Eur. J. Clin. Microbiol. Infect. Dis., April 1994, p. 293–298
0934-9723/94/04 0293-06 $ 3.00/0

Randomized Comparative Trial with Ampicillin/Sulbactam versus Cefamandole in the Therapy of Community Acquired Pneumonia

D. Williams[1], M. Perri[1], M.J. Zervos[1,2]*

In a randomized prospective study ampicillin/sulbactam and cefamandole were compared in the therapy of patients hospitalized with community acquired pneumonia. Patients receiving ampicillin/sulbactam (n = 37) and cefamandole (n = 38) were similar with respect to age (mean age 70 vs. 76 years respectively), clinical characteristics, severity of illness and underlying disease. Pathogens isolated from patients in the cefamandole and ampicillin/sulbactam group, respectively, were *Streptococcus pneumoniae* (7 vs. 7 patients), *Haemophilus parainfluenzae* (7 vs. 6 patients), *Haemophilus influenzae* (5 vs. 5 patients), *Staphylococcus aureus* (5 vs. 4 patients), *Escherichia coli* (4 vs. 4 patients), *Klebsiella pneumoniae* (3 vs. 3 patients), *Enterobacter* spp. (2 vs. 3 patients), *Moraxella catarrhalis* (1 vs. 2 patients), and organisms of the oral flora (4 vs. 3 patients). The rate of resistance to penicillin was 80 %, to clindamycin 76 %, to erythromycin 45 %, to ampicillin 43 %, and to cefazolin 18 %. Overall successful treatment rates of 81 % for cefamandole and 97 % for ampicillin/sulbactam (p = 0.05) were observed. Both cefamandole and ampicillin/sulbactam were shown to be effective agents for therapy of community acquired pneumonia; however ampicillin/sulbactam demonstrated superior overall clinical efficacy.

Pneumonia is the sixth leading cause of death in the USA and the fourth leading cause of death in persons over the age of 65 years. Traditional therapeutic guidelines for community-acquired pneumonia are based on knowledge of the usual causative agents. Definitive therapy is based on the results of culture of properly obtained sputum, blood or transtracheal specimens. In community-acquired pneumonia, ampicillin, erythromycin or a second-generation cephalosporin have commonly been the empiric choice for therapy (1–3). A number of reports have stressed the importance of *Staphylococcus aureus*, *Klebsiella* spp., beta-lactamase producing *Haemophilus* spp., *Moraxella catarrhalis*, and other gram-negative bacteria and anaerobes as pathogens, especially in patients requiring hospitalization (4–17) including high-risk patients (9) and the elderly (5–8, 16). Antibiotic resistance has increasingly been observed in these bacterial species.

[1] Department of Medicine, Division of Infectious Diseases, and [2] Wayne State University School of Medicine, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, Michigan 48073, USA.

The present study was undertaken to determine the spectrum of causative agents and the antibiotic resistance rates in bacteria currently responsible for community-acquired bacterial pneumonia. We also sought to evaluate in a randomized comparative study the safety and efficacy of ampicillin/sulbactam versus cefamandole in the therapy of community-acquired pneumonia.

Patients and Methods

Patients. Between February 1989 and December 1990, patients entering the William Beaumont Hospital with a primary diagnosis of community-acquired pneumonia were eligible for inclusion in this study. William Beaumont Hospital is a 975 bed community teaching hospital in Royal Oak, Michigan, USA. Inclusion criteria comprised the following: age over 18 years, approval of the attending physician, new pulmonary infiltrate demonstrated radiographically, fever, purulent sputum, leukocytosis (leukocytes > 11,000 cm^3), Gram stain of sputum showing fewer than 10 epithelial cells, more than 25 polymorphonuclear cells (PMNs) per low-power field and a predominant organism (18). Exclusion criteria comprised the following: diagnosis of pneumonia thought to be due

to chlamydia, virus, mycoplasma or *Legionella* spp., penicillin or cephalosporin hypersensitivity, resistance of the pathogen to the study drugs, prior therapy with parenteral antibiotics, presence of neutropenia or drug-induced immunosuppression, infection with HIV and patients moribund or with rapidly fatal illness. Patients were also excluded if they had received prior oral antibiotic therapy for the lower respiratory tract infection to which there appeared to be a response. Patients were eligible for the study if they had received an oral agent, but had progression of signs and symptoms of infection or signs of progression on chest x-ray resulting in hospitalization, or had an organism resistant to the oral agent used. The severity of underlying illness was categorized using the McCabe scale (19), whereby class 1 is a non-fatal disease, class 2 is an ultimately fatal disease (50 % chance of death within 5 years) and class 3 is a rapidly fatal disease (50 % chance of death within 2 months). Informed written consent was obtained from all patients.

