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Comparison of Trimethoprim-Sulfamethoxazole with Ampicillin in Acute Infectious Exacerbations of Chronic Bronchitis: A Double-Blind Crossover Study

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Two separate acute bacterial exacerbations of chronic bronchitis or chronic asthmatic bronchitis were treated in 20 patients in a double-blind crossover study. One course of treatment consisted of 320 mg of trimethoprim (TMP) plus 1,600 mg of sulfamethoxazole (SMZ) daily and the other of 2 g of ampicillin daily; each drug was given for 14 days. Patients were observed initially, twice a week during therapy, and weekly after therapy. Observations that were recorded included graded chest symptoms and physical findings, vital signs, pulmonary function, hematologic parameters, and objective sputum measurements (daily volume, purulence, differential quantitative cytology, quantitative bacterial counts, physical properties, levels of lactate dehydrogenase with its isoenzymes, levels of myeloperoxidase, and presence of deoxyribonucleic acid fibers). Both antibiotic regimens were effective in resolving these acute bacterial exacerbations. Paired *t*-test analysis revealed few and minor differences between TMP-SMZ and ampicillin during therapy, although three patients did not complete TMP-SMZ therapy because of adverse reactions. However, the period between the two bacterial exacerbations was significantly longer after ampicillin therapy. Innovative in this investigation are the study design and the objective quantitative measurements of inflammatory response and bacterial populations in sputum.

Acute bacterial bronchitic exacerbations are important clinical events in chronic bronchitis because of their contribution to morbidity. Although Koch's postulates are difficult to prove in this setting, the overwhelming conclusion based on experience is that treatment with antibiotics is temporally related to clinical recovery. Many antimicrobial agents appear to be effective in treatment of these acute bacterial exacerbations, and trimethoprim-sulfamethoxazole (TMP-SMZ) is among the more recent additions to this list. Like most of these antibiotics, TMP-SMZ has been experimentally demonstrated to be effective in acute bacterial bronchitic exacerbations by means of a limited number of objective measurements in randomly assigned, parallel investigations. To a large extent, the objective criteria of sputum volume, gross sputum purulence, bacterial culture, pulmonary function, and vital signs are only indirect measures of the infectious process. As such, they lack the preciseness needed for the determination of possible differences between alternative methods of therapy.

Methods developed by Chodosh and colleagues have been used to compare the efficacy of various types of antimicrobial therapy in acute bacterial exacerbations of chronic bronchitis. Some of the measurements provide criteria that more closely reflect the level of bronchopulmonary inflammation and the size of bacterial populations. In this study, these criteria were employed to compare the efficacy and safety of TMP-SMZ with the efficacy and safety of ampicillin in the treatment of acute bacterial exacerbations in patients with chronic bronchitis. The crossover design utilized in this double-blind study ensured that the two groups of patients treated were entirely similar.

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Materials and Methods

Selection of patients. Adult outpatients with

chronic bronchitis who developed an acute bronchial infectious exacerbation within two weeks of the initial visit to the clinic were volunteers for this study. Chronic bronchitis, chronic bronchial asthma, and emphysema were diagnosed by use of at least the minimal standards of the American Thoracic Society [1]. All patients were monitored in the clinic. Acute bronchial infectious exacerbations were defined by use of clinical and laboratory criteria. Clinical manifestations included increases in chest congestion, cough, and volume of sputum; changes in gross characteristics of sputum; dyspnea; fever; and chills. Detection of new pulmonary infiltrate on chest X ray excluded any patient from the study. On a patient's initial visit, the cellular composition and bacterial flora of the sputum were determined by use of a wet preparation [2] and a gram stain. The finding of >5% polymorphonuclear eosinophils or swollen bronchial epithelial cells with inclusion bodies excluded the patient from the study. The absence of an increase of bacteria morphologically resembling *Haemophilus influenzae* or *Streptococcus pneumoniae* or the predominance of organisms suggestive of *Pseudomonas*, *Klebsiella*, or *Staphylococcus* species also excluded the patient from the study. Only patients who had not received an antibiotic in the week before the initial visit, who were able to return for the required visits, and who gave their informed consent to be in the experiment were included. Patients who could not complete either of the two courses of therapy were excluded from the analysis.

Design of the study. Patients with the prerequisite criteria were assigned to one of two treatment programs by random selection. Patients were automatically assigned to the other of the two treatment programs if a second infectious exacerbation occurred. The randomization code was unknown to the investigators, patients, and technicians. Placebo capsules and tablets were concomitantly administered so that each dose was entirely similar for each couse of therapy. Both drugs were administered for 14 days. The dosage schedule for ampicillin was one 500-mg capsule four times a day; for TMP-SMZ it was two tablets twice a day, with each tablet containing 80 mag of TMP and 400 mg of SMZ. During each infectious exacerbation, the patient was seen initially (before therapy); at days 3, 7, 10, and 14 (all ±1) during therapy; and at days 7 and 14 after therapy. All other ancillary therapy was continued as regularly as was clinically feasible. Each patient was observed by a single investigator.

Observations. Clinical observations and studies of sputum and pulmonary function were made at each visit. These observations included oral temperature, pulse rate, and respiratory rate. The history of the acute infectious exacerbation was recorded at the initial visit, and the subjective pulmonary symptoms were recorded at each visit by use of a graded system. Frequency of cough in the morning, daytime, evening, and nighttime was reported and assigned a value of 0–20, with 0 signifying no cough, 20 signifying almost continuous cough, and 7 signifying one cough per hour. The average severity of cough was rated 1–20, with 7 representing easily perceptible cough not interfering with activities, 15 representing dizziness with cough, and 20 representing cough syncope. Dyspnea was rated 0–20, with 9 signifying shortness of breath after two flights of stairs and 20 representing shortness of breath at rest. (The scales were subdivided between these given examples.)

