RESPIRATORY MEDICINE

Cephalosporin-resistant pneumococcal pneumonia: does it, affect outcome?

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Abstract *Study Objectives:* Penicillin resistance has been reported in various studies to have no impact on the outcome of pneumococcal pneumonia. However, the importance of cephalosporin resistance has not been systematically studied. We conducted an analysis of patients with high-level cephalosporin-resistant *Streptococcus pneumoniae* pneumonia (H-CRSPP)–*Design:* Retrospective matched, case–control study. *Setting:* Two inner-city academic hospitals. *Patients:* Twenty-six patients with H-CRSPP admitted to the hospital between 1995 and 1999 were identified. Each patient was matched with two controls with cephalosporin-sensitive but oxacillin-resistant pneumococcal pneumonia admitted during the same time period. Matching was done based on pneumonia severity of illness index (PSI) and for other factors. *Interventions:* None. *Measurements and Results:* We evaluated a number of outcomes including mortality, length of stay in the hospital, and time to respond to treatment. Patients with H-CRSPP took longer to respond to treatment (6.5 ± 0.9 days *vs* 4.1 ±0.7 days, $P=0.05$) and had a longer length of stay in hospital (15.4 ± 2.2 days *vs* 9.2 ± 1.6 days, $P=0.02$), None of the other outcomes were different between the two groups. *Conclusions:* Overall, we have found that the presence of cephalosporin resistance does impact the course of pneumococcal pneumonia.

doi:10.1053/rmed.2002.1358, available online at http://www.idealibrary.com on IDEAL®

Keywords cephalosporin resistance; *streptococcus pneumonia*; pneumonia; matched case–control studies.

INTRODUCTION

Pneumonia is the sixth leading cause of death in the U.S. and is the most common cause of infection-related mortality (1). *Streptococcus pneumoniae* continues to be the leading cause of adult community-acquired pneumonia (CAP), accounting for approximately 30% of episodes (2). Penicillin-resistant strains of pneumococcal pneumoniae were first described 30 years ago (3). Since then, there has been a worldwide phenomenon of increasing resistance to penicillin and multiple other antibiotics, including cephalosporins (4).

Along with the emergence of this resistance, there has been an increased interest in the clinical sequelae of infection with these organisms. The first look at the problem came from Spain (5). Pallares and colleagues followed 504 patients with *S. pneumoniae* pneumonia, 116 of whom had penicillin-resistant *S. pneumoniae* (PRSP) and 29 patients had cephalosporin-resistant *S. pneumoniae* (CRSP). They found no excess mortality in patients with penicillin or cephalosporin-resistance. The other large study looking at PRSP and CRSP involved 49 patients with PRSP and 31 patients with CRSP (6). In this study, the authors concluded that drug resistance did not affect the outcome. Two recent papers have re-looked at the issue of outcome in patients with drug-resistant pneumococcus (7,8). In a study by Metlay and colleagues, presence of penicillin resistance did show increased risk of suppurative outcomes (8). In a large surveillance study by Feikin and colleagues, presence of extremely high-level penicillin resistance (minimal inhibitory concentration (MIC) $\geqslant$ 4.0) was found to be a risk factor for in-hospital mortality, after excluding patients who died during the first 4 days of the study. Also, high-level (MIC $\geqslant$ 2.0) resistance to cefotaxime but not penicillin was associated with late hospital deaths (7).

We wanted to determine if high-level cephalosporin resistance affected the outcome of hospitalized patients with pneumococcal pneumonia. We felt that mortality alone would be an insensitive outcome measure. Therefore, we looked at five other outcomes in patients with high-level cephalosporin-resistant pneumococcal pneumonia (H-CRSPP): (1) length of stay (LOS) in the hospital; (2) LOS in the intensive care unit; (3) number

Received 10 December 2001, accepted in revised form 1 April 2002.
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of antibiotics used during the hospital stay; (4) time to respond to therapy; and (5) failure of primary therapy.

METHODS

The ethics committees of our institutions approved the study protocol. Potential isolates were found by reviewing the records of the microbiology departments of Henry Ford Hospital (HFH) and the Detroit Medical Center (DMC) between 1993 and October 1999. Initial susceptibility to penicillin was tested by oxacillin disk diffusion test. Isolates resistant to oxacillin disk diffusion test were further evaluated by E-test with susceptibility breakpoints defined according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines (9,10). A pneumococcal isolate was considered susceptible to penicillin if the MIC was $\leq 0.06\,\mu g/ml$, to be of intermediate resistance if the MIC was between 0.12 and 1 $\mu g/ml$, to be highly resistant if the MIC was $\geq 2.0\,\mu g/ml$. The pneumococcal isolate was considered susceptible to cephalosporins if the MIC was $\leq 0.5\,\mu g/ml$, to be of intermediate resistance if the MIC was 1 $\mu g/ml$, to be highly resistant if the MIC was $\geq 2.0\,\mu g/ml$.

