Trimethoprim-sulfamethoxazole in chronic bronchitis

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Summary: Authentic tracheobronchial secretions / exudates (TBSE) were aspirated under direct vision via a sterile catheter passed through a fiberoptic bronchoscope from patients with chronic obstructive pulmonary disease complicated by chronic bronchitis. TBSE, saliva and blood were obtained during long-term administration of trimethoprim-sulfamethoxazole (TMP-SMX) and were assayed for drug content. Before and during treatment TBSE were cultured qualitatively and quantitatively for aerobic and anaerobic bacteria, fungi, mycoplasmas and viruses. Treatment with TMP-SMX was associated with a decrease in the recovery of *Hemophilus influenzae, H. parainfluenzae, Klebsiella pneumoniae, Escherichia coli* and *Proteus mirabilis;* however, little effect was observed on the typically nonpathogenic aerobic and anaerobic bacteria of the upper respiratory tract. TMP was found in saliva at concentrations greater than in serum. Both TMP and SMX entered TBSE in absolute and relative concentrations sufficient to take advantage of the potential for synergy against susceptible microorganisms. Patient tolerance of TMP-SMX was generally good and several patients reported a decrease in production of sputum during treatment.

Résumé: *Le triméthoprime-sulfaméthoxazole dans la bronchite chronique*

Sous vision directe, par un cathéter stérile introduit dans un bronchoscope à fibres optiques, nous avons aspiré des sécrétions et des exsudats trachéobronchiques (SETB) chez des malades souffrant de pneumopathies obstructives chroniques compliquées de bronchite chronique. Les SETB, la salive et le sang ont été prélevés au cours de l'administration à long terme de triméthoprime-sulfaméthoxazole (TMP-SMX) et ont été soumis aux essais biologiques quant à leur teneur en médicament. Avant et pendant le traitement nous avons cultivé les SETB, au double point de vue qualitatif et quantitatif, à la recherche de bactéries aérobies et anaérobies, de fongus, de mycoplasmes et de virus. Le traitement au TMP-SMX a eu pour résultat de diminuer la récupération des organismes suivants: *Hemophilus influenzae, H. parainfluenzae, Klebsiella pneumoniae, Escherichia coli* et *Proteus mirabilis.* Il n'a cependant eu guère d'effet sur les bactéries aerobies et anaérobies typiquement nonpathogènes des voies respiratoires supérieures. Nous avons décélé le TMP dans la salive à des concentrations supérieures à celles du sérum. Et le TMP et le SMX ont pénétré dans les SETB à des concentrations absolues et relatives suffisantes pour tirer parti du potentiel synergique des deux composants contre des microorganismes sensibles à leur action. La tolérance des malades au TMP-SMX a été généralement bonne et plusieurs malades ont signalé une réduction du volume des crachats pendant le traitement.

Both the frequency and the severity of bacterial lower respiratory tract infections are increased in patients with chronic obstructive pulmonary disease (COPD). Moreover, persistent infection, as chronic bronchitis, and acute exacerbations of infection, as acute bronchitis and/or bronchopneumonia, contribute to the progression of COPD.

The bacterial flora of the tracheobronchial tree of patients with COPD appears to be derived from the flora of the mouth and upper respiratory tract as aerosols of secretions containing microorganisms which are inhaled but are not removed because of compromised pulmonary defences. Antimicrobials may be of value in patients with chronic bronchitis complicating COPD (CB/COPD) if conventional dosage yields concentrations in tracheobronchial secretions/exudates (TBSE) that are active against the bacteria that are present in TBSE.

Authentic specimens of TBSE were obtained from patients with CB/COPD using the flexible fiberoptic bronchoscope. The microbial flora and the concentrations of antimicrobials were assessed before and during long-term treatment with trimethoprim-sulfamethoxazole (TMP-SMX).

Materials and methods

Patient population

Ambulatory adults of both sexes were accepted for study if they gave a history of chronic sputum production (at least 2 teaspoonsful per day for at least 4 days per week during 3 months of the year for 2 years) and showed pulmonary dysfunction by standard spirometry and lung volume determinations but lacked fever and had no infiltrative pulmonary disease by radiography. The patients must not have taken any antimicrobials for at least 2 weeks prior to entry into the study. The study group was composed predominantly of elderly white men with an average age of 57 years (Table I).