The chest examination was limited to six anterior and six posterior areas. Adventitious sounds, intensity of breath sounds, and prolongation of the expiratory phase were recorded with a graded system in which 0 represented a normal finding and 20 the most extreme finding. For each of the adventitious sounds (rales, rhonchi, and wheezes), the sum of the grades on both inspiration and expiration for the 12 auscultated areas was recorded, with a maximal possible score of 480.

The patient's impression of the course of the attack was noted for the interval between each pair of visits. The scale ranged from −7 (very much worse) to 0 (no change) to +7 (very much better), with intermediate changes graded between. The cumulative score over time was used in analysis.

The sputum observations were made with a collection of all material coughed up from deep in the chest during the 24 hr before each visit. After the volume of this material for the 24-hr period was recorded, aliquots were sampled by the method of Chodosh et al. [3]. Only representative material that was seen by microscopy to be of bronchopulmonary origin was used for all subsequent observations. The color of the sputum was graded, with

0 equal to clear, 4 equal to yellow, and 6 equal to green. One aliquot was used for cytologic and gram-stain preparations, a second for biochemical assays, and a third for bacteriologic cultures. The cytologic characteristics of the 24-hr sputum volume were determined qualitatively and quantitatively. The cell concentration was determined by counting in a hemocytometer, and the percentage of each cell type was differentially counted in Papanicolaou-stained sputum smears, as described by Medici and Chodosh [4]. From these values, the numbers of polymorphonuclear neutrophils, bronchial epithelial cells, histiocytes, and eosinophils excreted per day were calculated. Other types of cells were also differentiated, but the data will not be reported here. Average histiocyte size was determined from measurements of at least 50 consecutive cells in mounts of fresh, unfixed sputum.

Levels of L(+)-lactate dehydrogenase (LDH) were measured in duplicate assays with the model DU Beckman spectrophotometer (Beckman Instruments, Fullerton, Calif.) with sodium pyruvate and reduced nicotinamide adenine dinucleotide (NADH) at a pH of 7.4 [5]. The values were reported as μmoles of NADH oxidized/ml of homogenized sputum per min. Levels of isoenzymes of LDH were determined by paper electrophoresis [6]. Levels of myeloperoxidase were determined by a new spectrophotometric method that uses $NADH_2$ and the diorthoquinone-type polyphenol nordihydroguaiaretic acid in 0.05 M phosphate buffer at pH 7.0 and followed at 340 μm (B. Eichel, unpublished observations). DNA fibers were assayed histochemically by fluorescent microscopic examination of acridine orange-stained smears; the relative amount of these fibers was graded on a scale of 0 to 4 [6].

Bacteriologic studies included gram staining and colony counts of specific organisms. From the gram-stained preparations, the average numbers of each morphologic bacterial type per uniform oil-immersion field were determined for 20 adequate oil-immersion fields, as described by Chodosh and Medici [7]. An adequate field was defined as one with at least three cells originating from the bronchopulmonary system but no more such cells than would constitute a single cell layer. Although colony counts were made, the results will not be reported here.

The physical properties of apparent viscosity and adhesiveness were measured by the Chodosh inclined-tube method [8], in which the time-distance relations are measured as the sputum descends the 8° incline. The apparent viscosity factor reflects the internal forces that are keeping the sputum from stretching and is the product of the square of 10 times the slope of the first slow phase times the log of the time of the intercept of this slope at zero distance. The adhesiveness reflects the sticking of the sputum to the tube and is measured as the log of the time (in seconds) required for the sputum to move the first 2 mm down the tube.

The pulmonary function tests at each visit included determination of the forced expiratory flow between 200 and 1,200 cm^3 of the forced vital capacity, the forced expiratory volume in 1 sec, the forced vital capacity, and the slow vital capacity. A pulmonary function recorder spirometer (Airshields, Hatboro, Pa.) was used in these tests.

Statistical analysis. The mean, SD, and SE values for each observation at each visit were calculated. Comparisons between the value before therapy and all subsequent values and between values for the two drugs at each observation time were made by means of paired *t*-tests. Probability values of ≤ 0.05 were considered to be statistically significant. In the statistical tests, log transformations were used for the measurement of cells excreted per day and gram-stain quantitation. The Wilcoxon signed-rank test was used for analysis of the duration of the infection-free period after therapy.

Results

Twenty-one patients received both ampicillin and TMP-SMZ for a total of 42 separate acute infectious exacerbations of bronchitis. One patient had an anaphylactic-like reaction after the first dose of TMP-SMZ; when data for this patient were excluded, 20 pairs of exacerbations remained for use in our analysis. Twelve patients were men and eight were women, with a mean age of 53 years and an age range of 30–78 years. Eighteen of the patients had chronic bronchitis, and two had chronic asthmatic bronchitis; seven patients had associated chronic pulmonary emphysema, and five of the patients with chronic bronchitis also had

chronic bronchial asthma. Eight patients received ampicillin first, and twelve started with TMP-SMZ. For 17 patients the median interval before the next bacterial exacerbation could be determined after treatment with both agents; this interval was 96 days after ampicillin therapy and 62 days after TMP-SMZ therapy. For 13 of these 17 patients, the infection-free period was longer after ampicillin therapy than after TMP-SMZ therapy ($0.05 > P > 0.02$).

