positive blood culture back in the next day or 2 and meanwhile the patient is on oral therapy, a macrolide or quinolone, for example. When the patient is not doing very well, you may think you would reevaluate or admit him because he has a resistant bug. But you don't, you just follow him fairly closely.

Dr. Steinberg: The reality is that we are going to run into problems. Your discussion reminds me of a youngster we treated who had pneumococcal meningitis, pneumococcal bacteremia, and pneumococcal pneumonia. There were different susceptibilities among his culture sites. His pleural fluid grew out

pneumococcus with an intermediate susceptibility. His meningeal culture grew out the same MIC, but it was interpreted as resistant. We were most aggressive with that patient. In fact we did not take him off the vancomycin until we had the meningeal isolate back. It took a little bit longer than the pleural fluid isolate and its susceptibilities, but I didn't trust that the pleural fluid MICs were going to tell me everything I needed to know.

Host Susceptibility, Length of Hospitalization, and Serotypes

Dr. Steinberg: The February issue of *The American Journal of Public Health* published a study from the CDC that found a higher mortality rate among patients with pneumococcal organisms that had an MIC of 4 or greater [Feikin DR, et al. *Am J Public Health* 2000;90:223-229]. A multivariate analysis revealed a higher mortality rate at 4 days and beyond—or at least a mortality rate that was associated with the nonsusceptibility of the organism. So your point—that early mortality may just be a function of how well the patient is—is an important one. For example, if the patient is ill enough to be admitted to the intensive care unit, the mortality rate is likely to be in the range of 30% to 40%, no matter what the susceptibility of the organism is. The outcome within the first 24 to 48 hours may not be a result of the antibiotic. This has been true in the treatment of meningitis for many years. Therefore, a determination of the true antimicrobial failure may have to take into consideration the general health of the patient.

Dr. Spiritus: How many of us have seen a healthy person with no comorbid diseases who has died of pneumococcal pneumonia? That patient is hard to find. Almost all

of the patients with community-acquired pneumococcal pneumonia who die are either alcoholic, at an extreme of age, or have some underlying disease.

Dr. Nicolau: This might be an effect of the status of the host. But on the other hand, the serotype may be as important a determinant of outcome as MIC—maybe even more important. There is information that suggests this to be true. We know certain serotypes are certainly more virulent than others. Maybe we need to place more emphasis on the evaluation of new serotypes and not MICs.

Dr. Steinberg: I think that virulence does differ among serotypes. For example, in children, the 23-F serotype is a notoriously very, very bad player, when it comes to bacteremia and meningitis. Therefore, I think it's going to be extremely important to look at the differences in virulence along with non-susceptibility.

Dr. Koenig: Because we know that antibiotics probably do not affect the outcome in the first several days, has anyone examined mortality after 4 days?

Dr. Bishai: The outcome studies all generally involve hospitalized patients with differing lengths of stay and little follow up on what happens in the outpatient setting after discharge. I agree with you that outpatient outcomes are an important area where we need to look more carefully.

Dr. Nicolau: The issue of length of stay introduces some other considerations. Should we exclude from our studies cases of multiple comorbidities, which are likely to have a different length of stay? And if so, how should that be done?

Models of Quinolone-Resistance Promotion

Dr. Chaisson: Another paradox that you did not mention relates to the quinolones and to ciprofloxacin, in particular. In the late 1980s, a number of patients who were taking ciprofloxacin for Gram-negative infection developed life-threatening streptococcal infections. This drug, which had demonstrated *in vitro* activity against these Gram-positive organisms, had been approved for use in CAP, and it had been heavily marketed for CAP. The paradox was that ciprofloxacin, which should have been working against Gram-positive infection, wasn't working. Subsequently, its approval for use in CAP was withdrawn. Basically it was a bad drug for Gram-positive respiratory infections that was widely used and provided subinhibitory levels in many patients. It was a model for the promotion of resistance. This causes me to wonder about the relevance of ciprofloxacin to the emergence of quinolone resistance in Canada and whether that should be our model for the current quinolones in pneumococcal infections.

Ms. Brueggemann: The use of levofloxacin in the United States to treat respiratory infections has increased dramatically since its introduction into the US market. Unfortunately, since the activity of levofloxacin is as marginal as ciprofloxacin versus *S pneumoniae*, we may in fact be on the verge of an increase in fluoroquinolone-resistant *S pneumoniae* in the United States not unlike the recent Canadian experience.