Excluded from the study were all women who were pregnant or nursing. Any patient with a suspected or known idiosyncratic or allergic reaction to the antimicrobials under study was excluded, as were any patients with renal insufficiency (as evidenced by an elevation of the serum creatinine concentration) or with abnormal liver function (as evidenced by an elevated serum glutamic oxaloacetic transaminase [SGOT] concentration). The study was explained fully and signed informed consent was obtained from all participants.

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Baseline evaluation

Baseline studies done prior to the administration of TMP-SMX included: chest radiography, pulmonary function tests (PFT), measurement of arterial blood gases (ABG), complete blood count (CBC), differential count, platelet count (determined by presence on smear), measurement of serum sodium, potassium, chloride, glucose, total protein, albumin, calcium, inorganic phosphate, cholesterol, uric acid, creatinine, total bilirubin, alkaline phosphatase, creatine phosphokinase (CPK), lactic dehydrogenase (LDH) and SGOT, and blood urea nitrogen (BUN), urinalysis and bronchoscopy. Before and during treatment with TMP-SMX, TBSE were collected for qualitative and quantitative, aerobic and anaerobic cultures for bacteria and fungi. Some specimens were also cultured for viruses and mycoplasmas. TBSE, saliva and serum specimens were assayed for content of TMP-SMX by Burroughs Wellcome Laboratories (laboratory of S.R.M. Bushby, PhD).

Study

Following baseline evaluations two tablets (provided as Septra by the Burroughs Wellcome Company), each containing trimethoprim, 80 mg and sulfamethoxazole, 400 mg, were taken twice each day.

Patients were evaluated after 3, 6 and 12 weeks as to sputum production, dyspnea on exertion, auscultatory findings and faithfulness in taking TMP-SMX. Patient compliance was generally good as reported on follow-up visits and as indicated by blood and TBSE drug concentrations obtained during the study. In addition, laboratory studies of blood and TBSE (obtained by bronchoscopy) were carried out.

Collection of tracheobronchial secretions/exudates

Ingestion of food was proscribed from midnight prior to the morning of bronchoscopy; the morning dose of TMP-SMX was allowed. Local anesthesia was achieved with 0.25 ml of 2% lidocaine to the nares, and 2 to 4 ml of 4% lidocaine applied to the oropharynx and vocal cords via a hand nebulizer. The first 10 patients were then intubated and a flexible fiberoptic bronchoscope (Olympus, model #BF-5B2, New Hyde Park, New York) was passed through the endotracheal tube. The remaining patients were not intubated before the bronchoscope was passed. Patients were positioned in right lateral decubitus with the head lower than the feet. TBSE were then aspirated under direct vision via a sterile catheter passed through the lumen of the bronchoscope. The left mainstem bronchus was sampled first; if the specimen was insufficient, TBSE were collected from the carina. TBSE were collected in sterile disposable Lukens traps and were processed within 15 minutes after collection.

Cultures

Specimens were transferred to sterile rubber-stoppered tubes containing 10 to 15 glass beads. After homogenization by shaking for 2 to 5 minutes, aliquots were removed and decimal dilutions were made for quantitative cultures by use of an anaerobically sterilized 0.9% NaCl solution.

Aerobic cultures were planted quantitatively on 5% sheep blood, phenethyl alcohol-blood, chocolate, MacConkey, Thayer-Martin, Fildes peptic digest of blood and Sabouraud glucose agars. The plates were incubated in candle jars at 35°C; if no growth occurred after 1 week, the plates were discarded. Isolates were identified by standard methods.

Anaerobes were isolated using 5% sheep blood and phenethyl alcohol agars, incubating at 35°C in Gas-Pak anaerobic jars (Bio-Quest Laboratories, Baltimore, Maryland). Isolates were identified by the methods described by workers at the Virginia Polytechnic Institute.[1]

Specimens for the cultivation of mycoplasmas were diluted 1:10 in 0.5% solution of proteose peptone in distilled water and 0.1-ml portions were used as inocula. The agar medium developed by Hayflick[2] and the diphasic media of Kenny[3] were used for the cultivation of *Mycoplasma pneumoniae*. Diphasic tubes were subcultured to agar plates weekly for 6 weeks. These cultures were incubated aerobically at 36°C. For the cultivation of mycoplasmas other than *M. pneumoniae*, PPLO agar medium consisting of 10% horse serum and 1% yeast autolysate in PPLO agar (Difco) with penicillin (1000 units/ml), thallium acetate (0.5 mg/ml) and amphotericin B (0.5 μg/ml) was used.[4] Attempts to cultivate T-strains were carried out on the differential agar medium A-6 developed by Shepard and Lunceford.[5] These cultures were incubated anaerobically at 36°C.