The mean and SE values for graded symptoms and physical findings are shown in table 1. The cumulative ratings for changes in the course of recovery from the attack reflected significant improvement between each visit during treatment, regardless of which drug was being used. However, these values were not significantly different for the two drugs. Compared with values before therapy, the frequency of morning cough was significantly reduced starting on day 7 during treatment with either drug; the severity of morning cough was significantly reduced on days 3–21 with TMP-SMZ therapy and on days 7–28 with ampicillin therapy. Dyspnea was significantly reduced only on day 28 with ampicillin therapy. The severity of wheezing was significantly reduced on days 7–21 with TMP-SMZ therapy but only on day 28 with ampicillin therapy. Sputum thickness was significantly reduced beginning on day 7 of therapy with either agent. Vital signs did not change significantly during either type of therapy. Although all adventitious respiratory sounds decreased during therapy, no decrease was significant. The only statistically significant difference between drugs occurred on day 21, when the severity of morning cough was reduced to a greater extent in patients who had taken ampicillin. Adventitious sounds increased (although not significantly) after TMP-SMZ therapy was completed.

Table 1 also shows the results of pulmonary function tests. Although these values increased during ampicillin therapy, the changes were not statistically significant.

Table 2 shows the mean and SE values for findings in sputum: daily volume, gross appearance, specific cells excreted per day, and numbers of specific morphologic types of bacteria per oil-immersion field. Compared with values before therapy, sputum volume was decreased significantly at all observation times starting with day 3 of treatment with either drug. The percentage of sputum that appeared purulent was significantly reduced at the same observation times with ampicillin therapy but only on day 14 with TMP-SMZ therapy. The sputum color became significantly clearer starting on day 3 of therapy with either antibiotic. The number of polymorphonuclear neutrophils excreted in the sputum per day (an estimate of the inflammatory level) decreased significantly starting on day 3 of either type of therapy. The number of histiocytes excreted in the sputum per day (an estimate of host cellular response) did not change significantly, while the average size of histiocytes significantly increased on days 7 and 14 of TMP-SMZ therapy. The number of bronchial epithelial cells excreted in the sputum per day (a measure of mucosal damage) decreased significantly starting on day 3 of TMP-SMZ therapy and on day 10 of ampicillin therapy; bronchial epithelial cells with intracellular bacteria (an indicator of the level of mucosal infection) decreased significantly in number by day 10 of ampicillin therapy and by day 14 of TMP-SMZ therapy and remained reduced. The number of eosinophils excreted in the sputum per day increased significantly on day 10 of TMP-SMZ therapy. The number of *Haemophilus*-like microorganisms was significantly reduced on days 3–28 with ampicillin therapy and on day 3 and days 10–21 with TMP-SMZ therapy. The number of gram-positive pneumococci was significantly reduced on days 3–14 of either type of therapy and on day 28 with ampicillin therapy. Diphtheroid-like microorganisms were significantly reduced in numbers on days 3–14 of ampicillin therapy and on days 7 and 10 of TMP-SMZ therapy. Numbers of *Neisseria*-like microorganisms were significantly reduced on days 3–14 of TMP-SMZ therapy but not with ampicillin therapy. The few isolated differences between drugs did not reflect a persistent trend.

Table 3 shows changes in some biochemical constituents and physical properties of sputum and in peripheral blood. LDH activity of sputum was significantly reduced on days 7–28 with ampicillin therapy and on days 7–14 of TMP-SMZ therapy. The isoenzymes of LDH showed a variable pattern; for example, the activity of isoenzyme 3 was reduced with either drug (on days 7, 10, 21, and 28 with TMP-SMZ therapy and on day 21 with ampicillin therapy), whereas that of isoenzyme 5 did not change significantly with either type of treatment. Myloperoxidase activity in sputum decreased during recovery in the same

Table 1. Changes in symptoms, physical findings, and pulmonary function during treatment of acute bacterial exacerbations of chronic bronchitis with trimethoprim-sulfamethoxazole (TMP-SMZ) or ampicillin.

