Is an objective assessment of antibiotic therapy in exacerbations of chronic bronchitis possible?

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Chronic bronchitis is defined clinically as ‘the daily production of sputum for at least three consecutive months in two consecutive years’ (American Thoracic Society, 1962). Epidemiological studies in the USA suggest that up to 25% of adults have symptoms of chronic bronchitis (Woolcock, 1989). Patients with chronic bronchitis may experience several acute exacerbations of their disease in a year, particularly in the winter months. These are usually treated by general practitioners, although severe exacerbations can result in the patient being hospitalized.

Exacerbations of chronic bronchitis may occur due to environmental factors, such as exposure to airborne irritants or allergens, or as a result of infection. The role of bacterial infection in exacerbations of chronic bronchitis is unclear, since infections caused by common respiratory viruses and atypical pathogens, such as Mycoplasma pneumoniae, may also be associated with exacerbations. In addition, in published studies approximately half the patients have demonstrated no benefit from antibiotic treatment compared with placebo with the consequence that the value of antibiotic therapy has been disputed. However, in a recent, large double-blind study in which antibiotic therapy was compared with placebo (362 exacerbations; 182 treated with antibiotic, 180 with placebo), antibiotic treatment was associated with a significantly higher success rate (68% and 55% respectively). Moreover, the overall failure rate was 29% in the antibiotic group and 42% in the placebo group. In patients with less severe exacerbations, antibiotic treatment was not associated with any benefit (Anthonisen et al., 1987). This suggests that there may be a justification for placebo-controlled studies in some patients. However, as it is standard medical practice in most countries to prescribe antibiotics for exacerbations of chronic bronchitis, the conduct of any placebo controlled studies presents difficulties. In view of this, future studies with an active control group should be designed to include only patients in whom exacerbations are likely to have a bacterial cause.

Adult patients with stable chronic pulmonary disease, who have increased cough and/or dyspnoea, and increased sputum volume and purulence, should be studied. These characteristics have been shown to be associated with bacterial infection and have been used as inclusion criteria in two recent studies (Periti et al., 1990; Rademaker et al., 1990). Although this may limit the number of patients eligible for study entry, it would ensure that only patients with more severe exacerbations were included. Other symptoms and signs which may be present include chest discomfort, malaise, appetite loss, haemoptysis and increased wheezing, but individually these are of limited value in assessing response. Patients with suspected pneumonia should be excluded, ideally by chest X-ray to demonstrate the absence of pulmonary infiltrates. Important details, such as smoking history and concurrent therapy such as corticosteroids, need to be collected as both can influence clinical outcome.

The methodological aspects of antibiotic clinical trials continues to be a topic of discussion between regulatory authorities, the pharmaceutical industry and academia. New guidelines for drug evaluation are being produced by the Infectious Diseases Society of America (IDSA) as part of a contract with the Food and Drug Administration (FDA) (Gilbert, Beam & Kunin, 1990); European guidelines are in preparation. The IDSA guidelines on the conduct of clinical trials in exacerbations of chronic bronchitis give an outline of study design, patient population, assessment times and methods. The IDSA suggests that the major parameter of efficacy should be clinical response on the basis that sputum microbiology is often misleading and does not reflect clinical outcome. They do recognize, however, that sputum culture could still provide useful information on epidemiology.
and likely causes of treatment failure. They also propose that lung function tests should be incorporated.

More recently, a 'Points to Consider' document from the Division of Anti-Infective Drug Products of the FDA suggests that a minimum of two studies will be required for this indication. One study should use clinical (return to baseline) and microbiological endpoints as primary efficacy parameters. A second study should use the return to clinical baseline as the only primary efficacy endpoint; however, each patient must have sputum microbiology performed. In this second study patients should be analysed in two groups; those who are clinically evaluable and those who are clinically and microbiologically evaluable (Lumpkin & Burlington, 1992). The advantage of using the clinical endpoint as the primary efficacy parameter is that this will require a smaller sample size. The FDA 'Points to Consider' document is under review and is therefore subject to change; however, it does seem clear that for the foreseeable future microbiological documentation will still be required. It is easy to understand the reluctance of the FDA to abandon sputum microbiology as FDA approval is based on efficacy in eradicating specific pathogens for an indication. If the requirement for microbiological endpoints is removed it could lead to an all microbiological claim for new antibiotics.

Clinical trials in acute exacerbations of chronic bronchitis should be based on the randomized, comparative, double-blind design because of the subjective nature of clinical endpoints. The aim of many antibiotic trials is to demonstrate equivalent activity of two agents, or, at least, to ensure that the study does not miss a clinically significant difference (type II error). In reporting the clinical results it is important that the 95% confidence interval around the difference in outcome should be quoted. The Table gives the sample sizes required to show clinical equivalence between the cure rate on the standard therapy P1 and a new therapy, given that a treatment difference D1 is not considered to be clinically significant.

