Patient Misreporting May Lead to Underestimation of Cough Events

To the Editor:

It was with great interest that we read the article by Tutuian et al1 in a recent issue of CHEST (August 2006). The authors investigated temporal relationships between non-acid reflux and cough events in patients with persistent cough, utilizing impedance/pH monitoring and subjective recording of cough events by means of a diary and a self-operated digital data logger.

Examining temporal relationships is important since both cough and reflux are frequent events; hence, coexistence alone does not imply causation. Establishing a reflux-cough association within a given time period may help to determine cause and effect, and may allow better patient selection for surgical intervention. However, there are issues we would like to highlight regarding the identification of cough.

First, the authors reported a total median number of coughs of 8 (interquartile range, 3 to 21 coughs) over the entire 24-h monitoring period. This rate is orders of magnitude lower than those reported by Birring et al2 (mean [± SD] cough rate, 43 ± 8 coughs per hour) and those determined in our own department (median rate, 11.06 cough-seconds per hour; range, 1.06 to 46 cough-seconds per hour).3

Second, the use of the subjective reporting of cough correlates poorly with objectively monitored cough sounds,4 particularly at night.5 The symptom index is a ratio of the number of cough events preceded by reflux to the number of cough events during the monitoring period, expressed as a percentage, and is taken to be positive if ≥ 50%. It seems likely that subjective reporting misses cough events, thus altering this ratio and increasing the chance of an apparently positive relationship.

A validated ambulatory monitor, recording individual cough sounds, could be time-synchronized to the impedance/pH trace. This would enable a more accurate determination of the temporal relationship between cough and reflux.

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DOI: 10.1378/chest.06-2300

REFERENCE


Response

To the Editor:

We would like to thank Decalmer and colleagues for their thoughtful comments on our article1 (August 2006), in particular on the importance of having an objective cough detector when evaluating the association between reflux and cough. We also agree with their comment that detecting a higher number of cough episodes would have decreased the chance of finding a positive symptom association using the symptom index. Still, since we eliminate cough episodes that occur during eating periods due to the difficulty of separating true reflux from frequent swallows using impedance, we might have actually underestimated the total number of cough episodes.

In the same issue of CHEST, Smith et al1 reported on the low-to-moderate level of correlation between objective monitoring and subjective reporting of cough episodes in COPD patients. Having an objective cough detector synchronized with the impedance-pH monitor would not only increase the accuracy of detecting cough events but would also allow differentiating cough-reflux from reflux-cough sequences, the latter making a stronger argument for a cause-effect relationship between reflux and cough. The development of the proposed cough sound detector synchronized to the impedance-pH signal is certainly worthwhile pursuing. Such a system would allow detecting the association (and temporal relationship) between two episodes (cough and reflux) and not only between a reflux episodes and a cough event (subjectively recorded by the patient).

Other investigators have proposed using other cough detectors in evaluating the relationship between reflux and cough. Intrathoracic and intragastric pressure transducers to document cough (as a sudden rise in pressure on both sides of the diaphragm) in combination with impedance-pH monitoring has been previously used by Sifrim et al2 in a group of chronic cough patients who were not receiving acid suppressive medications. In this study,3 the authors noticed similar proportions of reflux-
cough and cough-reflux sequences in the instances when a patient-reported cough episode was preceded by reflux within a 2-min time window.

In clinical practice, we regard objective cough detectors as adjuncts to patient diaries. Drawing a parallel to the observation that not all (impedance-) pH-detected gastroesophageal reflux episodes induce symptoms, we dare assuming that patients will not perceive all cough episodes. Having the patient marking a cough event whenever he/she noticed a cough episode helps identifying which cough episodes are symptomatic.