Observation	Drug	Result on indicated day from initiation of therapy*						
		0	3	7	10	14	21	28
Symptom								
Course of attack (cumulative)	TMP-SMZ	0	3.4 ± 0.6†	7.3 ± 0.7†	9.8 ± 0.6†	12.0 ± 0.5†	13.0 ± 0.8	13.2 ± 0.8
	Ampicillin	0	3.9 ± 0.5†	7.2 ± 0.8†	11.3 ± 0.6†	13.2 ± 0.5†	14.5 ± 0.8	15.2 ± 0.7
Cough frequency (morning)	TMP-SMZ	9.9 ± 1.2	7.1 ± 1.3	5.7 ± 1.1‡	5.5 ± 1.1‡	4.1 ± 0.9‡	5.5 ± 1.1‡§	6.3 ± 1.2‡
	Ampicillin	9.6 ± 1.3	6.8 ± 0.9	5.1 ± 1.1‡	4.6 ± 0.9‡	4.2 ± 0.6‡	2.9 ± 0.7‡§	4.5 ± 1.0‡
Cough severity (morning)	TMP-SMZ	10.9 ± 0.5	7.7 ± 1.1‡	7.2 ± 1.1‡	6.8 ± 1.2‡	6.7 ± 1.0‡	7.1 ± 0.8‡	8.4 ± 1.2
	Ampicillin	9.8 ± 0.9	8.2 ± 0.9	6.8 ± 1.0‡	6.8 ± 0.9‡	7.3 ± 0.8‡	5.2 ± 1.0‡	6.8 ± 1.0‡
Dyspnea	TMP-SMZ	10.7 ± 1.0	9.6 ± 0.9	9.5 ± 1.0	9.6 ± 1.0	8.3 ± 1.0	8.5 ± 1.0	9.2 ± 1.1
	Ampicillin	10.4 ± 1.1	9.1 ± 1.1	9.2 ± 1.1	8.2 ± 1.2	7.6 ± 1.1	7.2 ± 1.2	6.6 ± 1.3‡
Wheeze severity	TMP-SMZ	4.6 ± 0.8	3.0 ± 0.7	2.2 ± 0.6‡	1.7 ± 0.5‡	1.3 ± 0.5‡	1.6 ± 0.5‡	2.7 ± 0.9
	Ampicillin	3.3 ± 0.6	2.4 ± 0.7	2.3 ± 0.9	2.3 ± 0.9	1.5 ± 0.7	1.5 ± 0.8	1.3 ± 0.7‡
Sputum thickness	TMP-SMZ	14.0 ± 0.7	15.1 ± 2.1	10.3 ± 0.6‡	10.5 ± 0.7‡	9.7 ± 0.8‡	9.4 ± 0.9‡	9.8 ± 1.0‡
	Ampicillin	13.5 ± 0.6	11.8 ± 0.6	10.8 ± 0.7‡	10.2 ± 0.9‡	9.9 ± 0.9‡	9.6 ± 0.9‡	10.1 ± 0.9‡
Physical finding								
Rales	TMP-SMZ	6.8 ± 2.8	5.9 ± 2.3	2.5 ± 1.8	3.5 ± 1.4	3.9 ± 2.1	5.7 ± 2.3	8.4 ± 4.5
	Ampicillin	9.2 ± 3.8	7.1 ± 3.0	4.2 ± 3.2	6.7 ± 2.9	6.9 ± 3.8	2.1 ± 1.0	6.3 ± 2.6
Rhonchi	TMP-SMZ	13.9 ± 3.8	6.1 ± 2.1	10.7 ± 3.7	13.3 ± 7.4	10.5 ± 3.2	9.1 ± 5.9	12.7 ± 6.1
	Ampicillin	18.5 ± 7.3	8.6 ± 3.4	7.7 ± 2.3	5.7 ± 1.8	10.6 ± 4.0	13.8 ± 4.9	4.2 ± 1.5
Wheeze	TMP-SMZ	48.3 ± 14.3	36.8 ± 15.1	38.3 ± 16.1	18.7 ± 11.2	25.1 ± 11.3	20.2 ± 9.2	40.7 ± 15.0
	Ampicillin	24.8 ± 10.7	28.2 ± 10.1	23.5 ± 11.8	19.0 ± 7.1	27.2 ± 11.9	12.1 ± 8.3	25.6 ± 9.9
Pulse rate (per minute)	TMP-SMZ	90.0 ± 3.6	78.7 ± 5.0	86.6 ± 3.2	84.4 ± 3.6	85.1 ± 2.6	80.0 ± 5.0	85.5 ± 3.0
	Ampicillin	96.2 ± 4.0	89.1 ± 2.1	90.1 ± 2.1	84.6 ± 5.4	91.0 ± 3.7	87.7 ± 2.9	89.6 ± 2.9
Pulmonary function‖								
FEV_1	TMP-SMZ	1.09 ± 0.13	1.04 ± 0.13	1.13 ± 0.13	1.15 ± 0.13	1.14 ± 0.14	1.18 ± 0.14	1.08 ± 0.12
	Ampicillin	1.12 ± 0.15	1.13 ± 0.13	1.22 ± 0.16	1.30 ± 0.16	1.28 ± 0.16	1.27 ± 0.15	1.11 ± 0.17
$FEF_{200-1,200}$	TMP-SMZ	62.0 ± 15.2	53.2 ± 12.6	63.0 ± 15.5	71.1 ± 16.3	60.9 ± 14.7	72.9 ± 17.9	59.2 ± 15.0
	Ampicillin	67.6 ± 19.6	76.9 ± 21.4	85.3 ± 23.1	103.4 ± 29.4	87.2 ± 21.9	89.5 ± 21.2	69.4 ± 19.4

NOTE. Twenty patients received each regimen for separate exacerbations in a double-blind crossover study.

* Values given are means ± SE. Results for all symptoms and for all physical findings except pulse rate are graded scores, as described in Materials and Methods. Values for day 0 were obtained just before initiation of therapy; those for days 3, 7, 10, and 14, during therapy; and those for days 21 and 28, after therapy.

† $P \leq 0.05$ compared with value at previous visit.

‡ $P \leq 0.05$ compared with value before therapy (day 0).

§ $P \leq 0.05$ between value for TMP-SMZ and that for ampicillin.

‖ FEV_1 = forced expiratory volume in 1 sec (liters); $FEF_{200-1,200}$ = forced expiratory flow between 200 and 1,200 cm^3 of the forced vital capacity (liters/min).

Table 2. Changes in sputum findings during treatment of acute bacterial exacerbations of chronic bronchitis with trimethoprim-sulfamethoxazole (TMP-SMZ) or ampicillin.