Records of all adult patients (age >18 years) with positive *S. pneumoniae* cultures from blood, sputum, or bronchoalveolar lavage (BAL) were then reviewed. Patients were defined to have pneumonia if they had (1) a new pulmonary opacity compatible with pneumonia on chest radiograph and confirmed by a radiologist; and (2) 1 or more signs and symptoms consistent with a lower respiratory tract infection, including temperatures greater than 38°C, new or increased cough, production of purulent sputum, crackles, rhonchi, or pleuritic chest pain or dyspnea; or (3) an elevated white blood cell count ($>10\times10^9$/L) or greater than 0.15 band forms. Patients were excluded if they met one of the following criteria: age <18 years; isolation *of S. pneumoniae* on a culture taken more than 3 days after admission; lack of admission to the hospital; transfer from another hospital; patients with ≥ 3 of the 19 possible pieces of data for the pneumonia severity index missing; previously enrolled patient. Cases were defined as patients with MIC ≥ 2.0 g/ml to cefotaxime. Controls were selected among patients with CAP who met the inclusion criteria and were infected with *S. pneumoniae* sensitive to cefotaxime (MIC ≤ 0.5) but resistant to oxacillin (≥ 20 mm zone of inhibition).

Pneumonia severity was assessed by means of the pneumonia severity of illness index (PSI) (11,12). The PSI is a validated disease severity classification based upon a number of factors (11,12). A PSI score was calculated for all potential cases and controls. The data to calculate these scores and obtain other potential information were obtained via chart review. Results of the initial laboratory tests done in the emergency department (ED) were used for scoring. In patients who did not have a particular test done in the ED, the first test results obtained after admission were used for the study. In cases of missing data, the variables were presumed to be normal. However, if three or more of the 19 data points needed to compute the PSI were missing for any one patient, that patient was excluded from further study.

Each case was matched to two controls by one of the investigators (BD) who was blinded to the clinical outcome of the patients. Cases from each institution were matched with controls from the same institution. Matching was based upon age, sex, PSI, year of admission, and other factors listed in Table 1. This method of matching has been used with good effect in previous studies investigating the attributable mortality and morbidity of nosocomial bacteremia (13,14). Although all the controls were oxacillin resistant, all were not resistant to penicillin. When matching, attempt was made to include patients with penicillin resistance as controls. The relative importance of the matching criteria is outlined in Table 1. The scoring system shown was derived prior to matching and was arrived at based upon a clinical impression of the relative importance of each factor, as has been done previously (13). This scoring system allowed us to assess the adequacy of matching by calculating a match score, with the best possible score of 30 points.

A data collection form was used to collect the outcome information from the medical record. The outcomes of interest were: (1) hospital mortality; (2) LOS in the hospital; (3) LOS in the intensive care unit; (4) number of antibiotics used during the hospital stay; (5) time to respond to therapy; and (6) failure of primary therapy.

The criterion of time to respond was developed based on a prior study looking at the validity of this measure (15). Response to therapy was defined as resolution of fever (temperature consistently less than 38°C), respiratory rate consistently less than 24, improvement of symptoms of pneumonia (as noted by the physician

TABLE 1. Matching criteria

Characteristic	Points
Pneumonia score ± 10	10
± 20	5
Age $\pm$ 10	5
Sex match	5
Year of admission ± 2	3
Presence of penicillin resistance in the control	3
Matching of bacteremia	2
Match of COPD	1
Diabetes mellitus	1

caring for the patient), resolution of hypoxemia and stability of abnormalities on radiograph. The respiratory rate and temperature had to be in the appropriate range for at least 48 h before response could be said to have occurred. In terms of radiographic stability, the radiograph was considered to be stable unless there was a radiograph done which showed worsening. In patients on mechanical ventilation, the time to respond was defined as the day the patient had satisfied all of the above criteria and was extubated. In patients discharged before 48 h were over, it was presumed that the patients did not have any recurrence of symptoms. The time (in days) that it took for this to occur was defined as the time to respond. If the patient died without ever developing a clinical response, they were excluded from further analysis on this variable although they were counted as failure of primary therapy (see below).