Specimens for virus isolation were stored at -70°C prior to inoculation of monolayers of human amnion cells, in tubes, with 0.1 ml of each sample. The cells were incubated at 36°C in minimal essential medium (Eagle's) in balanced salt solution (Earle's) with 2% heated fetal calf serum and gentamicin (15 μg/ml), clindamycin (25 μg/ml), ampicillin (100 μg/ml) and amphotericin B (15 μg/ml). The cultures were observed daily for cytopathic effects and after 4 weeks a hemadsorption test was performed using human type O erythrocytes.

Drug assay

Portions of specimens of TBSE, saliva and serum obtained at the time of bronchoscopy were frozen immediately and stored at -70°C until shipment on dry ice to the Burroughs Wellcome Laboratories. The concentrations of trimethoprim and sulfamethoxazole in samples of saliva, TBSE and sera were determined by the quenching fluorometric assay.[6]

Table I—Patient characteristics and tolerance to trimethoprim-sulfamethoxazole

Patient	Age	Sex	Blood count†	Urinalysis*	Tolerance*
W.B.	47	M	8% eos.	-	N
T.G.	62	M	N	-	N
E.B.	66	M	N	1 + prot.†	N
L.H.	61	M	N	N	N
S.M.	56	M	N	N	N
C.T.	69	M	N	-	Eructations nausea
G.T.	60	M	N	-	N
V.Z.	79	M	N	N	N
C.E.	54	M	N	N	N
J.H.	63	M	N	-	N
H.L.	57	M	N	-	N
L.M.	18	F	N	-	N
C.B.	61	M	Hb 17.5† PCV 53	N	N
J.C.	49	M	N	-	N
F.B.	56	M	N	N	N
R.A.	48	M	N	-	Bloating
O.Z.	62	F	N	-	N
H.M.	69	M	N	-	N
L.V.	50	M	N	-	N
Average age	57				

*During administration of trimethoprim-sulfamethoxazole.

N = Normal or no symptoms.

†Abnormality present before administration of trimethoprim-sulfamethoxazole.

Results

Tolerance of TMP-SMX

Of the 21 patients who began the study, 2 refused to continue because of the requirements for evaluation. Although two other patients experienced gastrointestinal distress, which may have been in part related to the ingestion of TMP-SMX, both patients were able to complete the study (Table I).

In one patient the eosinophil percentage rose from 4 to 8% (absolute values, 244 and 536/mm^3); there were no clinical manifestations of allergy. No abnormalities of platelets or neutrophils were observed on inspection of smears. Two patients had a decrease in hemoglobin concentrations (C.B., 18.3 to 17.5 g/dl; H.L., 16.3 to 14.5 g/dl). Anemia, granulocytopenia and thrombocytopenia were not observed. In three patients a slightly elevated CPK was observed at either the baseline (two patients) or subsequent (two patients) examinations. Renal function, as assessed by BUN and creatinine concentrations, remained normal in all patients.

Antimicrobial concentrations

The concentrations of TMP-SMX in sera are shown in Fig. 1. The wide range in concentrations is probably due in part to variation in the interval from the last dose to the collection of specimens. A few patients failed to take the morning dose of TMP-SMX prior to bronchoscopy.

The penetration of TMP and SMX into saliva and TBSE is shown in Fig. 2. The relative concentrations of TMP and SMX varied from a ratio of 1:20 in serum to 1:5 for TBSE and 3:1 for saliva. The mean concentrations of TMP and SMX in serum, TBSE and saliva are given in Table II. The relative concentrations of each drug in TBSE and saliva are shown in comparison with the value in the corresponding serum. TMP was present in serum and TBSE in approximately equal concentrations, whereas TMP was actually concentrated in saliva. SMX entered both TBSE and saliva, attaining concentrations less than those simultaneously present in serum.