Observation in sputum	Drug	Result on indicated day from initiation of therapy*						
		0	3	7	10	14	21	28
Volume (ml/day)	TMP-SMZ	34.6 ± 5.8	18.9 ± 3.4†	14.4 ± 2.5†	16.7 ± 3.3†	14.6 ± 2.5†	13.0 ± 2.3†	15.5 ± 3.2†
	Ampicillin	36.8 ± 6.2	21.6 ± 2.5†	20.1 ± 4.0†	14.4 ± 2.8†	13.5 ± 2.5†	10.8 ± 1.8†	16.7 ± 3.3†
Purulence (%)	TMP-SMZ	77 ± 2	77 ± 3	71 ± 3	69 ± 5	69 ± 3†	73 ± 3‡	69 ± 5
	Ampicillin	81 ± 2	72 ± 3†	66 ± 4†	66 ± 5†	66 ± 5†	59 ± 6†	70 ± 3†
Color§	TMP-SMZ	4.7 ± 0.3	3.7 ± 0.2†	3.5 ± 0.2†	2.8 ± 0.2†	2.8 ± 0.2†	3.1 ± 0.2†	3.5 ± 0.4†
	Ampicillin	4.6 ± 0.3	3.6 ± 0.3†	2.8 ± 0.3†	3.2 ± 0.3†	3.0 ± 0.3†	2.9 ± 0.4†	3.4 ± 0.3†
Neutrophils	TMP-SMZ	574 ± 137	211 ± 83†	76 ± 22†	103 ± 34†	82 ± 24†	86 ± 26†	177 ± 47†
(per day × 10^6)	Ampicillin	726 ± 218	242 ± 62†	144 ± 30†	59 ± 16†	83 ± 20†	103 ± 33†	138 ± 47†
Histiocyte size	TMP-SMZ	2,980 ± 323	3,602 ± 457	4,110 ± 430†	3,920 ± 397	4,730 ± 691†	3,950 ± 437	3,420 ± 229
(average in μm^3)	Ampicillin	3,780 ± 377	3,810 ± 378	4,470 ± 376	3,860 ± 394	4,520 ± 547	4,200 ± 322	3,380 ± 350
Histiocytes	TMP-SMZ	8.2 ± 1.7	8.3 ± 2.6	4.8 ± 1.3	7.9 ± 3.1	6.1 ± 1.8	3.5 ± 1.1	7.5 ± 3.0
(per day × 10^6)	Ampicillin	6.6 ± 2.4	8.6 ± 2.0	8.1 ± 1.9	6.4 ± 1.9	8.6 ± 2.5	5.2 ± 1.3	4.6 ± 1.6
Bronchial epithelial	TMP-SMZ	64.7 ± 13.6	27.7 ± 7.7†	18.4 ± 5.9†	24.4 ± 7.4†	15.2 ± 4.6†	12.9 ± 5.5†	19.6 ± 5.3†
cells (per day × 10^6)	Ampicillin	61.6 ± 16.7	30.2 ± 6.1	27.4 ± 5.9	12.4 ± 3.5†	13.7 ± 3.6†	14.9 ± 4.6†	19.3 ± 5.7†
Bronchial epithelial	TMP-SMZ	8.0 ± 1.5	19.9 ± 14.7	6.5 ± 2.8	5.4 ± 2.4	2.6 ± 0.7†	3.3 ± 1.2†	2.9 ± 0.7†
cells with bacteria	Ampicillin	8.8 ± 1.9	6.9 ± 1.7	6.5 ± 2.2	2.9 ± 0.7†	3.1 ± 0.8†	2.5 ± 0.6†	4.0 ± 1.1†
(per day × 10^6)								
Eosinophils	TMP-SMZ	0.38 ± 0.16	0.58 ± 0.28	5.60 ± 4.58	1.29 ± 0.41†‡	2.67 ± 1.42	0.79 ± 0.23	1.05 ± 0.54
(per day × 10^6)	Ampicillin	1.04 ± 0.41	1.47 ± 0.69	2.67 ± 1.18	0.28 ± 0.11	0.73 ± 0.38	0.54 ± 0.20	3.41 ± 1.80
Haemophilus-like	TMP-SMZ	31.34 ± 10.23	1.32 ± 0.29†	7.22 ± 7.00	0.75 ± 0.46†	6.81 ± 6.48†	5.83 ± 4.10†	10.90 ± 5.44
microorganisms‖	Ampicillin	29.73 ± 8.36	3.99 ± 2.85†	1.18 ± 0.94†	0.77 ± 0.31†	1.26 ± 0.81†	6.36 ± 4.38†	7.04 ± 5.99†
Gram-positive	TMP-SMZ	3.43 ± 1.24	0.39 ± 0.12†‡	0.23 ± 0.07†	0.20 ± 0.08†	0.29 ± 0.07†	1.00 ± 0.48	3.88 ± 2.08
pneumococci	Ampicillin	4.97 ± 1.56	0.12 ± 0.04†	0.10 ± 0.02†	0.23 ± 0.07†	0.19 ± 0.06†	1.81 ± 0.61	1.51 ± 0.52†
Diphtheroid-like	TMP-SMZ	2.90 ± 1.25	0.38 ± 0.19	0.29 ± 0.15†	0.10 ± 0.04†	0.52 ± 0.13	0.65 ± 0.29	0.59 ± 0.19
microorganisms‖	Ampicillin	1.60 ± 0.66	0.14 ± 0.06†	0.19 ± 0.12†	0.05 ± 0.02†	0.21 ± 0.13†	1.03 ± 0.67	0.70 ± 0.32
Neisseria-like	TMP-SMZ	17.79 ± 8.19	0.19 ± 0.05†	0.19 ± 0.08†	0.37 ± 0.22†	0.27 ± 0.15†	1.63 ± 1.19	3.34 ± 1.94
microorganisms‖	Ampicillin	3.73 ± 1.80	0.44 ± 0.20	0.29 ± 0.11	2.28 ± 1.87	0.36 ± 0.15	2.51 ± 2.22	2.12 ± 1.86

NOTE. Twenty patients received each regimen for separate exacerbations in a double-blind crossover study.

* Values given are means ± SE. Results are expressed as indicated in far left column. Values for day 0 were obtained just before initiation of therapy; those for days 3, 7, 10, and 14, during therapy; and those for days 21 and 28, after therapy.

† $P \leq 0.05$ compared with value before therapy (day 0).

‡ $P \leq 0.05$ between value for TMP-SMZ and that for ampicillin.