Failure of primary therapy was defined as the occurrence in one of the two ways. Either the patient had to show a lack of response (as discussed above) despite greater than 72 h of therapy or the patient had evidence of worsening on therapy as shown by a need for intubation or death after at least 24 h of therapy.

Statistical analysis

All the statistical tests were done after accounting for the matched design of the study. Continuous outcome variables were compared using a paired *t*-test.

Demographic continuous data were reported as the mean $\pm$ standard deviation. Continuous data that were obtained by comparing the two groups were reported as a least-square mean $\pm$ standard error. Categorical variables were compared using conditional logistic regression. Because of the potential importance of PSI in predicting outcomes, we analyzed outcomes after controlling for PSI, even though it was a matching variable (16). We also controlled for age, sex and year of admission where it was appropriate. That is, we evaluated the significance of these variables in each model. When the *P* value for the variable was $\leq$0.10, it was left in the final model. All the analyses were done with Statistical Analysis Software Package (SAS Institute, Cary, NC, U.S.A). In all instances, an alpha level of 0.05 was used to decide whether the null hypothesis of no difference between the two groups could be rejected.

RESULTS

From 1995 to 1999, a total of 3033 isolates of *S. pneumoniae* were found in blood, sputum or BAL fluid in the microbiology laboratories of HFH and DMC. Of the 3033 isolates, 664 (21.9%) were oxacillin resistant. Three hundred and nineteen isolates (10.5%) had intermediate resistance and 135 isolates (4.5%) had high-level resistance to penicillin. One hundred and eleven (3.7%) isolates were found to have intermediate resistance to cephalosporins and 54 (1.8%) isolates had high-level resistance to cephalosporins. Of the 54 isolates with high-level resistance to cephalosporins, 21 had multiple drug resistance, i.e. resistance to two other antibiotic groups in addition to penicillin and cephalosporins. Thirteen patients were excluded due to age $<$18 years, 12 patients were excluded as the patients did not have pneumonia, two patients were excluded as the patients were not admitted to the hospital and one patient was admitted twice for H-CRSPP. Thus, we had 26 cases.

For each case, we chose two controls. These controls were chosen from a group of 121 patients (62 from HFH and 59 from DMC) who had CAP due to *S. pneumonia* resistant to oxacillin but sensitive to cefotaxime. Cases and controls were similar and there was no statistically significant difference between the two groups except that more patients in the case group presented with dyspnea (Table 2). Of the 52 controls matched with the cases, 37 (71%) were resistant to penicillin and the rest were resistant to oxacillin disk, but sensitive to penicillin.

The average PSI scores were similar in the two groups. Also, the percentage of patients in the highest risk class, IV and V, was similar in the two groups (43% *vs*. 44%, P=1.00). Matching scores were 25.2 $\pm$ 2.9 (range 17–30, median 25) for the patients from Henry Ford Hospital and 24.1 $\pm$3.8 (range 19–30, median 24.5) for patients from Detroit Medical Center. In 41 out of 52 matches, the patients were matched within $\pm$10 points for PSI score. Given the fact that we were able to match within 10 points only 79% of the time, we adjusted for PSI in evaluating outcomes for all of the subjects. In other words, we included PSI in all of our final multivariate regressions so as to decrease the potential for it to confound the relationship between the presence of H-CRSPP and the outcomes of interest.

The treatment regimens used initially in the two groups are shown in Table 3. There was no difference in these regimens. After adjusting for age, sex, PSI, year of admission and presence of bacteremia, we found no difference in mortality, number of patients intubated, ICU admission rates or the number of antibiotics used between the two groups (Table 4). No patient was readmitted within the 1 month of discharge, but there was a trend towards patients with H-CRSPP being more likely to fail treatment (27 *vs* 12%, P=0.10; RR=2.9 (0.82,10)). In addition, vancomycin was used more often in the case group (50 *vs* 15%, P=0.001; RR= 3.25 (1.59, 6.65)).