Dr. Chaisson: Well, when you go back and look at the ciprofloxacin licensing studies, and those for pneumococci in particular, the cure rates were not good. They were 80%, whereas in every other category, and for the comparator drugs, it

was always 97%. That somehow slipped past the Food and Drug Administration [FDA].

Lack of Power in Study Groups Promotes Uncertainty

Dr. Nicolau: It is an issue of study group numbers. Until recently people didn't examine the effect on individual pathogens. Now, a research project may pursue a very well-designed prospective, randomized, blinded clinical trial, but deliver data on less than 15 isolates per treatment group. In that case, it's hard to satisfy the criteria for clinical significance.

Dr. Steinberg: Consider the bewildering paradox that if trovafloxacin had been triaged appropriately as an antibiotic, we might not have seen as much liver failure in 5 to 6 years. The only reason why we saw the development of liver failure this quickly is because the drug was being indiscriminately used.

Dr. Nicolau: The experience with another compound, grepafloxacin, helps to make some sense of exactly what you said about contemporary standards. When grepafloxacin came out, it was available in the 400-mg and the 600-mg doses. With the early studies that were done for acute exacerbations of chronic bronchitis, which judging from the package insert were completed with 400 mg, the drug's clinical and microbiologic success was in the high 70% range, not unlike ciprofloxacin. However, when the dose was increased to 600 mg for CAP, again its activity against pneumococcus was very, very different. It was impressive. Grepafloxacin's effectiveness is really dependent on the dose selected and is not dependent on the patient's renal function because of its elimination pathway.

Dr. Spiritus: If you were a business

person and considered the drivers of a lot of these drugs, you would look at the fluoroquinolones and note that 4 have been pulled off the market: That is \$200 million for 4 that are not used today, and yet people are still talking about trying to develop them.

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Experience of a Drug in the Patient Population: The True Measure of Safety

Dr. Nicolau: The reality is that none of these antibiotics belongs in a box. We put them there. It's unfortunate, but structure/activity relationships and some of the things that we have learned about drug-host interactions from a toxicodynamic standpoint are not well understood. You cannot predict success from trials with small clinical populations. You have to wait until the drug gets a large patient population. That's the true test.

Dr. Tanigawa: Well, the health plans are often criticized for their lack of speed in adding new drugs to their formularies. In the most recent years we have seen an accelerated rate of drugs being approved by the FDA. Enterprise-wide PacifiCare has pharmacy coverage models that have open formularies. We can look at a drug's experience in markets where members get access to it as soon as it is out. That allows us to look at its experience before we add it to the formulary.

Dr. Nicolau: Yes, and that brings up the issue of numbers. How many

thousands of patients are necessary to evaluate for those low-incidence adverse effects? Is 200,000 enough? Is 500,000? And although the FDA did not mandate the withdrawal of trovafloxacin, it clearly pegged it in a place where no one can use it from a medicolegal standpoint. However, it's still not clear what contributed to the drug's toxicity in the relatively small number of cases studied.

Managed Care's Formulary and Approval Process

Dr. Browne: From the perspective of managed care, you raise an interesting issue. Should we wait until we have accrued 200,000 patients with national exposure? We are struggling with that right now with the 2 new quinolones and asking: Do you wait 6 months, 1 year, or 2 years? Another development that has complicated approval from a health plan perspective is related to the fact that in the United States the time from application to approval has become so much shorter than previously. In 1989 or 1990, it took about 31 months to gain approval. I think we are now somewhere around 17 or 18 months for approval. Also, we used to be able to look at the experience with some agents in Europe and be able to say, for example, that among X-million patients in Europe there was no hepatic toxicity. And even though that information wasn't formally included in the approval processes for the FDA, at least we were able to use the information for approval by a health plan. We don't have that now.

Dr. Yoder: Some of these drugs that are authorized by the health plan get used for indications outside their labeling. The argument has been made in the case of cisapride that if had it been used appropriately, there would not have been any problems with it. And the QT prolongation with

these quinolones? There are some drug classes that are worse for QT prolongation than some of the quinolones, yet they are still being used. If you use drugs indiscriminately in high-risk patients, you are going to see these problems. We saw this practice within the health plan, but it is hard to control the physicians' prescribing patterns.

Dr. Nicolau: And this practice is true among the anti-infectives. Some of the most popular anti-infectives used for indications like sinusitis, haven't received approval for such use. That's the case with azithromycin. Although I forget the most recent IMS data, azithromycin has about 20% to 30% of the oral sinusitis tablet market. But it is a drug that does not have such an indication.