§ Results are graded scores: 0 = clear; 4 = yellow; 6 = green.

‖ Results are expressed as numbers of microorganisms per oil-immersion field in gram-stained preparations.

pattern as was noted for LDH. Values for DNA fibers in sputum were decreased during and after therapy, but not significantly. Physical properties of sputum, measured by the inclined tube method, did not change significantly except for a decrease in adhesiveness on day 28 with ampicillin therapy. The white blood cell count in peripheral blood decreased significantly on days 7–21 with TMP-SMZ therapy and on day 7 and days 14–28 with ampicillin therapy, although all of the mean values were within the normal range. The platelet count decreased significantly on day 3 and days 10–28 with ampicillin therapy and on days 14 and 21 with TMP-SMZ therapy. Levels of hemoglobin decreased significantly only on day 21 with TMP-SMZ therapy.

Table 4 lists the adverse reactions described as probably or possibly related to TMP-SMZ and ampicillin. Diarrhea was more commonly noted during therapy with ampicillin. All 21 patients completed the prescribed course of ampicillin, but three patients discontinued TMP-SMZ therapy because of adverse reactions. One patient stopped taking TMP-SMZ after a single dose because of an anaphylactic-like reaction, a second because of a painful cracked tongue, and a third because of nausea and vomiting. The number of patients with adverse reactions and the number of reactions were otherwise similar for the two drugs.

Discussion

This investigation confirmed the efficacy of TMP-SMZ, as noted by other investigators, in the treatment of acute bacterial exacerbations of chronic bronchitis. However, the expectation, based on our earlier report [9], that TMP-SMZ might be more efficacious than ampicillin was not realized. Various ratios of TMP and SMZ employed by other investigators have been found to be comparable or superior to other commonly used antibiotics for the treatment of acute bacterial bronchitic exacerbations. Drew et al. [10] used a total daily dose of 500 mg of TMP plus 1,000 mg of SMZ for cases in which other types of treatment had failed; the results were uniformly successful. In another study, Bam and co-workers [11] obtained comparable results with total daily doses of either 160 mg of TMP plus 800 mg of SMZ or 600 mg of methacycline. Other investigators [12–14] used 320 mg of TMP plus 1,600 mg of SMZ daily and compared the results with those of either ampicillin or tetracycline therapy. In general, this dosage of TMP-SMZ was more effective than the other agents. Pines [15] further demonstrated that 480 mg of TMP plus 2,400 mg of SMZ was significantly more effective than tetracycline. Investigations by Hughes et al. [16] and Pines et al. [17] of different dosages of TMP-SMZ indicate that a total daily dosage of either 500 mg of TMP plus 1,000 mg of SMZ or 480 mg of TMP plus 2,400 mg of SMZ was more effective than the dosage of 320 mg of TMP plus 1,600 mg of SMZ used in the present investigation; however, the latter dosage was more effective than a dosage of 200 mg of TMP plus 2,000 mg of SMZ. It would appear from these data that the dose of TMP is related to the degree of efficacy of treatment.

The results of the present investigation support the comparability of effectiveness of TMP-SMZ and that of ampicillin during the active treatment period. However, changes during the observation period after therapy suggested that the effects of accepted dosages of TMP-SMZ are not as persistent as those of ampicillin. Although these changes were not significant compared with baseline values, increases of cough severity, rales, rhonchi, wheezing, and bacterial numbers were noted 14 days after discontinuation of TMP-SMZ therapy. Since the majority of the patients in this study had new bacterial exacerbations sooner after TMP-SMZ therapy than after ampicillin therapy, it is possible that these changes in the two weeks after therapy had some predictive value.

A number of important factors influence the choice of therapy for acute exacerbations of chronic bronchitis. First, the probable etiology of the exacerbation must be ascertained. If the etiology is bacterial, the next consideration is the selection of the antimicrobial agent most likely to elicit a prompt response and to exert a sustained suppressive effect that will prolong the infection-free period. Other considerations relate to compliance of the patient with the regimen. The level of toxicity of the drug should be low, and the dosage schedule should be conducive to compliance. The overall goal is to reduce morbidity among these chronically ill patients. The design of investigations of the efficacy of antimicrobial agents in acute bacterial exacerbations of chronic bronchitis should promote as objective an assessment of these factors as possible.

Judgments about the efficacy of antibacterial

Table 3. Changes in sputum and blood during treatment of acute bacterial exacerbations of chronic bronchitis with trimethoprim-sulfamethoxazole (TMP-SMZ) or ampicillin.