In terms of failure of primary therapy, there was no statistical difference in the mode of failure with the majority of patients failing because of worsening after 24 h of therapy (5/7 of the cases and 4/6 of the controls). When further evaluating failure of primary therapy, one might be interested in whether the initial antibiotic

Table 2. Characteristics of case and control groups

Patient characteristics	Cases (n=26)	Controls (n=52)	P value
Demographics			
Mean age (years) ± SD	53 ± 17.5	53.4 ± 18.4	0.92
Males	18 (69%)	30 (58%)	0.46
Co-existing conditions			
Mean co-morbid illness per patient	0.85	0.83	1.0
Use of intravenous drugs	6 (23%)	7 (13%)	0.45
Total immunocompromised	6 (23%)	12 (23%)	1.0
Non-HIV	4 (15%)	9 (17%)	
HIV	2 (8%)	3 (6%)	
Bacteremia	8 (31%)	21 (40%)	0.56
Active smokers	14 (54%)	25 (48%)	0.81
Current alcohol use	10 (38%)	18 (35%)	0.93
Symptoms			
Cough	23 (88%)	42 (81%)	0.59
Chest pain	14 (54%)	23 (44%)	0.57
Dyspnea	19 (73%)	23 (44%)	0.03
Fever	20 (77%)	36 (69%)	0.66
Physical examination findings			
Altered mental status	3 (12%)	12 (23%)	0.36
Pulse ⩾125/min	7 (27%)	12 (23%)	0.93
Respiratory rate ⩾30/min	7 (27%)	11 (21%)	0.78
Systolic blood pressure <90 mmHg	6 (23%)	4 (8%)	0.12
Temp <35°C or ⩾40°C	2 (8%)	3 (6%)	1.0
Laboratory and radiological findings			
Blood urea nitrogen ⩾30 mg/dl	5 (19%)	12 (23%)	0.92
Glucose ⩾250 mg/dl	0 (0%)	4 (8%)	0.36
Hematocrit <30%	2 (8%)	4 (8%)	1.0
Sodium <130 mmol/l	2 (8%)	6 (12%)	0.90
Oxygen sat <90 or PaO2 <60 mmHg	11 (42%)	18 (35%)	0.68
Arterial pH <7.35	1 (4%)	8 (15%)	0.26
Pleural effusion	9 (35%)	12 (23%)	0.42
Multilobar pneumonia	9 (35%)	16 (31%)	0.93
Initial treatment			
Mean ± SD hours for first antibiotic dose	10.7 ± 13.4	8.1 ± 6.5	0.38
Patients who received dose within 8 h	14 (54%)	32 (62%)	0.44
Patients intubated in the ED	3 (12%)	10 (19%)	0.59
Mean PSI ± SD	89 ± 44	91 ± 43	0.91
Risk Class IV and V[a]	11 (42%)	23 (44%)	1.00

[a]Risk class based on Pneumonia Severity Index of Illness calculations at the time of admission (15,16).

Table 3. Initial antibiotic regimens as well as rate of treatment failure for the regimen

Initial antibiotic regimen	Cases (26)	Controls (52)	Failure rate
Second generation cephalosporins ± macrolide	10 (38%)	17 (33%)	18.5%
Vancomycin ± any other drag	4 (15%)	5 (10%)	0%
Third-generation cephalosporins ± macrolide	2 (8%)	6 (12%)	12.5%
Co-trimoxazole and or macrolide	5 (19%)	13 (25%)	22.2%
Penicillin G	1 (4%)	4 (8%)	0%
Co-trimoxazole+second-generation cephalosporins	0 (0%)	4 (8%)	25%
Others	4 (15%)	3 (6%)	28.6%

Table 4. Outcomes in case and control groups

Outcome	Cases (26)	Controls (52)	*P* value
Death	1 (4%)	3 (6%)	1.0
Failed treatment	7 (27%)	6 (12%)	0.10
Mean number of antibiotics ± SD	3.4 ± 2.1	2.9 ± 2	0.16
Patients admitted to the ICU	10 (38%)	15 (29%)	0.18
Vancomycin use	13 (50%)	8 (15%)	0.003

