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Bacteria, antibiotics and COPD

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ABSTRACT: Bacterial infection is one of several important causes of exacerbations of chronic obstructive pulmonary disease (COPD) that may coexist. COPD is a heterogeneous condition and the incidence of bacterial infection is not uniform; mucus hypersecretion may be an important risk factor.

The bacteriology of infections varies depending on the severity of the underlying airway disease. There is now a much better understanding of the pathogenesis of bacterial infections of the respiratory mucosa. Lower airway bacterial colonization may be a stimulus for chronic inflammation and may influence the interval between exacerbations.

Antibiotic resistance has increased in all the major pathogens. Antibiotics are an important part of the treatment of acute exacerbations of COPD and the decision about whether to give an antibiotic can be made on clinical grounds. It is more difficult to decide, on the available evidence, whether patient characteristics and the risk of antibiotic resistance should influence choice of empiric antibiotic treatment.

Most new antibiotics are modifications of existing structures, suggesting that every effort should be made to conserve the sensitivity of current antibiotics by using them appropriately.
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Chronic obstructive pulmonary disease (COPD) encompasses several conditions (airflow obstruction, chronic bronchitis, bronchiolitis or small airways disease and emphysema) that often coexist. Patients suffer exacerbations of their condition that are usually associated with increased breathlessness, and often have increased cough that may be productive of mucus or purulent sputum. The frequency with which bacterial infection causes an exacerbation may vary depending on which condition is the dominant pathology. Patients with chronic bronchitis are more susceptible to bacterial bronchial infections than those at the emphysema or asthma end of the spectrum. Mucus hypersecretion, which is the hallmark of chronic bronchitis, is particularly associated with mortality from an infectious cause [1]. These observations may be explained by the affinity with which bacteria adhere to mucus, and the delay in mucociliary clearance that occurs in chronic bronchitis, partly due to loss of ciliated cells that are replaced by goblet cells [2]. Thus, bacteria that are inhaled or aspirated into the bronchial tree may utilize stationary mucus as the first step to colonize the mucosa.

Although impairment of respiratory function does not in itself make patients susceptible to infection, it does influence the outcome of a lower respiratory tract infection (LRTI) [3]. Severe airflow obstruction, hypoxaemia and the presence of hypercapnia are all risk factors leading to poor outcome [4]. In persons with a forced expiratory volume in one second (FEV_1) of less than 0.75 L, the approximate mortality at 1 yr and 10 yrs is 30% and 95%, respectively, although longitudinal studies have shown that some patients survive for many years beyond the average [5]. The reason for this appears to be that death usually occurs as a result of a medical complication, such as acute respiratory failure, pneumonia or a cardiac arrhythmia, and this is dependent on unpredictable extraneous factors. Therefore, the impact of an LRTI on a COPD patient's health status varies markedly depending not only on the severity of the infection, but also on their lung condition, age and general health, which will influence the risk of medical complications [4].

Antibiotics are commonly prescribed empirically to patients presenting with an acute exacerbation of COPD to treat presumed bacterial infection. The rise in

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bacterial resistance to antibiotics has focused attention on the benefit of this practice, and more fundamentally, on the importance of bacterial infection in COPD and its role in stimulating bronchial inflammation. A recent analysis of acute exacerbations of COPD in the USA illustrated the size of the problem [6]. The authors used 1994 data in order to make their calculations. They estimated that there were 280,000 hospital admissions and 10 million outpatient visits due primarily to COPD. The majority of patients in both groups were aged $\geqslant 65$, and older patients had a longer hospital stay. The average cost of a doctor's office visit was estimated to be US$74, whereas the average cost of a hospital admission was US$5,516. Antibiotics accounted for only a small percentage of the latter cost. The study emphasizes two points. Firstly, most patients were given an antibiotic, so the volume of antibiotics prescribed for this indication is enormous. Secondly, if an effective therapy could be found which would reduce the need for hospitalization, it would be highly cost-effective because of the large difference in the cost of care in the two settings.