Therapy. Patients were randomized in a non-blinded manner to receive ampicillin/sulbactam 1.5 to 3.0 g intravenously every 6 h or cefamandole 1 to 2 g intravenously every 6 h. Dosages were adjusted on the basis of renal function. No other antibiotics were given during administration of the study drug which was given for three or more days. All other forms of therapy were administered at the discretion of the attending physician. Oral antibiotics were permitted at the end of therapy with the study drug.

Bacteriological Investigations. In all patients Gram stain of sputum smears and blood and sputum cultures were performed. Investigations were performed in the clinical microbiology laboratory of William Beaumont Hospital. Gram stains were reviewed and correlation with the culture results was needed for the organism to be considered a pathogen. Bacteria were isolated from the sputum and susceptibility determined by standard methods (20, 21). *Haemophilus* spp. were identified as described in detail previously (22, 23). Bacteria were considered pathogens if moderate or abundant growth (growth in the third and fourth streak respectively) was noted from a purulent specimen. All strains except *Streptococcus pneumoniae* were tested for production of beta-lactamase using nitrocefin (Becton Dickinson, USA) impregnated disks. Susceptibility of all isolated bacteria to ampicillin, penicillin, erythromycin, cefazolin, ampicillin/sulbactam and cefamandole was determined in vitro by microdilution methods. Ampicillin/sulbactam was evaluated at concentration ratio of 2:1.

Evaluation of Efficacy and Safety. The following criteria were used to determine the clinical response to therapy: cure, defined as the disappearance of presenting signs and symptoms by the end of therapy and their continued absence at the end of one to two weeks of follow-up; improvement, defined as the partial alleviation of presenting signs and symptoms (cough, fever, leukocytosis) by the end of study drug therapy and their continued absence at the end of one to two weeks of follow-up, but administration of oral antibiotics after study drug therapy; failure, defined as no significant effect on presenting signs and symptoms; indeterminate, defined as results not evaluable. Microbiologic efficacy was determined using the following criteria: eradication, defined as the elimination of the principal pathogen(s) at the end of therapy and their continued absence at the end of one to two weeks of follow-up; superinfection, defined as the emergence of a different pathogen during or immediately after therapy with concurrent signs and symptoms of infection; persistence, defined as the continued presence of the principal pathogen at the end of therapy.

All adverse advents were recorded along with severity and outcome and designated as study drug or non-study

Table 1: Demographic and clinical characteristics of patients in the two study groups at presentation.

Characteristic	Ampicillin/sulbactam group	Cefamandole group
No. of patients evaluable	37	38
No. of males/females	19/18	20/18
Mean age in years (range)	70 (29–105)	76 (33–93)
No. (%) receiving prior antibiotics	8 (22)	10 (26)
No. (%) by underlying disease:		
COPD	23 (62)	25 (66)
Cardiovascular disease	13 (35)	22 (58)
Genitourinary disease	11 (30)	10 (26)
Diabetes	9 (24)	3 (8)
Total	29 (78)	31 (82)
No. (%) by severity of illness:		
Class 1	21 (57)	23 (61)
Class 2	16 (43)	15 (39)
Class 3	0 (0)	0 (0)

COPD: Chronic obstructive pulmonary disease.

drug related. Therapy was required to be given for a minimum of three days for the outcome to be evaluated. Statistical comparisons were made using Student's t test for continuous variables, and Fisher's exact test or chi-square analysis with the Yate's correction was used for dichotomous variables.