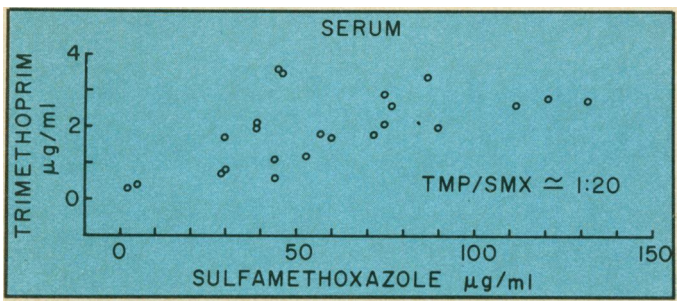

FIG. 1—Antimicrobial concentrations in the serum of patients with chronic bronchitis complicating chronic obstructive pulmonary disease after administration of trimethoprim-sulfamethoxazole for 6 or 12 weeks. The data refer to 23 observations in 17 patients. The mean ratio of TMP-SMX is 0.0469 ± 0.0074 (mean ± SE) from the 23 observations.

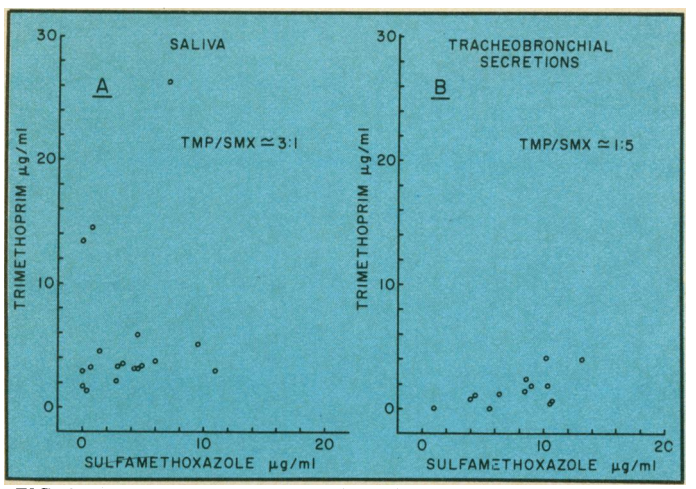

FIG. 2—Antimicrobial concentrations in the saliva and tracheobronchial secretions of patients with chronic bronchitis complicating chronic obstructive pulmonary disease after administration of trimethoprim-sulfamethoxazole for 6 or 12 weeks. Saliva: the data refer to 18 observations from 14 patients. The mean ratio of TMP-SMX is 2.91 ± 1.24 (mean ± SE) calculated from 15 paired observations. Bronchial secretions: the data refer to 13 observations from 10 patients. The mean ratio of TMP-SMX is 0.198 ± 0.032 from 11 paired observations.

Microbial flora

Specimens of TBSE yielded from 1 to 10 different kinds of aerobic bacteria, and from 0 to 8 different kinds of anaerobic bacteria. The most common aerobes isolated from TBSE were *Streptococcus viridans* and nonhemolytic streptococci, diphtheroids and *Neisseria* sp., as shown in Fig. 3. The anaerobic bacteria most frequently isolated from TBSE are shown in Fig. 4 (*Veillonella* sp.; *Peptococcus* and *Peptostreptococcus* sp.; *Fusobacterium* sp.). Treatment with TMP-SMX did not alter the frequency of recovery or the numbers (paired t-test) of these bacteria.

The recovery of *Hemophilus influenzae* and *H. parainfluenzae* was decreased by TMP-SMX, as is shown in Table III. Only a few isolates of *Klebsiella pneumoniae, Escherichia coli* and *Proteus mirabilis* were obtained in this study; when taken together such isolations were less frequent during treatment with TMP-SMX. *Staphylococcus aureus* was isolated on two occasions in the baseline samples only. The recovery of *Pseudomonas aeruginosa* and *Bacteroides melaninogenicus* was not influenced by treatment. Other bacterial species that were infrequently isolated and not apparently influenced by treatment included: *Staphylococcus epidermidis, Lactobacillus* sp., *Mima polymorpha, Citrobacter* sp., *Moraxella* sp., *Propionibacterium* sp., *Campylobacter* sp. and *Eubacterium* sp. Species of *Bacteroides* other than *melaninogenicus* were isolated from nine patients; *B. fragilis* was not isolated from any patient. Species of *Clostridium* were isolated from two patients; *Actinomyces* sp. and *Succinovibrio* sp. were each recovered on one occasion. *Nocardia asteroides* was repeatedly isolated from one patient (L.M.); treatment with TMP-SMX was associated with symptomatic improvement and a decrease in the numbers of *N. asteroides* that were recovered.