Bacterial infection and acute exacerbations of chronic obstructive pulmonary disease

This topic has caused much debate, and contrasting views have been expressed [7, 8]. On the one hand, bacteria are seen as passengers that are only occasionally the primary cause of an exacerbation [7]. On the other hand, bacterial infections are judged to cause at least half of exacerbations, and it is advised that the choice of antibiotic is important because the rise in bacterial resistance has made older agents less effective [8]. The fact that a debate about antibiotic prescription continues to wage, is due, in the main, to the evidence for either view being inconclusive. Proponents of the former view usually advise that corticosteroids are given to control airway inflammation, and antibiotics, if used at all, should be older agents that are inexpensive and safe. One study showed that antibiotics did not provide any extra benefit *versus* oral prednisolone alone for exacerbations of mild-to-moderate airflow obstruction, but few patients in the study had evidence of infection and some had predominant asthma [9]. The role of corticosteroids in the management of COPD is equally controversial. Several recent long-term trials of inhaled corticosteroids in COPD have shown that there is no beneficial effect on the annual decline in lung function. In patients with severe COPD there is a small beneficial effect on quality of life and reduction in the frequency of exacerbations [10–13]. In severe exacerbations, systemic corticosteroids are beneficial and improve the speed of recovery [14].

Only one of four prospective studies has shown that more frequent episodes of infection cause a more rapid decline in lung function [15]. Placebo-controlled studies involving small numbers of patients have provided conflicting evidence of the efficacy of antibiotics in acute exacerbations of COPD [8]. A recent meta-analysis of nine placebo-controlled trials concluded that, overall, there was a small but significant benefit from antibiotic treatment of acute exacerbations of COPD in terms of overall recovery and change in peak flow [16]. There have also been nine prospective, placebo-controlled, randomized trials to investigate whether continuous antibiotic treatment reduces the frequency of exacerbations [15]. There have again been conflicting results. Five trials showed no reduction in the frequency of exacerbations whereas four did show a significant reduction *versus* placebo. Two of the five trials that showed no benefit did show significantly less time lost from work in the antibiotic group, even though the frequency of exacerbations was not different from the placebo group. Patients most likely to benefit from continuous antibiotic treatment were found to be those suffering frequent exacerbations, which was judged to mean $\geqslant 4 \cdot yr^{-1}$.

The study of ANTHONISEN *et al.* [17] is often cited as supporting antibiotic treatment. In this study, 173 patients with COPD were followed for 3.5 yrs during which time they had 362 exacerbations. Antibiotics or placebo were given in a randomized, double-blind, crossover fashion. Three levels of severity of exacerbation were recognized: the most severe (type 1) comprised of worsening dyspnoea with increased sputum volume and purulence, type 2 was any two of these symptoms and the least severe grade (type 3) was any one of these symptoms with evidence of fever or an upper respiratory tract infection. Three antibiotics were used: amoxycillin, trimethoprim-sulphamethoxazole and doxycycline; the choice being made by the physician. There was a significant benefit from antibiotics that was largely accounted for by patients with type 1 exacerbations, whereas there was no significant difference between antibiotic and placebo in patients who had only one of the defined symptoms. However, even with type 1 exacerbations, 43% of patients recovered in the placebo group within 21 days, which emphasizes the difficulty in differentiating between the benefits of different antibiotics when recovery is the primary end-point of the trial. A major criticism of this study was that no microbiology was performed, so the role of bacterial infection in type 1 exacerbations is inferred, rather than proven. The ANTHONISEN *et al.* [17] study also showed that, in patients with multiple exacerbations, the duration of antibiotic-treated exacerbations averaged 2.2 days less than those treated with placebo ($p = 0.02$). However, when all patients were considered and treatment failures were eliminated from the analysis, the benefit from antibiotics on speed of recovery was only 0.9 days (not significant). Peak flow returned to baseline in both groups during the study period, but the rate of increase was faster in antibiotic-treated exacerbations.