Results

A total of 97 patients were admitted to the study. Patients were excluded from the efficacy evaluation for the following reasons: the duration of treatment was less than three days (n = 14) (the patients improved, therapy was changed to oral agents and the patients discharged); therapy was discontinued at the discretionary judgement of the attending physician (n = 5); and resistance of the pathogens to the study drug (n = 3). Of the patients who were eligible for the study 37 were randomly allocated to receive ampicillin/sulbactam and 38 to receive cefamandole. Patients in the two treatment groups were similar with respect to demographic and clinical characteristics, including the severity of illness (Table 1). The mean age was 70 years (range 29–105 years) in the ampicillin/sulbactam group and 76 years (range 33–93 years) in the cefamandole group. There were no significant differences in underlying disorders between the two treatment groups. The admission diagnosis in the ampicillin/sulbactam group was lobar pneumonia in 28 patients, bronchopneumonia in seven patients, pneumonia/empyema in one patient and pneumonia/lung abscess in one patient. Thirty-four cefamandole-treated patients were admitted with lobar pneumonia and four with bronchopneumonia.

Table 2: Bacteriologic findings (number of strains isolated) in the two study groups.

Organism	Ampicillin/ sulbactam group	Cefamandole group
Streptococcus pneumoniae	7	7
Haemophilus parainfluenzae	6	7
Haemophilus influenzae	5	5
Staphylococcus aureus	4	5
Escherichia coli	4	4
Klebsiella pneumoniae	3	3
Enterobacter spp.	3	2
Moraxella catarrhalis	2	1
Normal oral flora	3	4
Total	37	38

Table 2 summarizes the bacteriological findings in the two groups. Overall, the organisms most frequently isolated were *Streptococcus pneumoniae* (18.6 %), *Haemophilus parainfluenzae* (17.3 %), *Haemophilus influenzae* (13.3 %) and *Staphylococcus aureus* (12 %); no pathogen was found in 9 % of patients in the two treatment groups. Table 3 summarizes the in vitro susceptibility results for the pathogens. Twenty-nine isolates produced beta-lactamase, including 2 *Haemophilus influenzae*, 9 *Staphylococcus aureus*, 5 *Enterobacter* spp., 6 *Klebsiella* spp., 4 *Escherichia coli* and 3 *Moraxella catarrhalis*. Twenty-four percent of all isolates were susceptible to clindamycin, 55 % to erythromycin, 82 % to cefazolin, and 100 % to both cefamandole and ampicillin/sulbactam.

Table 3: Comparative in vitro susceptibility of pathogens isolated.

Organism	MIC90 (μg/ml)*						
	Penicillin	Erythromycin	Ampicillin	Clindamycin	Cefazolin	Cefamandole	Ampicillin/ sulbactam
Streptococcus pneumoniae (n = 14)	0.06 (100)	< 1.0 (100)	< 1.0 (100)	< 1.0 (100)	< 1.0 (100)	< 1.0 (100)	< 2/1(100)
Haemophilus spp. (n = 23)	> 100 (0)	0.5 (91)	1.0 (91)	> 100 (0)	1.0 (91)	4.0 (100)	2/1 (100)
Staphylococcus aureus (n = 9)	> 100 (0)	> 100 (22)	> 100 (0)	> 100 (22)	1.0 (100)	1.0 (100)	4/2 (100)
Other (n = 22)	> 100 (0)	> 100 (0)	> 100 (18)	> 100 (0)	> 100 (54)	8.0 (100)	8/4 (100)

*Percentage of strains susceptible is shown in brackets.

In the ampicillin/sulbactam group, 34 patients were cured, two improved and one experienced failure, whereas in the cefamandole group 28 were cured, three improved and seven experienced failure ($p = 0.05$; Table 4). Only one case of pathogen persistence (3 %) was seen in each group. Clinical failure of ampicillin/sulbactam therapy was associated with *Staphylococcus aureus* in one patient. Clinical failure of cefamandole therapy in seven patients was associated with the following pathogens isolated pre-therapy: *Haemophilus influenzae* (n = 2), *Enterobacter* spp. (n = 2), *Klebsiella pneumoniae* (n = 1), *Streptococcus pneumoniae* (n = 1) and *Moraxella catarrhalis* (n = 1). The mean duration of therapy was 4.7 days (range 3–12 days) in the ampicillin/sulbactam group versus 5.6 days (range 3–14 days) in the cefamandole group (Table 4). The mean duration of fever and leukocytosis was longer in cefamandole-treated patients (Table 4).