Dr. Browne: A lot of factors come into play. For example, going back to your point regarding appropriate use, I think that in 1998 there were about 1.2 million company representative "detailing" visits for trovafloxacin/alatrofloxacin alone. Sildenafil was at about 770,000 visits. In any event, trovafloxacin/alatrofloxacin was one of the most heavily detailed drugs in the United States, and that may lead not only to inappropriate use but also just a lot of use.

Dr. Bishai: Your data suggest that there may be a threshold at which drugs may not only be ineffective in the patient but also predispose to the development of resistance. Has the *in vivo* development of resistance been demonstrated in animal models?

Dr. Nicolau: Well, there have been. I think resistance is a cat-and-mouse game. You have to realize that there is a population of organisms within a patient or an animal within which there are resistant mutants. When we test for susceptibility, we are testing the predominant, if you will, organ-

ism. A liability exists when testing animals that the use of such a high inoculum necessary to present enough resistance in the subpopulation of organisms actually kills the animal due to the induction of an overwhelming sepsis. We know that the mutation rate is very, very different for different compounds and different organisms, so it has been difficult to do that. Some investigators have examined minimally effective exposures of agents like azithromycin *in vitro* and shown that it is possible to select out for resistance. They have also completed some *in vivo* work that suggests that drugs that provide less exposure for prolonged periods of time again, select out for resistance. Duplication of those data has been incredibly difficult for a variety of reasons; there is a pattern.

Dr. Steinberg: One of the key considerations is whether you are a lumpner or a splitter. Among certain guidelines there is more of a lumping mentality—specifically when differences between azithromycin and clarithromycin are discussed. This issue of concentration disposition is very important, particularly in the selection of an antibiotic. Some of the best data came out of the Dagan et al collaborative, multinational study investigating the performance of azithromycin in childhood otitis media [*Pediatr Infect Dis J* 2000;19:95-104]. The investigators found only a 68% eradication of *S pneumoniae* and only 36% eradication of *H influenzae*. When they went to look at the concentration relative to the MIC, the concentrations in the *H influenzae* component of the study were greater than the *H influenzae* MICs. They had to postulate that the drug was somewhere other than where the bug was. If you then assess the concentration in both the cell medium and cell-free compartments, you find a wide disparity for azithromycin: virtually nothing in the extracellular fluid and

everything in the PMN. This knowledge of the agents' propensities for extracellular versus intracellular concentration allows us to more effectively target different kinds of organisms. We can even assign not only desired concentrations and area under the concentration curve [AUC] to MIC ratios, but AUC/MIC ratios compartmentally. This information is not typically referred to in guidelines.

Dr. Nicolau: The point that is well taken is that when everything is incredibly susceptible, you do not have to worry about the splitters and lumpers. But now some of the slighter differences in exposure are going to have profound effects on clinical outcome. We experienced this process with the cephalosporins. Now we're starting to appreciate that macrolide resistance is growing and that maybe not all macrolides are the same. We are also starting to see that with the quinolones.

Dr. Spiritus: I do not think I have ever seen really good studies that match laboratory results with the practical reality of the fact that 30% of patients are not taking the drug at all. Are those 30% of patients in fact the reservoir for resistance? The laboratory piece is very elegant, and the breakpoints are really interesting, but then when you throw the dynamics of the patient and the physician into the mix, the situation is hard to tease apart. For example, the patient may not take his medication or tell his doctor that he has stopped taking it. Or, not doing well, he returns and, not disclosing his failure to take the medication, is prescribed another antibiotic. Then there is the finding that 12% to 15% of patients who receive an antibiotic for a respiratory tract infection are going to get a second antibiotic, and we do not know what percentage of patients took the first drug or even the second. I think that the people on the managed care side

are going to have to come together with you in the laboratory to really start to look at this.

Dr. Nicolau: We have a group who is trying to put together some guidelines for the treatment of CAP and address the question: What is the correct duration of therapy? Is it 7 to 14 days? Some people are looking for 5 days of therapy now. But in reality, how long do people really take their medication for CAP? If they are feeling better in 2, 3, or 4 days, as you said, perhaps they have stopped anyway. We do not even have good benchmarking data. Furthermore, maybe drugs that are more potent have more activity and better bioavailability or absorption; maybe they don't need to be dosed as long if the rate of kill is maximized quickly.