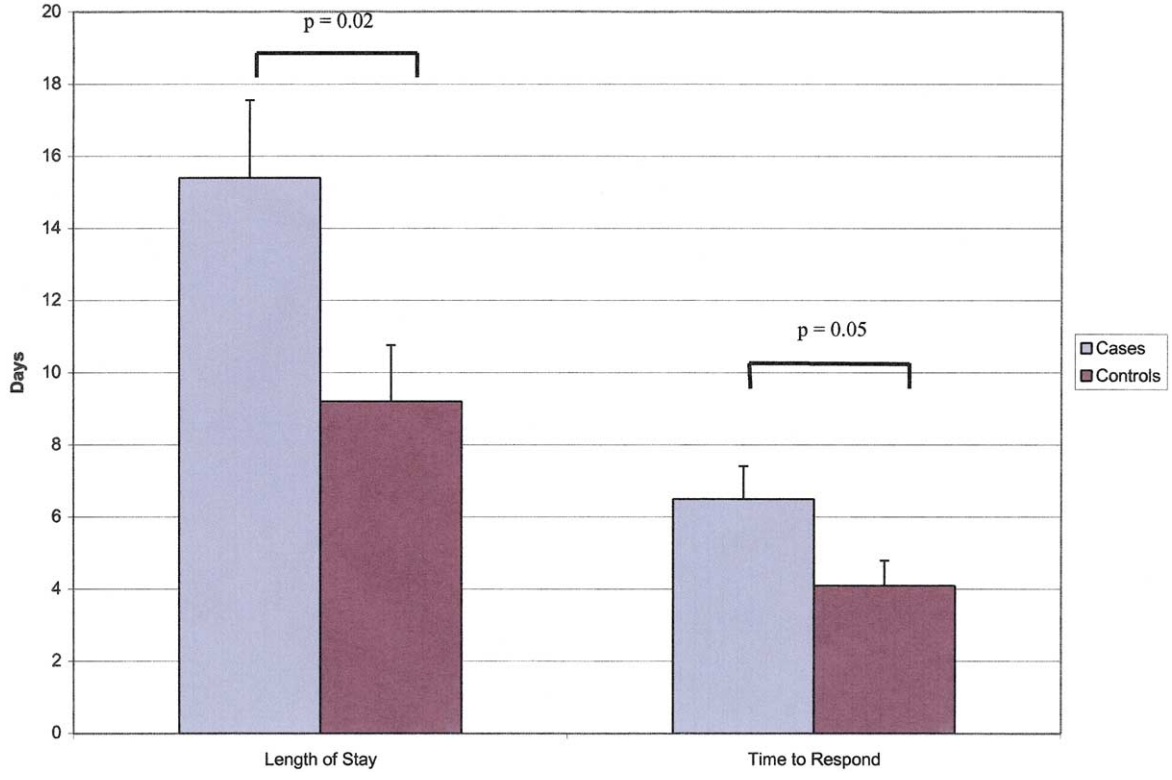

Fig. 1. Length of stay and time to respond (mean ± standard error) after adjusting for PSI, age, and year of admission in the case and control groups.

regimen was independently associated with likelihood of failure. The slight differences in failure rates shown in Table 3 were not significantly different ($P=0.64$). Most importantly, there was no evidence that antibiotic choice in any way confounded the relationship between cephalosporin resistance and outcome. Also, these outcomes were not due to extremely high-level penicillin resistance (MIC $\geq$ 4.0) as only four of the cases had such levels.

The main differences in outcome are noted when looking at the time to respond to therapy and length of stay in the hospital. After controlling for year of admission, cases took, on average, 2.4 more days to respond (6.5 ± 0.9 *vs* 4.1 ± 0.7, $P=0.05$; 95% CI for difference: (0.1, 4.7)) (Fig. 1). Also, after controlling for age and year of admission, they were in the hospital for a mean of 6.2 more days (15.4 ± 2.2 *vs* 9.2 ± 1.6, $P=0.02$; 95% CI for difference: (0.9, 11.5)) (Fig. 1). They seemed to have a 5 day longer LOS in the ICU, although this was not quite statistically significant (8.1 ± 2.1 *vs* 3.1 ± 1.5, $P=0.07$; 95% CI for difference: (−0.3, 10.3)).

DISCUSSION

In this case–control study, we found that patients with H-CRSPP took longer to respond to therapy and have a longer length of stay. We also found that the likelihood of failing primary therapy was higher in these patients.

Besides being the largest study on H-CRSPP, our results are notable, in particular, because of their difference from the major previous studies (5,6).

A review of the prior studies may help point out potential reasons for the differences in results (5,6). Prior studies included only a small number of patients with high-level cephalosporin resistance (four patients in the Pallares study and nine patients in the Ewig study). Therefore, their studies were likely underpowered especially given that the main outcome they looked at was mortality. In fact, we too were unable to find a difference in mortality as our study also lacked the power to adequately evaluate this end point. However, by examining factors such as length of stay in the hospital and time to respond to treatment, we were able to show differences between the two groups. Our study is the first study to show that patients with H-CRSPP have a higher morbidity.