Most antibiotic trials have compared a new antibiotic with an established compound for the purpose of new product registration and licensing. Equivalence is the desired outcome of such trials, because this is what is demanded by the licensing authorities, and as a consequence, patients have been included with poorly defined disease of uncertain severity [18]. These trials have contributed very little to current knowledge about infection and COPD. Even trials that have enrolled patients on the basis of the ANTHONISEN *et al.* [17] criteria previously defined, have failed, using standard

criteria of recovery as judged by the clinician at the end of treatment or shortly afterwards, to show that increased antibiotic potency *in vitro* translates into clinical superiority [19]. In a study of moxifloxacin, a new quinolone antibiotic, *versus* the macrolide antibiotic clarithromycin, in patients with Anthonisen type 1 or 2 acute exacerbations of chronic bronchitis, the quinolone was much more active *in vitro* against *Haemophilus influenzae* which was the commonest bacterial pathogen isolated. As a result, seven days post-treatment a successful bacteriological response was obtained for 77% (89 of 115 patients with positive sputum bacteriology results) of patients in the moxifloxacin group and 62% (71 of 114) of patients in the clarithromycin group, indicating superiority of moxifloxacin. However, the clinical cure rates were 89% (287 of 322) and 88% (289 of 327) of patients for moxifloxacin and clarithromycin respectively. Bacteriological eradication and clinical success was the most common outcome, while bacteriological eradication and clinical failure was a rare occurrence. However, bacteriological failure associated with clinical success was quite common in the clarithromycin group. The result of this study suggests that the level of inflammation in the airway during an exacerbation can fall in the presence of persistent infection, and might be taken to show that bacterial infection is not causing the exacerbation. An alternative explanation might be that a fall in bacterial numbers occurs with antibiotic treatment, to levels which do not attract a significant inflammatory response, or that the benefit from clarithromycin has come from the anti-inflammatory properties of the macrolide antibiotic rather than its antibacterial action [20]. Another possibility is that bacteriology in clinical studies is derived from sputum samples that may not reflect the level of infection in the smaller airways, particularly since many studies do not apply stringent criteria to exclude nasopharyngeal contamination.

A major problem is that most antibiotic studies are not powered adequately to demonstrate superiority, particularly as they compare one antibiotic with another rather than placebo (for ethical reasons), and since nearly half of patients recover spontaneously, and a proportion of those that fail do so for reasons other than persistent bacterial infection [17]. Meta-analyses of comparative antibiotic trials performed for registration purposes have been carried out, which individually gave equivalent results. These analyses can be criticized because the outcomes analysed are usually not the original primary end-points of the trials. However, they do show that when large numbers of patients are included, there may be differences between antibiotics with respect to important criteria such as requirement for hospital admission and overall mortality [21]. Another way of improving the chances of differentiating between antibiotics would be to use other parameters in addition to recovery at the end of treatment (which is often decided rather crudely by lack of requirement for further antibiotic treatment) to judge antibiotic efficacy. Several proposals have been made *e.g.* speed of recovery, health-related quality of life questionnaires and time until next infective exacerbation [22, 23]. For example, comparison of a new quinolone antibiotic gemifloxacin with clarithromycin, confirmed the result described above with moxifloxacin *i.e.* bacteriological superiority of the quinolone, but no difference in clinical cure rate at the end of treatment. However, patients in the gemifloxacin group had a significantly ($p < 0.05$) longer period until their next infective exacerbation compared to clarithromycin [24]. This result suggests that persistent bacterial infection in patients taking clarithromycin does not prevent recovery from the acute exacerbation, but does lead to a shorter period between exacerbations.