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DOI: 10.1378/chest.07-0206

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Decrease in Drug Resistance in Pneumococcal Community-Acquired Pneumonia

To the Editor:

Valles et al. reported significantly reduced rates of pneumococci nonsusceptible to \( \beta \)-lactams among adults patients with community-acquired pneumonia admitted to a single center in Barcelona, Spain, between 1999 and 2002 compared with a previous study. Although the authors suggested that the decrease in drug resistance could be partially related to the introduction of heptavalent pneumococcal conjugate vaccine, it seems unlikely that any significant vaccine impact occurred in Barcelona area during the study period due to very low vaccine uptake in that time period (4.8% estimated vaccine coverage in 2002). Nevertheless, vaccine coverage increased gradually since then, reaching an estimated 40 to 50% for the target population in Spain in 2005, and therefore conjugate vaccine may have had a significant role in further declines seen in pneumococcal resistance rates since 2002 (A. Fenoll, PhD; personal communication; May 2006). Changes in pneumococcal resistance rates during the study period can be fully explained by reduction in antibiotic consump-

tion and clonal dynamics of serotype 1. Nonsusceptible pneumococci declined gradually in Spain from 53% in 1997 to 43.9% in the first half of 2001 (just prior to vaccine licensure), along with a significant decrease in overall antibiotic use from 21.66 defined daily doses per 1,000 inhabitants per day in 1998 to 19.71 defined daily doses per 1,000 inhabitants per day in 2002 (p < 0.001). Serotype 1 was overrepresented in the study population (8.2%). Increased emergence of this penicillin susceptible serotype in Spain may have also contributed to reduction in drug resistance. This highly pathogenic serotype has been associated with dramatic temporal changes in epidemiology of invasive pneumococcal disease, and to this regard we have seen a significant increase in pneumococcal type 1 pediatric empyema in Southern Spain in recent years. It would be interesting to know whether the adults patients with pneumococcal pneumonia due to serotype 1 in the study showed the typical epidemiologic profile described for such patients (relative young age, lack of underlying disease, and low mortality).

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DOI: 10.1378/chest.06-3363

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Response

To the Editor:

Obando et al argued in their letter that the decrease observed in pneumococci not susceptible to \( \beta \)-lactam therapy in adult patients with community-acquired pneumonia (CAP) in our article could not be explained by the introduction of the heptavalent pneumococcal conjugated vaccine (HPCV) given to infants in Spain, since the coverage of this vaccine was very low during the study period (4.8%). We pointed out the possible impact of the HPCV based on the coverage of serotypes that are found mostly in children with carrier status who are more prone...
to be associated with the nonsusceptibility to antibiotics as has been previously observed. Nonetheless, this was a hypothesis based on the introduction of the HPCV throughout the private sector in Spain. In fact, a dramatic increase was observed in the coverage of children, achieving a rate of 34% during the period from 2002 to 2004 as Obando et al indicated.

At the time of the submission of our article, vaccine coverage in children was not available, and the article referred to was published at the same time as ours. We agree that the impact, if any, of pediatric vaccination during our study period was negligible with respect to the incidence of nonsusceptible pneumococcal CAP among adults. Nevertheless, our hypothesis could be relevant on the grounds of the decrease in the number of strains that are not susceptible to macrolide and β-lactam that have been described among children; thus, an indirect impact may be expected in the adult population in the near future. On the other hand, Obando et al pointed out that our findings could be fully explained by the decrease in antibiotic consumption in Spain (as we already stated) and the dynamics of clonal serotype 1. We observed a relatively high overrepresentation of serotype 1 compared with previous series, but the absolute number was still low (10 of 122 strains isolated). Surveillance in future years should confirm this trend.

As suggested by Obando et al, we examined the epidemiologic profile of the patients with serotype 1 CAP but did not find any differences compared with the population (mean age, 67.8 years; comorbidity, 40%; and no deaths). Furthermore, the low numbers analyzed were not conclusive.