Dr. Bishai: Dr. Nicolau, have any of your human immunodeficiency virus [HIV] studies looked at carriage rates of susceptible and resistant pneumococci in HIV-infected patients who take chronic trimethoprim/sulfamethoxazole [TMP/SMX] or azithromycin?

Dr. Nicolau: We should have done that but we have not. We do not know if those data are available. I did a randomized, crossed-over compliance study of MAC prophylaxis and so probably should also have looked at the pneumococcal carriage rate. The patients who entered into the study were on azithromycin 1 gram a week or clarithromycin 500 mg q12. The problem is that many patients, while they are supposed to be on 500 mg q12, do not take 500 mg q12. Again, how does that actual adherence impact resistance?

Dr. Chaisson: We found that HIV patients who had high CD4 counts tend not to be colonized, but those with low CD4 counts have higher rates of colonization. People with low CD4 counts get put on TMP/SMX or

azithromycin, usually for prophylaxis. We found that TMP/SMX did not affect colonization one way or the other and did not affect resistance with pneumococci. Being on azithromycin or clarithromycin was associated with a reduction in the risk of carriage and no resistance. The numbers in the study were small; overall about 450 patients died but the rate of carriage was lower than anticipated, because of the antibiotic effect.

β -Lactam Effectiveness

Dr. Steinberg: A publication by Gleason [*Arch Intern Med* 1999; 159:2562-2572] recently noted that the mortality rate was significantly higher for ampicillin sulbactam when combined with a macrolide than it was for either the second- and third-generation cephalosporins with a macrolide or a fluoroquinolone. The units of dosing for ampicillin sulbactam are 750 and 1500 mg, whereas we seem to give cephalosporins in either 1 or 2 gram quantities. I wonder if it is the total exposure to β -lactam that is making a difference rather than the difference between ampicillin plus sulbactam and the cephalosporin.

Dr. Nicolau: The question is, can we use ampicillin in those patients over the age of 65 who are admitted with CA?. And the answer is no, because it is not an issue of *H influenzae* and *M catarrhalis* with β -lactamase production. It is an issue of pneumococcus.

Dr. Steinberg: Well, it certainly brings up again the issue of breakpoint MICs and whether they should be segregated for ampicillin away from penicillin. I think probably not, as demonstrated by the mortality data.

Dr. Chaisson: I do have a question. The patients from community hospitals with a bad track record tend to come

having been given ampicillin/sulbactam, whereas those from hospitals with a better track record are more likely to have been given cefotaxime. And so the choice of which intravenous β -lactam you use tends to be a quality marker. Now, I'm speculating, but I wonder if it is not a drug issue but a quality-of-care issue.

Dr. Steinberg: I think it does have to do with quality of care. In our institution we have put ampicillin/sulbactam on and off the formulary 3 different times. Some clinicians use Unasyn instead of ampicillin for situations where ampicillin could have readily been used. I get concerned because the dosages, in terms of β -lactam effectiveness, may not provide sufficient dosage and potency comparable to those of the parenteral cephalosporins.

Guideline Versus Empirically Based Therapy

Dr. Yoder: Although I enjoy the academic rigor that goes into the guidelines, I do not see them used very often within regular practices. For example, a lot of time the physician will say, "I treated this patient because he is an outlier; he does not quite fit the guidelines, and I chose this treatment even though it is outside the guidelines' recommendations." Or others repeat a course of a macrolide when most physicians would try something else.

Dr. Chaisson: I think that the most important thing that the guidelines could do is to get physicians to order a chest X ray and to stop treating upper respiratory infections and bronchitis with these drugs. I am hopeful that that will happen. I just think that diagnosis is very important and underemphasized.

Dr. Tanigawa: I think that the pharmaceutical companies promote the use of the quinolones in upper respi-

ratory infections; more rational detailing could actually aid us in promoting appropriate utilization.

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Dr. Yoder: They promote them with the cost-containment message: You do not have to hospitalize this patient; you can treat her as an outpatient and save a lot of money. Most of the time treatment is empiric. Believe me, I would love to see the use of doxycycline go up for empiric treatment. It would help contain our prescription drug costs and keep this benefit affordable.

Dr. Tanigawa: We are going to continue to see a lot of empirical treatment. The delay in getting the X-ray results back to either the treating or the follow-up physician can very well be 5 days. Your patient has almost completed the course of treatment before you get the study results. The hospital setting is a place where you can really impact treatment guidelines, particularly among cases of CAP.