Several recent studies have used bronchoscopy techniques to avoid nasopharyngeal contamination of expectorated sputum [25–27]. The protected specimen brush (PSB) catheter, which is introduced during bronchoscopy, is used to sample lower respiratory tract secretions, and has a lower risk of nasopharyngeal contamination, since the distal catheter plug is only dislodged when the bronchoscope is in position to take the sample. The technique is well established in patients with pneumonia who have not received antibiotics, but its application in COPD, where there is not an area of consolidation to direct the investigation, has been less well investigated. Other investigators have used lavage taken at bronchoscopy to investigate LRTIs, and this approach has some advantages in that a larger area is sampled and inflammatory mediators can be measured in the fluid, but has the disadvantage that upper respiratory tract contamination during insertion of the bronchoscope is more likely. These studies have confirmed results from older studies using sputum culture (reviewed in [8]) and shown that significant numbers of bacteria are present in the bronchial tree in about half to three-quarters of exacerbations. However, several factors make it difficult to determine the proportion of exacerbations in which bacterial infection is the major cause: spontaneous recovery is seen when the host defences are successful in overcoming the superficial mucosal infection; there may be more than one cause of the exacerbation *e.g.* viral infection and bacterial infection if it occurs is a secondary event; and lack of a noninvasive technique to reliably determine the presence and level of infection in the lower airways. The spectrum of pathologies in COPD and the range in severity of lung damage that is present also complicate antibiotic studies. For example, a viral infection may precipitate deterioration in the asthmatic component of COPD, as well as secondary bacterial infection. In this scenario, antibiotics given alone may eradicate the infection, but fail to deal with the increased airflow obstruction, so the patient would not recover.

Bacteriology of acute exacerbations of chronic obstructive pulmonary disease

There is general agreement that the bacterial species most commonly isolated from sputum during acute exacerbations of COPD are nontypable *H. influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* [8, 15], but several studies have shown that these species can be isolated from patients during stable periods, as well as during exacerbations [28–31]. One study did find an increase in the frequency with which bacteria

were isolated from the same patients during exacerbations compared to stable periods [32], but this has not been a uniform finding. Greater bacterial numbers may be isolated during an exacerbation compared to a stable phase. In one study a sputum Gram stain showed fewer than two organisms per oil immersion field when patients were stable, but 8–18·field^{-1} at the time of an exacerbation [33]. MONSO *et al.* [25] studied 40 COPD patients during a stable phase of their illness, and found positive PSB cultures defined as $\geqslant 10^3$ colony forming units (cfu)·mL^{-1} in one-quarter of patients. *H. influenzae* and *S. pneumoniae* were the predominant species detected. Another group of patients were studied during an exacerbation. The number with positive PSB cultures was ~50% of the patients and although the same species were predominant, the bacterial counts were higher. Twenty-four per cent of patients had more than 10^4 bacteria·mL^{-1} during an exacerbation, compared with only 5% of the stable patients.

Several recent studies have suggested that Gram-negative species, more commonly associated with bronchiectasis patients, are also isolated in COPD, and that there is a correlation between lung function and the bacterial species isolated. *H. influenzae* is still the most common isolate overall in these studies. In patients with mild airflow obstruction, *S. pneumoniae* and other Gram-positive cocci are more frequently isolated, whereas *Pseudomonas aeruginosa* and other Gram-negative bacilli account for a significant number of isolates in patients with severe airflow obstruction, but are rare in mild cases [34–36]. It could be speculated that: frequent prescription of antibiotics in patients with severe airflow obstruction has driven the bacteria colonizing the airways towards more resistant Gram-negative species, but no evidence has been presented that this is the case; and that high-resolution computed tomography (HRCT) might demonstrate unsuspected bronchiectasis in cases with *P. aeruginosa* infection as has been found in some COPD cases presenting with frequent infections [4].

FAGON *et al.* [27] studied patients with severe exacerbations of COPD that lead to hypercapnic respiratory failure, intubation and mechanical ventilation. Within 24 h, prior to any antibiotics being given, a PSB sample was taken from the segmental bronchus with most secretions. There was bacterial infection in half of the cases, but the species detected were much more diverse, and included *P. aeruginosa* and other Gram-negative bacilli. *H. parainfluenzae* was the most frequent isolate in this study. With the exception of fever, which was significantly higher in those patients with a positive PSB culture, the clinical features of the exacerbation were similar in patients with and without infection. Outcome measures were also similar in the two groups, although the majority of those patients with negative PSB cultures did receive empirical antibiotics.