The importance of this increased length of stay can be appreciated when one considers the costs of treating CAP. Recent national data suggest that each day in the hospital for the treatment of pneumonia costs approximately $1 027 (17). Therefore, 6.4 extra days would cost $6 573 per patient of H-CRSPP. From 1988 to 1994, the average number of patients admitted yearly for CAP has been 1.135 million (17). Given that *S. pneumoniae* accounts for 30% of all causes of CAP and the prevalence of high-level cephalosporin-resistant pneumococcus is 4% (12,18), the number of patients with H-CRSPP will be 13,620 per year. Therefore, the excess costs associated with these infections would be close to $90 million per year.

Since mortality is a relatively uncommon end point in CAP, we used length of stay and other markers like "time to respond to therapy" and "failure of primary treatment" to indicate poor outcomes. The end points of "time to respond to therapy" and "failure of primary treatment" could be questioned because they involve subjective criteria. Nevertheless, these outcomes were based on previous studies and/or obvious clinical end points. The criterion of time to respond was developed based on a study looking at "time to resolution of morbidity" (TRM) in 100 patients with pneumonia (15). In that study, TRM had been found to correlate better with length of stay than APACHE II. One might be concerned that time to respond could be overly affected by whether the patients were intubated in the ED as patients had to be extubated to be considered to have responded to therapy. Although this is a reasonable concern, it did not influence our results as a greater percentage of the controls in this study were intubated in the ED (19 *vs* 12%).

The other subjective criterion used was "failure of primary treatment." We developed this criterion for the study and there have been no papers looking into this or a similar outcome. As in the case of "time to respond," we had fairly well-defined criteria for this outcome. Though we used subjective end points, based on the above discussion, we think these end points are valid.

Another potential limitation of our study is the matched case–control design. The validity of any matched case–control study is limited by the strength of the matching and the appropriateness of the matching criteria. In this study, we matched for PSI, age, sex, year of admission, presence of resistance to penicillin, presence of bacteremia, presence of chronic obstructive pulmonary disease and diabetes mellitus. Except for the study by Metlay and colleagues, none of the previous studies on this subject controlled for severity of illness on presentation (5–8). An important factor to consider in comparing outcomes between two groups with a disease entity is to make sure that the patients have similar severity of illness (16). This is especially true when investigating resistance, as the presence of a resistant organism may be a marker for a more severe disease. We therefore used PSI score to control pneumonia severity of illness in the design and analysis of this study as this score has been validated in over 50,000 patients (12).

Another limitation of our study is that, as it was retrospective, we could not control the therapy that was administered. Systematic differences in treatment based upon the organisms' sensitivities could have biased the study. In fact, we did show that the group with H-CRSPP did receive more vancomycin than the comparison group. Although this could suggest that this group was sicker, we feel that this is in fact a reflection of the sensitivity patterns as 62% of the cases who received vancomycin did so only after the sensitivities were reported. More importantly, this difference in treatment could have led to us finding less of a difference between groups than would have been shown if they received similar treatments. As such, our estimate of the morbidity associated with H-CRSPP may be conservative.

A reevaluation of empiric therapy for CAP is warranted in the light of our findings that H-CRSPP is associated with increased morbidity. Current guidelines recommend empiric therapy for hospitalized patients with CAP with either a third-generation cephalosporin plus a macrolide or a fluoroquinolone (19). Given the fact that the morbidity seen in our patients with H-CRSPP was not severe, we would not recommend a change in these empiric recommendations based upon our data. However, if the prevalence of high-level cephalosporin resistance in a community is elevated ($>5\%$), one might consider empiric treatment with a quinolone as there does not seem to be a correlation between cephalosporin resistance and quinolone resistance (20,21). Also, in patients with documented H-CRSPP, antibiotic therapy should be tailored to their sensitivity pattern.

In summary, we feel that our results are not invalidated by any potential limitations. As such, we can conclude that patients with H-CRSPP take longer to

respond to therapy and have a longer length of stay. These differences in the course of H-CRSPP are important as they can be translated into excess costs of close to $$90 million in the U.S. Larger prospective studies looking at the risk factors for H-CRSPP and impact of early intervention in patients at risk for H-CRSPP are needed.

Acknowledgements

We thank Mary Dunn and William Brown, PhD from the department of microbiology of Henry Ford and Detroit Medical Center, respectively, for the help in collecting patients for this study. No financial support was obtained for this study.

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