Observation	Drug	Result on indicated day from initiation of therapy*						
		0	3	7	10	14	21	28
Sputum								
Lactate dehydrogenase (LDH)†	TMP-SMZ	48.1 ± 15.7	18.6 ± 4.7	12.9 ± 2.4‡	7.6 ± 1.9‡	13.6 ± 5.4‡	15.4 ± 5.4	17.3 ± 5.6
	Ampicillin	49.3 ± 14.4	24.7 ± 6.3	10.5 ± 1.9‡	9.9 ± 3.0‡	9.7 ± 3.0‡	7.2 ± 1.9‡	13.3 ± 3.5‡
LDH isoenzyme 3 (% of total LDH)	TMP-SMZ	11.2 ± 1.8	8.1 ± 1.4	4.2 ± 1.3‡	4.1 ± 1.4‡	8.8 ± 2.1	4.6 ± 1.5‡	5.4 ± 1.9‡
	Ampicillin	7.9 ± 1.5	6.3 ± 1.2	6.8 ± 1.3	4.5 ± 1.5	4.5 ± 1.3	3.7 ± 1.2‡	5.5 ± 1.4
LDH isoenzyme 5 (% of total LDH)	TMP-SMZ	58.8 ± 4.6	64.0 ± 4.4	69.4 ± 6.7	49.5 ± 9.0	43.7 ± 6.9	52.2 ± 8.2	49.5 ± 9.4
	Ampicillin	58.0 ± 5.5	60.0 ± 6.8	53.0 ± 6.6	52.3 ± 7.7	53.6 ± 8.1	45.7 ± 9.2	54.5 ± 8.5
DNA fibers§	TMP-SMZ	1.27 ± 0.27	1.30 ± 0.28	1.09 ± 0.24	1.07 ± 0.22	1.07 ± 0.24	0.92 ± 0.23	0.74 ± 0.23
	Ampicillin	1.08 ± 0.27	1.00 ± 0.22	0.97 ± 0.24	0.65 ± 0.22	0.92 ± 0.23	0.73 ± 0.22	0.91 ± 0.23
Apparent viscosity factor§	TMP-SMZ	1.24 ± 0.33	1.30 ± 0.42	1.02 ± 0.34	1.13 ± 0.35	1.18 ± 0.58	1.87 ± 1.00	0.99 ± 0.28
	Ampicillin	1.46 ± 0.55	1.35 ± 0.41	1.37 ± 0.49	1.38 ± 0.45	1.33 ± 0.40	1.49 ± 1.03	0.59 ± 0.14
Adhesiveness (log of time in sec at 8 mm)§	TMP-SMZ	2.80 ± 0.26	2.72 ± 0.20	2.58 ± 0.30	2.80 ± 0.23	2.75 ± 0.24	2.31 ± 0.34	2.16 ± 0.28
	Ampicillin	2.44 ± 0.26	2.58 ± 0.17	2.12 ± 0.28	2.23 ± 0.25	2.54 ± 0.35	2.12 ± 0.35	1.68 ± 0.25‡
Blood								
Hemoglobin (g/100 ml)	TMP-SMZ	14.2 ± 0.4	13.6 ± 0.5	13.5 ± 0.4	13.5 ± 0.4	13.1 ± 0.4	12.9 ± 0.4‡	13.6 ± 0.4
	Ampicillin	13.9 ± 0.4	13.5 ± 0.3	13.5 ± 0.4	13.4 ± 0.4	13.4 ± 0.3	13.6 ± 0.3	13.4 ± 0.4
White blood cells (per mm^3)	TMP-SMZ	7,580 ± 410	6,780 ± 400	6,160 ± 320‡	5,640 ± 260‡	5,920 ± 190‡	6,230 ± 420‡	9,920 ± 19
	Ampicillin	8,500 ± 810	7,250 ± 580	6,670 ± 420‡	6,710 ± 370	6,390 ± 350‡	6,230 ± 350‡	6,370 ± 400‡
Platelets (per $mm^3 \times 10^3$)	TMP-SMZ	244 ± 15	229 ± 20	203 ± 16	196 ± 19	200 ± 15‡	191 ± 11‡	240 ± 19
	Ampicillin	256 ± 12	203 ± 13‡	294 ± 21	195 ± 16‡	183 ± 13‡	199 ± 9‡	209 ± 10‡

NOTE. Twenty patients received each regimen for separate exacerbations in a double-blind crossover study.

* Values given are means ± SE. Results are expressed as indicated in the far left column. Values for day 0 were obtained just before initiation of therapy; those for days 3, 7, 10, and 14, during therapy; and those for days 21 and 28, after therapy.

† Results are expressed as μmoles of reduced nicotinamide adenine dinucleotide oxidized/ml of sputum.

‡ $P \leq 0.05$ compared with value before therapy (day 0).

§ Results are expressed in arbitrary units, as described in Materials and Methods.

agents should be made only on the basis of results with patients who clearly have acute bacterial exacerbations of chronic bronchitis. The common clinical practice of presumptively diagnosing bacterial infection based on acute worsening of chest symptoms is an insufficiently precise means of selecting appropriate subjects for investigations. The symptoms of increased cough, chest congestion, change of sputum color to yellow or green, increased dyspnea, feverishness, and malaise are not specific to bacterial infection. Nonbacterial infection, allergy, and secretion clearance problems are frequently the basis for this clinical syndrome. The diagnosis of bacterial infection should be based on objective evidence of increased bacterial flora and increased inflammatory level [18, 19]. These conditions are best determined by direct observation of the sputum.

The criterion for increased bacterial flora is the observation of at least 8, 15, or 25 pneumococcus-like, *Haemophilus*-like, or mixed organisms, respectively, per oil-immersion field in a gram-stained preparation of sputum. Most investigators have depended on the recovery of potential pathogens from cultures for estimation of the bacterial flora, but in our studies this criterion has been less specific than gram-stain criteria. Even careful quantitative colony counts of each bacterial type are only poorly correlated with both the clinical course and the gram-stain observations. Pathogens from the resident flora in the bronchi or the oropharynx are frequently recovered from the sputum of patients with chronic bronchitis, even when their condition is stable.

The level of inflammation in the bronchial tree can be directly assessed by a determination of the number of polymorphonuclear neutrophils excreted in the sputum per day. This value is dependent on the volume of exudate and secretions produced by the lung, on the concentration of cells in this sputum, and on the percentage of these cells that are neutrophils. Investigators who depend on only one or two of these determinants of the inflammatory level are accepting an undesirably high margin of error in the selection of appropriate subjects. Also, unless the level of inflammation before infection has been documented, any change becomes a matter of subjective interpretation. Other investigators have used criteria that indirectly measure the neutrophilic inflammatory level of the lung, such as the purulence, levels of LDH, and presence of DNA in the sputum. These determinations may be correlated with the degree of inflammation, but because they are not very specific an additional source of error in the selection of subjects is introduced.