In studies of chronic bronchitis, cure rates of 80% can be expected. The FDA policy document indicates that for a success rate of 80% in a control group, D1 should be no greater than 0.15 i.e. to satisfy this requirement 224 patients would need to be studied. The sample size would double for studies with a bacteriological outcome as the primary parameter of efficacy, as up to 50% of patients will be unevaluable.

In order to achieve consistency in multicentre studies important clinical signs and symptoms should be defined and simple 3 or 4 point scoring scales for their evaluation should be adopted. For example, sputum appearance has been described as: mucoid (egg white appearance with traces of pus); mucopurulent (up to 50% pus) and purulent (greater than 50% pus) (Bachand, 1991). Dyspnoea has been categorized as: none; present only on unusual exertion; present during normal activity; and present at rest (Anthonisen et al., 1987). Attempts to accurately quantify sputum volume are not practical as patients will invariably swallow an unknown amount of the sputum produced.

More detailed grading systems have been used in an attempt to standardize clinical assessments and in one method each symptom was given a score from 1 to 20 according to severity (Chodosh et al., 1982). Such methods can be useful in a single centre study but are too detailed and can lead to inconsistencies in a multicentre study.

Clinical assessment should be performed before treatment, every three to five days during treatment and at the end of treatment. Duration of treatment is generally seven to ten days but this period is not fixed as a three or five day course of the new macrolide azithromycin has been shown to be effective. A follow-up assessment between one and two weeks after completing treatment will provide valuable information on the rates of early relapse and must be included in assessment of the overall response. Ideally, within a centre, all assessments should be carried out by the same person.

Definitions of clinical response should ideally be limited to cure (return to baseline), failure (no change in, or worsening of symptoms) or unevaluable (a response cannot be determined). If other terms such an improve-

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*Calculations performed using 80% power and 5% significance level; D1, Difference; P1, Statistical power.
Measurement are used, they must be clearly defined and should not include patients requiring further therapy who are in fact treatment failures. Longer term follow-up to determine the post-treatment infection free period has been proposed as a method for comparing the effectiveness of antibiotics (Chodosh, 1991). While accepting that this knowledge is clinically important, the length of follow-up required and the danger of different drop-out rates confounding the results, makes this impractical for the initial evaluation of a new antibiotic. In addition, caution must be exercised if infection free periods are being compared from different clinical trials as the patient populations may not be comparable.

Lung function tests produce quantitative results and can therefore be viewed as more objective than clinical symptoms. Guidelines for performance of lung function tests have been produced by the American Thoracic Society (American Thoracic Society, 1987) and the European Community for Coal and Steel (Quanjer, 1983); these give information on equipment and subject performance. More recently, the selection of reference values and interpretation of results has been reviewed (American Thoracic Society, 1991).

Like all clinical measurements pulmonary function tests are subject to technical variation related to instrument, procedure, observer and subject; biological variation, and variation caused by dysfunction or disease. The tests which have been proposed are forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and peak expiratory flow rate (PEFR). In one study where lung function tests were used, a significantly faster increase in PEFR was observed in patients who were treated with antibiotic compared with placebo during acute exacerbations (Anthonisen et al., 1987).

The practical issues in incorporating lung function tests into studies need to be addressed. Equipment for spirometry will be available in hospital respiratory units and in larger general practice centres and portable equipment could be provided by the study sponsor though at a significant cost. However, the conduct of these tests is time-consuming and results may depend upon the skill of the person performing the test. An added difficulty is that because of diurnal variation in the individual patient, testing needs to be carried out at the same time each day.

Measurement of PEFR is simpler but different types of peak flow meters can produce results which do not correlate even though the reliability of readings taken with the same instrument may be high (Harm, Kotses & Creer, 1984). It is therefore important that all centres use the same make of peak flow meter. With this proviso patients can be given peak flow meters to allow twice daily monitoring at pre-determined times and results can be recorded on a diary card; a system already used extensively and successfully in asthma clinical trials.

A major problem in evaluating antibiotic therapy in exacerbation of chronic bronchitis is the difficulty in defining microbiological parameters for the diagnosis of the infection, and for determining the efficacy of the agent being studied.

Reasons for this are related to the difficulty in obtaining appropriate material for microbiological evaluation and the fact that the organisms responsible for the infection may colonize the respiratory tract in those with chronic bronchitis. At least half the patients will have *Streptococcus pneumoniae* or non-encapsulated *Haemophilus influenzae* (or both) as persistent colonizers of the respiratory tract; these are the most likely pathogens responsible for exacerbations. *Moraxella catarrhalis* and *Haemophilus parainfluenzae* may also be isolated, although the latter is not recognized as a pathogen by all authorities. Colonization can present difficulties in the interpretation of culture results. Residual colonization in a patient whose clinical symptoms have returned to baseline may be of no significance, although in some circumstances it may be associated with relapse; for example, persistence of *S. pneumoniae* after quinolone treatment (Maesen et al., 1986).

Sputum should be obtained for microbiological examination, including susceptibility testing, at the pre-treatment assessment, and if it is still being produced, upon treatment completion and at a follow-up assessment performed between one and two weeks after stopping treatment. Sputum samples should be transported promptly to the laboratory, if necessary by courier, as delays of 2 to 5 h at room temperature reduce the isolation of pathogens such as pneumococci and allow overgrowth of upper respiratory tract contaminants (Jefferson et al., 1975).