Recoveries of *Candida albicans* were made on two occasions and other *Candida* sp. were obtained on four occasions. Single

Table II—Antimicrobial concentrations in serums, salivas and tracheobronchial secretions / exudates (TBSE)

	Trimethoprim	Sulfamethoxazole
Concentrations*		
Serum	1.93 ± 0.21 (23)	59.4 ± 7.05 (23)
Saliva	5.73 ± 1.47 (18)	4.26 ± 0.82 (15)
TBSE	1.97 ± 0.33 (17)	7.90 ± 0.95 (13)
Relative concentrations†		
TBSE/serum	1.12 ± 0.16 (14) 1:1	0.149 ± 0.027 (12) 1:7
Saliva/serum	3.21‡ ± 0.54 (17) 3:1	0.048 ± 0.0089 (12) 1:21

*The mean concentration in µg/ml ± SE is shown. The number of observations is in parenthesis.

†The average ratios ± SE are shown. The number of paired observations is in parenthesis. The approximate proportion is given below.

‡$P < 0.001$ that this ratio is unity.

isolations were made of *Torulopsis glabrata* and *Rhodotorula* sp.

Eleven paired specimens of TBSE and saliva from six patients were cultured for mycoplasmas. Species of *Mycoplasma* were isolated from 3 of 11 salivas and from TBSE in 1 of 11 cultures. *M. pneumoniae* and T-strains were not recovered.

Virus isolations were attempted with 35 specimens of TBSE from 14 patients. Only one culture developed viral cytopathic effects.

Effect on chronic bronchitis

The impact of prolonged administration of TMP-SMX on several clinical manifestations of chronic bronchitis has been tabulated for those patients for whom valid, paired data are available, and is shown in Table IV. The majority of patients reported either improvement or no change in sputum production and dyspnea. The examining physician recorded improvement in auscultatory findings in six and worsening in two patients. No consistent changes could be detected in weight, vital capacity, 1-second forced expiratory volume or arterial P_{O_2}.

Discussion

During long-term administration of TMP-SMX patient tolerance was good and the drugs were present in serum in a ratio of 1:20 (TMP:SMX) as others have reported.[7,8] TMP was present in authentic specimens of TBSE in approximately the same concentrations as in companion serums; however, the concentration of TMP in the saliva was about three times that of the serum. In contrast, SMX was present in both TBSE and saliva in lower concentrations than in serum. This difference in penetration of TMP and SMX into TBSE and saliva results in a change of the TMP:SMX ratio from 1:20 in serum to 1:5 for TBSE and 3:1 for saliva. The different ratios in TBSE and saliva provide evidence for the validity of TBSE testifying to a lack of heavy contamination by saliva. Synergistic effects have been observed between the two drugs in ratios of 1:1 to 1:20.[9] Thus, the combination as administered in this study enters TBSE in absolute and relative amounts sufficient to take advantage of the potential for synergy against susceptible microorganisms. Because TMP is a weak base (pKa 7.3) it is unlikely to become concentrated in saliva (pH 7.8 to 8.8) by passive mechanisms. In contrast to our results Stamey, Bushby and Bragonje[10] found that the saliva/serum ratio was < 1.0; however, this was determined under conditions of constantly increasing TMP serum concentrations in a short-term experiment rather than the more nearly steady state conditions employed here.

The organisms recovered most frequently and in greatest numbers from TBSE were the typically nonpathogenic bacteria of the upper respiratory tract (Figs. 3 and 4), confirming and extending our earlier observations.[11] However, *H. influenzae, H. parainfluenzae, Klebsiella* sp., *E. coli* and *P. mirabilis,* bacteria that are potentially pathogenic and susceptible to TMP-SMX, were recovered significantly less often from patients taking TMP-SMX. This reduction in the carrier state occurred in association with concentrations of antimicrobials in TBSE that would be expected to inhibit these microorganisms.[12,13]

One half of the patients reported definite improvement in sputum production and/or dyspnea after administration of