These basic prerequisites for inclusion in an evaluation of antimicrobial efficacy have been adhered to in the present investigation. With effective antibacterial therapy, these objective findings, as well as the subjective symptoms, should improve. A decrease of the bacterial numbers seen in gram-stained preparations should precede the decrease of sputum inflammatory level, and this decrease in the bacterial population should persist after therapy is discontinued. The subjective

Table 4. Adverse reactions noted during treatment of acute bacterial exacerbations of chronic bronchitis in 21 patients with trimethoprim-sulfamethoxazole (TMP-SMZ) or ampicillin.

	No. of patients with reaction to indicated regimen*	
Reaction	TMP-SMZ	Ampicillin
Painful, cracked, or burning tongue	4	3
Sore mouth	2	1
Dry lips	1	1
Nausea	5	5
Vomiting	4	2
Epigastric pain or heartburn	2	1
Anorexia	0	1
Eructation	0	1
Diarrhea or loose stools	2	8
Constipation	1	0
Abdominal pain	1	0
Flatulence	2	0
Bronchospasm (anaphylactic-like)	1	0
Photophobia or painful eyes	1	1
Vaginitis	0	1
Weakness	0	1
Nervousness	1	0
Exacerbation of gouty arthritis	0	1
Total	27	27

* Each patient experienced at least two acute bacterial bronchitic exacerbations, one of which was treated with TMP-SMZ and the other with ampicillin. A total of 12 patients had one or more adverse reactions to TMP-SMZ, and 13 patients had such reactions to ampicillin. Three patients discontinued treatment with TMP-SMZ because of adverse reactions.

symptoms should also return to the stable levels noted prior to the acute exacerbation.

The methodology developed for objective measurements in sputum and for the more critical clinical observations has permitted definitive comparison of antibacterial agents in the treatment of acute bacterial exacerbations of chronic bronchitis. The same techniques have been used to study allergic bronchial inflammation in asthma [20] as well as in other sputum-producing lung diseases [21]. Indeed, the sputum produced in a variety of bronchopulmonary diseases provides an unusual opportunity to study the myriad aspects of the inflammatory process virtually in vivo at the human level. Some of the sputum observations in this investigation offer insight into the inflammatory process during an infectious insult to the bronchial tree. For example, the extent of the bacterial infectious process can be assessed by a determination of the number of exfoliated bronchial epithelial cells containing intracellular bacteria. The decrease during therapy coincides with clinical and objective improvement. Although viability of these bacteria cannot be determined by the methods used in this study, their presence at the end of therapy lends support to the observation of Hers [22] that *H. influenzae* was recovered from mucosal biopsies at the end of a course of antibacterial therapy. The persistence of bacteria in the bronchial mucosa is consistent with the assumption that available antibacterial agents are capable of reducing but not eliminating the bacterial load in the lung tissue. The recurrence of acute bacterial infections in the patients in this study may well be attributable to this resident population of bacteria, but the evidence does not exclude the etiologic importance of newly inhaled bacteria.

The changes in the number of bronchial histiocytes provide a measure of how closely the acute inflammatory process is actually paralleling the expected progression. The expected increase in the number of macrophages as the number of neutrophils decreases during recovery was not demonstrated in this group of patients. However, the size of bronchial histiocytes did increase during recovery from the bronchial infection. This observation is consistent with the entry of small macrophages into the bronchial exudate during active infection—probably as blood monocytes whose protoplasmic mass increases with their phagocytic activity.

LDH activity in sputum has been used by other investigators as a measure of inflammation [6]. The decrease of LDH activity noted during recovery is consistent with the observations of these investigators, but the difference in the responses of the various LDH isoenzymes appears to be a new finding. Although the total activity of LDH decreases with recovery, the percentage of LDH isoenzyme 5 remains consistent throughout the course of the attack, while the percentage of isoenzyme 3 decreases. The cellular source of these isoenzymes in sputum and the basis for this difference are not known. The relative distribution of the isoenzymes in sputum is different from the pattern observed in blood.

Sputum myeloperoxidase is thought to represent the peroxidase of polymorphonuclear leukocytes important in intracellular bacterial killing. In our patients, myeloperoxidase activity decreased during recovery in the same pattern as was noted for LDH. The decrease was not proportional to the total number of sputum neutrophils—a fact suggesting that the relation of myeloperoxidase to polymorphonuclear leukocytes needs to be more carefully examined.

Other investigators have used the number of DNA fibers in sputum as an index of inflammation [6]. As measured by the technique used here, these fibers reflect the amount of cellular breakdown. The results of the current investigation do not support the significant decrease in the number of DNA fibers reported by others, although the values did decrease with recovery.

Measurement of physical properties of sputum—e.g., apparent viscosity and adhesiveness—does not confirm the subjective impression of patients that their sputum becomes thinner during recovery. It is possible that patients relate other changes in their sputum to thickness or that the method for measuring these factors in sputum is inadequate to detect changes [8].

The results of this investigation suggest that the use of some definitive and some subtle objective measurements facilitates the comparison of antibacterial drugs in this clinical setting. The use of each patient as his or her own control also makes

the assessment more reliable. In addition, mechanisms of the inflammatory process can be examined at the human level.

Results of the comparison of TMP-SMZ and ampicillin in this investigation appear to favor ampicillin in that the duration of the infection-free period was longer after ampicillin therapy and the adverse reactions to TMP-SMZ were more substantive clinically. The literature suggests that use of a higher daily dose of TMP-SMZ might have resulted in a better response to this agent.

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