Adverse events occurred in 14 patients (Table 4). Four (10.8 %) ampicillin/sulbactam-treated patients experienced adverse events. Ten (26.3 %) cefamandole-treated patients experienced adverse events. The most frequent adverse event was gastrointestinal disturbances (3 ampicillin/sulbactam- and 8 cefamandole-treated patients). Diarrhea occurred in three ampicillin/sulbactam-treated patients. Diarrhea occurred in six and nausea and vomiting in two cefamandole-treated patients. Generalized pruritus occurred in one ampicillin/sulbactam-treated patient. Eosinophilia occurred in one and a minimally elevated prothrombin time in another cefamandole-treated patient. Superinfection occurred in one ampicillin/sulbactam-treated patient (*Candida albicans* in urine) and in one cefamandole-treated patient (*Enterobacter* nosocomial pneumonia). Two patients died (one in each treatment group), death being attributed to failure of early treatment. Both patients had bacteremic *Streptococcus pneumoniae* with respiratory failure which developed within 24 hours of admission.

Discussion

The present study was designed to compare the efficacy of two antibiotic regimens for treatment of community-acquired pneumonia. We excluded patients in whom an initial Gram stain of sputum showed no predominant bacterial organism. Thus the etiology of community-acquired pneumonia

Table 4: Outcome of therapy and clinical course in the two study groups.

	Ampicillin/sulbactam group (n = 37)	Cefamandole group (n = 38)	P value
Clinical outcome			
No. (%) cure	34 (92)	28 (74)	0.05
No. (%) improvement	2 (5)	3 (8)	
No. (%) failure	1 (3)	7 (18)	
Bacteriologic outcome			
No. (%) eradication	33 (89)	33 (87)	NS
No. (%) negative initial culture	3 (8)	4 (10)	
No. (%) persistence	1 (3)	1 (3)	
Mean duration (range) of fever in days	2.5 (1–5)	2.8 (1–6)	NS
Mean duration (range) of leukocytosis in days	1.8 (1–4)	3.6 (1–6)	0.01
Mean duration (range) of treatment in days	4.7 (3–12)	5.8 (3–14)	NS
No. (%) with adverse events	4 (11)	10 (26)	0.04
Gastrointestinal disturbances	3	8	
Other	1	2	

NS = not significant.

was not studied since cases of pneumonia with organisms such as mycoplasma and viruses, which could be expected to occur more commonly in certain patient populations (24–26), were not evaluated. The study focussed on therapy of community-acquired pneumonia of bacterial etiology in persons requiring hospitalization for acute care.

Demographic features and clinical and laboratory findings in our study population were similar to those described in earlier reports on community acquired pneumonia (4–17, 27, 28). Patients in the two treatment groups were similar in these respects. Advanced age (mean age ≥ 70 years), prior antibiotic therapy to which there was no response (24 %) and underlying cardiorespiratory or metabolic disease (80 %) were common. Severity of illness was similar in the two treatment groups. The etiology of pneumonia remained uncertain in 9 % of patients, despite study inclusion criteria designed to include only patients with bacterial pneumonia. These patients were presumed to represent cases of community-acquired pneumonia caused by atypical respiratory pathogens.

Surprisingly, resistance of pathogens to agents used for therapy of community-acquired pneumonia was common. Beta-lactamase production occurred in 43 % of isolates. The implied increasing resistance in isolates causing pneumonia is disturbing. These high rates of resistance are probably related to the particular species found on culture in this elderly patient population. In addition, many patients studied had serious underlying cardiorespiratory, neoplastic or metabolic disease and had experienced failure of oral antimicrobial outpatient therapy. Such clinical settings contribute to the selection of relatively resistant bacterial strains, and are the setting for many of the types of patients currently admitted to US acute care hospitals for management of pneumonia.