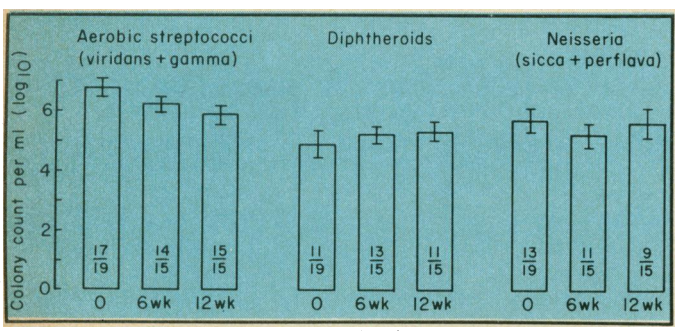

FIG. 3—Aerobic flora of tracheobronchial secretions/exudates from patients with chronic bronchitis complicating chronic obstructive pulmonary disease before (0) and after 6 and 12 weeks of treatment with trimethoprim-sulfamethoxazole. The geometric mean ± SE is shown. The numerator represents the number of patients with positive cultures; the denominator represents the number of patients studied at the time indicated.

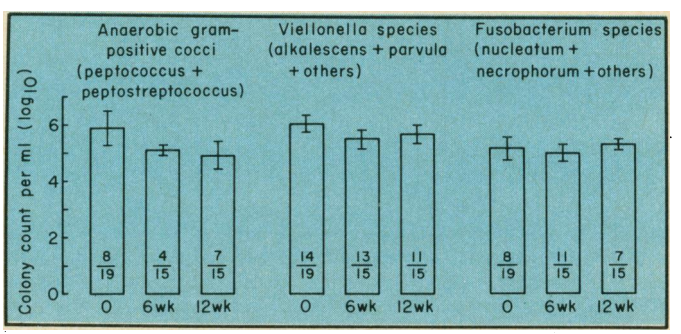

FIG. 4—Anaerobic flora of tracheobronchial secretions/exudates from patients with chronic bronchitis complicating chronic obstructive pulmonary disease before (0) and after 6 and 12 weeks of treatment with trimethoprim-sulfamethoxazole. The geometric mean ± SE is shown. The numerator represents the number of patients with positive cultures; the denominator represents the number of patients studied at the time indicated.

Table III—Effect of trimethoprim-sulfamethoxazole on potential pathogens harboured in the tracheobronchial tree of patients with chronic bronchitis complicating chronic obstructive pulmonary disease

		Baseline	6 weeks	12 weeks	Significance*
Hemophilus influenzae	Present	8	2	3	0.05 > P > 0.025
(11 patients)	Absent	3	8	6	
Hemophilus parainfluenzae	Present	7	2	1	0.01 > P > 0.005
(7 patients)	Absent	0	4	4	
Klebsiella sp. (3 patients)	Present	4	1	0	0.05 > P > 0.025
Escherichia coli (1 patient)	Absent	1	3	4	
Proteus mirabilis (1 patient)					
Pseudomonas aeruginosa	Present	2	3	3	NS
(4 patients)	Absent	2	1	0	
Bacteroides melaninogenicus	Present	5	2	3	NS
(8 patients)	Absent	3	4	4	

*Tested by chi-square; P > 0.05 considered not significant (NS)

TMP-SMX; only one patient reported more severe symptoms. It should be noted that this study was not placebo- or observer-controlled and that objective measurements were not altered by treatment. Furthermore, subjective benefit could not be correlated with a decrease in the numbers of bacteria in TBSE.

In summary, we have demonstrated the penetration of TMP-SMX into TBSE and saliva and have been able to show a decrease in the frequency of isolation of certain susceptible bacteria from TBSE. Based on these findings, it is reasonable to use the TMP-SMX combination in the treatment of pulmonary infections caused by susceptible bacteria. The TMP-SMX combination may also be used to eliminate or suppress the carriage of susceptible bacteria. The usefulness of TMP-SMX in the treatment of chronic bronchitis uncomplicated by acute infection remains to be established by appropriately controlled studies.

Table IV—Clinical effects of trimethoprim-sulfamethoxazole in patients with chronic bronchitis complicating chronic obstructive pulmonary disease

	Improved*	No change*	Worse*	Total†
Sputum production	9	8	1	18
Dyspnea on exertion	5	5	0	10
Auscultation	6	10	2	18
Weight ($\Delta \geq 5$ lb)	0	13	2	15
Vital capacity ($\Delta \geq 10\%$)	2	8	1	11
FEV_1 ($\Delta \geq 100$ ml)	2	6	2	10
Arterial PO_2 ($\Delta \geq 10$ mm Hg)	2	7	0	9

*In comparison with baseline condition.

†Number of patients having paired observations.

Δ = change from baseline status.

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