Dr. Spiritus: Regarding the importance of a chest X ray in the diagnosis of pneumonia, it has reached the point that, at least for Medicare billing purposes, if you do not have a chest X ray you will not get paid for a diagnosis of CAP.

Drivers of Treatment Choices

Dr. Spiritus: What we are finding is that by giving patients a personal clin-

ical pathway you take the issue of the treatment to the person who really needs it, the patient. Now you can say, "You have pneumonia, this is what it is, here is how the diagnosis is made, and here are the common organisms." The patients are the ones who are going to say, "Wait a minute, do I really have pneumonia?" Approximately 20% of them are going to the Internet and looking at the guidelines. Then they say, "Why am I on this drug when it is not even mentioned here in the guidelines?"

Dr. Koenig: With the Chen data and the resistance data in Hong Kong, I am a little surprised that the IDSA didn't come down a little harder on the fluoroquinolones. Why do you think that was?

Dr. Chaisson: I think the rationale was that they did not see evidence of a problem. But given the quinolone resistance, the CDC could see it's a potential problem.

Dr. Steinberg: I thought that the IDSA would come back with a little bit more restriction. And I don't think trovafloxacin/alatrofloxacin would have gotten into nearly the trouble it did if some organizing body hadn't offered its rubber stamp saying that quinolones were fine as a first-line choice for CAP.

Dr. Nicolau: It seems that the guidelines should be proactive not reactive. We should anticipate issues of fluoroquinolone resistance. Unfortunately, the CDC guidelines did not even mention gatifloxacin and moxifloxacin, which were out 6 or 7 months before.

Dr. Chaisson: One thing that I think affects the IDSA guidelines is the history of emergence of resistance and how it never seems to follow anyone's predictions. For example, in the 1980s norfloxacin was extensively used to treat neutropenic cancer

patients at the Johns Hopkins Cancer Center. Despite this widespread exposure, the prevalence of fluoroquinolone resistance at the end of 10 years was the same as it was before.

Dr. Spiritus: Another contributing phenomenon is related to the fact that almost all of the infectious diseases specialists are hospital based and never, ever see CAP in nonhospitalized patients; and their approach to this disease is so skewed by the 20% of people that they see.

Dr. Steinberg: I think there is still an *in vivo/in vitro* discordance of another type—a gap between the time that the collected data reveal microbiologic problems, their eventual effects on clinical outcomes, and the time when it is being published. The IDSA, looking at clinical outcomes, and the CDC, with its attempt to restrict quinolones based on resistance patterns, would tend to develop 2 sets of guidelines. I think that we are both after the same thing: seeing the smoke as fire and balancing preferred clinical choices against developing resistance patterns.

Has Drug Resistance Really Altered Economics?

Dr. Bishai: If this were 1965, when we were treating pneumonia with penicillin and erythromycin, and if you adjusted the numbers for cost, do you think there would be a significant difference in the proportions of where the cost of care was going? Do you think that the emergence of drug resistance in the 1990s has really altered the economics?

Dr. Spiritus: I don't think so. I suspect that if you looked at rates of hospitalization and therefore cost on a risk-adjusted basis, or inflation, you'd probably find we are spending less money on patients hospitalized today

than we did back in the 1970s and 1980s. In 1970, everybody got hospitalized with pneumonia for 7 to 10 days. Most people who had insurance were not covered for outpatient therapy. It did not make any difference what their pneumonia was. Over the past number of years we have driven down the duration and number of hospital stays. Even though we have had resistance increase, the practice of care hasn't changed.

Dr. Chaisson: Given this scenario for this disease, one might ask what is the benefit? What are the costs? A pharmacoeconomic analysis generally takes the perspective of society or of the payer. But the decisions always seem to be made from the perspective of the pharmacy, and the Pharmacy and Therapeutics [P&T] committees and insurers cannot seem to expand their vision beyond the pharmacy budget. In some cases there is good reason for that because the pharmacy budget is compartmentalized and saving money in one area does not bring it into the pharmacy.

Dr. Spiritus: Sitting now in a hospital administrative position and looking at the whole picture, I would say to you that that is becoming less of a problem.

Dr. Chaisson: But I think, for example, that the only reason many P&T committees approve low-molecular weight heparin is because it gets patients with deep vein thrombosis [DVT] out of the hospital and therefore no longer costs the hospital pharmacy money. This decision only happens to coincide with the greater good of reducing healthcare costs. However, if people got sent home and the hospital pharmacy had to give them their low-molecular weight heparin every day, believe me only heparin would be on the formulary.