Three percent of patients (one patient in each treatment group) in the present study died. This figure is comparable to the 4 % to 24 % mortality reported in patients hospitalized with community-acquired pneumonia in earlier studies (1, 8, 12, 13, 15, 26, 29). Patients in both treatment groups were comparable with respect to clinical presentation, severity of underlying illness, laboratory and radiographic findings. Ampicillin/sulbactam proved to be significantly ($p = 0.05$) more effective clinically than cefamandole, a satisfactory outcome being obtained in 97 % and 81 % of patients, respectively. The rate of eradication of the pathogen was similar in the two groups. The reasons for these findings could not be determined. The cure rates are similar to those reported in earlier studies of cefamandole in the therapy of pneumonia (30–32). Rapid defervescence and prompt clinical responses were noted in the majority of patients, regardless of treatment group, with a mean duration of therapy needed of only 5.1 days. Serious side effects, superinfections and allergy were infrequent in both groups. Cefamandole was associated with a significantly higher rate (21 % vs. 8 %) of mild gastrointestinal disturbance, however.

The results of this study show that both cefamandole and ampicillin/sulbactam are effective agents for therapy of community-acquired pneumonia, ampicillin/sulbactam showing greater efficacy. Resistance of pathogens to agents used in the treatment of patients with community-acquired pneumonia was common. Cost considerations favor use of agents such as penicillin, ampicillin or erythromycin for empiric therapy. However, broad-spectrum therapy may be desirable as early empiric therapy in certain patient sub-groups which might be at high risk for infection caused by beta-lactamase-producing isolates. These groups include the elderly, patients experiencing failure of oral outpatient regimens, and patients with chronic underlying diseases. We also conclude that for some patients hospitalized with community-acquired pneumonia, only a short course of intravenous antibiotic therapy is necessary.

Acknowledgement

This study was supported in part by the William Beaumont Hospital Research Institute and by Pfizer Roerig Pharmaceuticals, New York, NY.

References

1. **Donowitz GR, Mandell GL:** Empiric therapy for pneumonia. Reviews of Infectious Diseases 1983, Supplement 5: 40–51.
2. **Lode H:** Initial therapy of pneumonia. American Journal of Medicine 1986, 80 Supplement 5C: 70–74.
3. **Finch R, MacFarlane JT, Selkon JD, Watson J, White RJ, Winter JH, Woodhead MA:** Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. British Journal of Hospital Medicine 1993, 49: 346–50.
4. **Berntsson E, Blomberg J, Lagergard T, Trollfors B:** Etiology of community-acquired pneumonia in patients requiring hospitalization. European Journal of Clinical Microbiology 1985, 4: 268–272.