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DOI: 10.1378/chest.07-0646

Antibiotics Selection for Bacteremic Pneumonia

To the Editor:

I read with interest the article by Metersky and coworkers (February 2007) regarding antibiotics for bacteremic pneumonia. The authors showed improved outcomes with macrolides but not with fluoroquinolones. The authors reviewed the charts of 2,209 patients admitted to the hospital with bacteremic pneumonia between 1998 and 2001 and concluded that the initial antibiotic coverage with a β-lactam along with a macrolide was associated with an improved outcome. In contrast, treatment with fluoroquinolones was related to worse outcome. According to blood culture results, bacteremic pneumonia was due to Streptococcus pneumoniae (35%) followed by Staphylococcus aureus (14%) and Streptococcus spp. (other; 14%) (Table 1). The most common antibiotics used as monotherapy or as combination therapy within 24 h of hospital admission are shown in Table 2.

When reading this article, the main message is that early administration of a macrolide plus a β-lactam lead to a better outcome of bacteremic pneumonia, confirming the results of previous studies. However, there are two main points that need to be addressed: (1) the authors do not mention the used dose of levofloxacin (500 mg qid, 500 mg bid, or 750 mg/d); and (2) as the authors used in the title the term fluoroquinolones (probably they mean respiratory quinolones), what would be the potential therapeutic benefit of moxifloxacin in these patients (especially in elderly patients)?

Regarding levofloxacin, it is well known that at a dose of 500 mg bid maintains an area under the curve/minimum inhibitory concentration ratio of 95 (with a ratio of area under the curve over 24 h/minimum inhibitory concentration >30 to 40 h an optimal antimicrobial activity against Gram-positive microorganisms is achieved). In addition, monotherapy with moxifloxacin has been found to be superior in the treatment of community-acquired pneumonia compared to a standard combination regimen including a β-lactam and a β-lactamase inhibitor with or without a macrolide.

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DOI: 10.1378/chest.07-0706

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DOI: 10.1378/chest.07-0646

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Response

To the Editor:

We wish to thank Dr. Dimopoulos for his interest in our study.1 Dr. Dimopoulos raises three issues. First, he asks if only respiratory fluoroquinolones were included in the fluoroquinolone group. We suspect that Dr. Dimopoulos is concerned that the poor activity of ciprofloxacin against Gram-positive organisms such as Streptococcus pneumoniae could explain why patients receiving fluoroquinolones had poorer adjusted outcomes than patients receiving macrolides. While we included patients receiving ciprofloxacin in the fluoroquinolone group, only 12 received fluoroquinolone monotherapy (1.3% of the fluoroquinolone patients), and only 1 of these patients died (8.3%); thus, it is unlikely that poorer outcomes in this small group explained our results. Dr. Dimopoulos correctly notes that various dosing regimens for levofloxacin are used around the world, and suggests that dosages >500 mg/d have theoretical benefit based on pharmacokinetic and pharmacodynamic parameters. Although we did not abstract antibiotic dosages, we suspect that most patients received 500 mg/d of levofloxacin because other dosing regimens were not commonly used for community-acquired pneumonia prior to 2001 in the United States. However, we are not aware of any convincing data to suggest that higher doses of levofloxacin result in improved outcomes in patients with community-acquired pneumonia. Finally, Dr. Dimopoulos notes that in contrast to our results, randomized, controlled trials have demonstrated equivalent or superior outcomes with fluoroquinolones when compared to regimens including macrolides. As mentioned in our article,1 others have noted disparate results of randomized trials (almost all antibiotic registration studies) vs retrospective studies2,3 of patients with community-acquired pneumonia. This may be because patients enrolled in antibiotic registration trials are not representative of most pneumonia patients,2 or because retrospective studies are subject to bias from potentially important patient-related factors not being included in the multivariable analyses. Only a large randomized trial can answer this important question.

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Dr. Metersky has served on an advisory board/speaker’s bureau for the following pharmaceutical companies: Aventis, Bayer, Ortho, Pfizer, Schering.

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DOI: 10.1378/chest.07-0880

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