Research Criteria: A Product of Competing Interests

Dr. Spiritus: I think the real issue for everybody is that the economic data are so fuzzy that it can always be sliced and diced to look the way someone wants it to look. When you consider drug A versus drug B versus drug C, and there are 3 As, 3 Bs, and 3 Cs on the basis of pharmacoeco-

“I think there is still an in vivo/ in vitro discordance of another type—a gap between the time that the collected data reveals microbiologic problems, their eventual effects on clinical outcomes, and the time when it is being published.”

—Irving Steinberg, MD

nomics, those studies are just really hard to play with. First of all, most of them are in fact, paid for and conducted through the pharmaceutical industry. Second, nobody agrees on the front side what the parameters are.

Dr. Nicolau: It is interesting that we have many industry people who are willing to partner with managed care and provide an opportunity to affect some change. However, it is still a hard sell when you take that data back to your administrator and say, “Hey, the reality is the drug is going to be more expensive. But in this other silo we might win.” Regardless of who designs the study, if that is what it shows, it is still hard to get that buy in.

Dr. Yoder: I face the silo mentality all the time because it is very easy to quantify the increased cost of a drug on the pharmacy side. You can never show medical cost savings, and it makes my job extremely hard. It

makes any pharmacy director's job extremely hard.

One of the things I have said to the drug companies that come to me is, "All right. If you want to do this program and you want me to partner with this, I want you to be able to show me at the end that we have some kind of outcome. I want you to design a study that's publishable, has power, and can show what you're trying to tell me you can show." Eighty percent of them walk away and say, "Well, we cannot do that." And that is because they know they can't do it.

The Difficulty of Interpreting Pharmacoeconomics

Dr. Spiritus: Interpreting the pharmacoeconomic significance of a study is extremely difficult. A study reporting a difference of 1 or 2 patients and 4 or 5 patient days is a little tough to hang your hat on. If you say, "Out of 900 patients in this group only 3 people were admitted, and in another group 5 people were admitted, and in another one 7 people were admitted," one could say that the results are not statistically significant. The problem is that we are hanging our hat on each of these studies. But in the aggregate, nobody really knows. Because if we did, then we would be able to write the guideline tomorrow morning that says, "This is the drug." But we can't do it; and that is why the guideline says "A, B, or C."

Dr. Steinberg: But there are so few studies that are looking at the total cost of care. And so many of these studies are retrospective in nature and do not approach any kind of clinical significance to the practitioner. I would like to see studies carried out a little bit more prospectively and with the intent of examining the economics of care for a particular entity while the clinical comparison is ongoing.

Dr. Spiritus: The problem is that these are extremely expensive studies to do. And frankly, for most academics, it is not really the kind of hard science with which you would be going up the rank in your academic department. These studies are still relatively soft.

Dr. Browne: A comment about company sponsorship: For many of these studies, even if there are very minor differences in the study design, the companies know exactly which area to concentrate on so that their particular product turns out, predictably, to be the better product. It depends on what they wish to emphasize, and so we are very cautious about those kinds of pharmacoeconomic studies and which ones we take on. Also, they bring information to substantiate their claim that their product is the least expensive, overall. It has reached the point now that if the study has not been published in a peer-reviewed journal, through the pharmacy administration/pharmacoeconomics group of a college of pharmacy, for example, we probably are not going to include it in any of our P&T.

Dr. Steinberg: But the flip side of that is there needs to be coventuring between managed care and academic centers. I will chastise my own. At the University of Southern California, the pharmacoeconomics people did a study on respiratory syncytial virus immunoglobulin. The analysis basically showed that after 1 dose of a 5-dose schedule, it became a cost loser rather than a cost benefit. How were they going to take care of this? They took this basic analysis of 28- to 32-week premature neonates and turned it into a generational analysis and claimed the drug saved so many lives and productivity of the progeny of those premies, making the drug more cost effective on paper but of remote connection to the more realistic clini-

cal concerns in using this agent. Therefore, pharmacoeconomic analysis done purely by academia sometimes has no relationship to clinical reality. I believe such research has to be coventured.

Dr. Yoder: We have coventured in a number of projects. But I think you hit on a key point in that you have to

have control over the final product. You have to get control not only of the final product, in terms of editorial content, but also of the study design. You shouldn't retrospectively analyze your previously prospective data and change the methodology to make it look good. We just do not have the resources to do these studies on our own as a health plan.