5. **Bently DW:** Bacterial pneumonia in the elderly: clinical features, diagnosis, etiology, and treatment. Gerontology 1984, 30: 297–307.
6. **Berk SL, Wiener SL, Eisner LB, Duncan JW, Smith JK:** Mixed *Streptococcus pneumoniae* and gram-negative bacillary pneumonia in the elderly. Southern Medical Journal 1981, 74: 144–146.
7. **Dorff GJ, Rytel MW, Farmer SG, Scanlon G:** Etiologies and characteristic features of pneumonias in a municipal hospital. American Journal of the Medical Sciences 1973, 266: 349–358.
8. **Ebright JR, Rytel MW:** Bacterial pneumonia in the elderly. Journal of American Geriatrics Society 1980, 28: 220–223.
9. **Griffith DE:** Pneumonia in chronic lung disease. Infectious Disease Clinics of North America 1991, 5: 467–484.
10. **Garb JL, Brown RB, Garb JR, Tuthill RW:** Differences in etiology of pneumonias in nursing homes and community patients. Journal of the American Medical Association 1978, 240: 2169–2172.
11. **Garibaldi RA:** Epidemiology of community-acquired respiratory tract infections in adults. American Journal of Medicine 1985, 78 Supplement 6B: 32–37.
12. **Karnad A, Salvador A, Berk SL:** Pneumonia caused by gram-negative bacilli. American Journal of Medicine 1985, 79 Supplement 1A: 61–67.
13. **Klimek JJ, Ajemian E, Fontecchio S, Gracewski J, Klemas B, Jimenez L:** Community-acquired pneumonia requiring admission to hospital. American Journal of Infection Control 1983, 11: 79–82.
14. **MacFarlane JT, Finch RG, Ward MJ, MacRae AD:** Hospital study of adult community-acquired pneumonia. Lancet 1982; ii: 255–258.
15. **Sullivan RJ, Dowdle WB, Marine MW, Hierholzer JC:** Adult pneumonia in a general hospital. Archives of Internal Medicine 1972, 129: 935–942.
16. **Verghese A, Berk S:** Bacterial pneumonia in the elderly. Medicine 1983, 62: 271–285.
17. **White RJ, Blainey AD, Harrison KJ, Clark SKR:** Causes of pneumonia presenting to a district general hospital. Thorax 1982, 36: 566–570.
18. **Murray PR, Washington JA:** Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clinic Proceedings 1975, 50: 339–344.
19. **McCabe WR, Jackson GG:** Gram-negative bacteremia. I: Etiology and ecology. Archives of Internal Medicine 1962, 110: 847–855.
20. **National Committee for Clinical Laboratory Standards:** Performance standards for clinical laboratory standards. Approved Standard M7-A2, NCCLS, Villanova, PA, 1990.
21. **National Committee for Clinical Laboratory Standards:** Performance standards for microdilution susceptibility tests. Approved Standard M2-A4. NCCLS, Villanova, PA, 1990.
22. **Rhind GB, Gould GA, Ahmad F, Croughan MJ, Calder MA:** *Haemophilus parainfluenzae* and *Haemophilus influenzae* respiratory infections: comparison of clinical features. British Medical Journal 1985, 291: 707–708.
23. **Foweraker JE, Cooke NJ, Hawkey PM:** Ecology of *Haemophilus influenzae* and *Haemophilus parainfluenzae* in sputum and saliva and effects of antibiotics or their distribution in patients with lower respiratory tract infection. Antimicrobial Agents and Chemotherapy 1993, 37: 804–809.
24. **Fekety FR, Caldwell J, Gump D, Johnson JE, Maxson W, Mulholland J, Thoburn R:** Bacteria, viruses, and mycoplasmas in acute pneumonia in adults. American Review Respiratory Disease 1971, 104: 499–507.
25. **Fiala M:** A study of the combined role of viruses, mycoplasmas in acute pneumonia in adults. American Journal of Medicine Science 1969, 257: 44–51.
26. **Larsen RA, Jacobson JA:** Diagnosis of community-acquired pneumonia: experience of a community hospital. Comprehensive Therapy 1984, 10: 20–25.
27. **Karalus NC, Cursons RT, Leng RA, Mahood CB, Rothwell RPG, Hancock B, Cepulis S, Wawatai M, Coleman L:** Community acquired pneumonia: aetiology and prognostic index evaluation. Thorax 1991, 46: 413–418.
28. **Fang GD, Fine MJ, Orloff J, Arisumi D, Yu VL, Kapoor W, Grayston JT, Wang SP, Kohler R, Muder RR, Yee YC, Rihs JD, Vickers RM:** New and emerging etiologies for community acquired pneumonia with implications for therapy. Medicine 1990, 69: 307–316.
29. **Farr BM, Sloman AJ, Fisch MJ:** Predicting death in patients hospitalized for community-acquired pneumonia. Annals of Internal Medicine 1991, 115: 428–436.
30. **Engle JC, Lifland PW, Schleupner CJ:** Comparison of ceftazidime with cefamandole for therapy of community-acquired pneumonia. Antimicrobial Agents and Chemotherapy 1985, 28: 146–148.
31. **Wallace RJ, Niefield SL, Waters S, Waters B, Awe RJ, Wiss K, Martin RR, Greenberg SB:** Comparative trial of cefonicid and cefamandole in the therapy of community-acquired pneumonia. Antimicrobial Agents Chemotherapy 1982, 21: 231–235.
32. **Weber DJ, Calderwood SB, Karchner AW, Pennington JE:** Ampicillin versus cefamandole as initial therapy for community acquired pneumonia. Antimicrobial Agents Chemotherapy 1987, 31: 876–882.