Microscopy is valuable in assessing the quality of the specimen, to confirm that it is not heavily contaminated with upper respiratory tract secretions. In a study comparing results from sputum samples and paired transtracheal aspirates 94% of sputum samples with <10 squamous epithelial cells (SECs) and
> 25 WBCs per low power field ( \times 100 \) grew the same potential pathogen as paired transtracheal aspirates; correlation was reduced to 79% if the only criteria used was < 25 SECs (Geckler et al., 1977). Samples with > 25 SECs should be regarded as unsuitable regardless of the number of leucocytes they contain. Gram's stain has been reported to confirm the presence of bacteria e.g. *S. pneumoniae, H. influenzae* or *M. catarrhalis* characterized by their morphology; in an oil immersion field ( \times 1000 \) \( \geq 12 \) haemophilus-like, \( \geq 8 \) pneumococcus-like or \( \geq 18 \) moraxella-like organisms are likely to indicate acute bacterial exacerbation; stable patients have few bacteria per high power field (Chodosh, 1991). In a study comparing Gram's stain and culture, microscopic examination of the Gram's stain was found to be superior to culture with approximately 50% of organisms microscopically identified as pneumococci failing to grow (Medici et al., 1988).

Microbiological culture therefore, may or may not confirm the Gram's stain findings, but the Gram's stain may more accurately reflect the clinical findings.

Microbiological response should be defined in terms of eradication or persistence of the original pathogen(s), appearance of a new pathogen(s) (superinfection), and should also include a definition for reinfection and reasons for unevaluability. Eradication may be presumptive in the absence of a patient being able to produce suitable material for culture accompanied by clinical cure.

Acute exacerbations of chronic bronchitis are usually managed with antibiotic therapy and evidence suggests that this results in a reduction in morbidity. It is generally recognized that studies in this indication should be of a double-blind comparative design; no such consensus exists on how efficacy should be determined.

An adequate sample size, based on sound statistical advice, is required. In comparative studies recruitment of large numbers of patients is advantageous and is likely to ensure that the two groups being compared will be balanced.

The clinical response should be based on a small number of strictly defined signs and symptoms, using simple rating scales of change. Lung function tests can contribute to the clinical assessment as they are objective, but only PEFR is likely to offer the simplicity and reproducibility necessary for multicentre studies.

The value of microbiological endpoints is disputed and yet these are still required by regulatory authorities for a new drug to be registered in this indication. Microbiological response, based on sputum culture, has to be interpreted in the light of the clinical response, as a positive culture can be seen post-treatment in association with a clinical cure. In general, the semi-quantitative assessment of organisms and white cells in sputum, using a Gram's stain, is more likely to be related to clinical outcome and this information should be used in conjunction with sputum culture results.

Clear guidelines for evaluation of antibiotics in this indication which are acceptable to investigators, the regulatory authorities and the pharmaceutical industry are required and would lead to studies of a higher, more consistent quality being performed. Until such guidelines are published, future studies of antibiotics in this indication will continue to use a wide variety of end-points making the comparison of results from different clinical trials unreliable.

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References


New directions in the diagnosis and treatment of pelvic inflammatory disease

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Newly recognized limitations of the traditional approach to the diagnosis and treatment of pelvic inflammatory disease (PID) require the development of new perspectives. The current pattern of care emphasises clinical diagnosis of obvious disease, microbiological laboratory testing, antibiotic treatment, and operative intervention in the case failure. This approach has been characterized by Weinstein & Dalton (1968) as an emphasis upon the ‘bug and the drug.’ A degree of complacency has resulted because this strategy has been accompanied by a reduction in the morbidity of PID; fewer women now require operative care for pelvic abscesses. Despite this acknowledged advancement in care, many of observations illustrate the shortcomings of this strategy. Many pelvic infections seem currently with a poor outcome are clinically ‘silent’. Laparoscopic studies of infertile women find many to have irreversible tubal damage due to prior infection, without a history of salpingitis, or even in most instances, cervicitis. Improved antibiotics have not been shown to improve clinical results as of yet; the percentage of women with tubal occlusion after antibiotic treatment is constant, as the modern antibiotic regimens that are more bactericidal and broader in antibacterial activity. This suggests that in preventing tubal occlusion the timing of antibiotic treatment may be more important than the selection of antibiotics. This remains an unresolved hypothesis, because of our limited ability to make an early and accurate diagnosis of PID.

An important impediment to any fresh analysis of this problem is the reliance upon an outmoded classification of this particular disease; infection of the female pelvis in the non-pregnant state is PID. Unfortunately, as defined this disease runs the gamut from the asymptomatic to the overt. The latter presents with excruciating abdominal and pelvic pain, and a purulent cervical discharge which yields Neisseria gonorrhoeae or alternatively, the sick patient with a pelvic mass accompanied by a reduction in the morbidity of PID; many to have irreversible tubal damage accompanied by the.