Most bacterial species that infect the bronchial tree also form part of the commensal flora of the nasopharynx *e.g. H. influenzae*, or are opportunistic pathogens *e.g. P. aeruginosa*. Mucosal infections are usually superficial and the majority of bacteria reside in the lumen associated with secretions, while a proportion adhere to the epithelial surface, particularly in areas of epithelial damage, and some may infiltrate the mucosa [2, 37]. All the respiratory pathogens that the present authors have studied *in vitro*, adhere avidly to mucus and areas of epithelial damage (fig. 1). Mucus contains high molecular weight glycoproteins called mucins that have O-glycoside-linked carbohydrate side chains which provide plentiful receptors for bacterial adherence [2]. In healthy airways this facilitates removal of bacteria on the mucociliary escalator, but in diseased airways excess mucus is produced that is poorly cleared, and under these conditions, adherence to mucus favours infection. It is, therefore, not surprising that mixed infections are common in COPD, nor that several studies [38, 39] have shown that current cigarette smoking which impairs mucociliary clearance is associated with lower airway bacterial colonization (LABC).

Bacterial pathogenesis in chronic obstructive pulmonary disease

Repeated injury from high-dose inhalation of atmospheric pollutants or tobacco smoke leads to mucus hypersecretion, loss of ciliated cells, an increase in the number of goblet cells, and mucosal gland hypertrophy. These changes in the morphology of the airway make it susceptible to bacterial infection. Bacterial

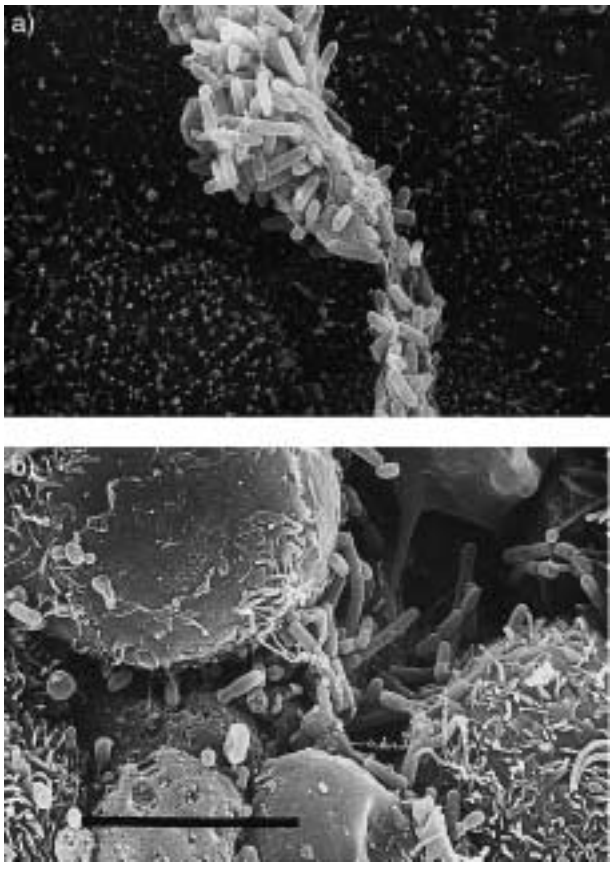

Fig. 1. – Nontypable *Haemophilus influenzae* adhering to mucus (a) and damaged epithelium (b) in an organ culture model.

products impair residual host defences and are one stimulus of neutrophilic inflammation. Within the mucosa, there are lymphocytes that are predominantly of the CD8+ T-cell phenotype, monocytes and macrophages. These cell populations have an important role in releasing mediators that orchestrate different aspects of chronic inflammation [40, 41]. Epithelial cells are also active participants in the inflammatory processes, since they release pro-inflammatory mediators including cytokines, arachidonic acid metabolites and nitric oxide (NO) [42]. Neutrophils and, to a lesser extent, eosinophils are attracted into the airway lumen by host factors such as interleukin (IL)-8, leukotriene B4 (LTB4) and complement factor 5a (C5a), and by chemotactic bacterial products [43–46]. Neutrophils release proteinase enzymes and reactive oxygen species during phagocytosis that are incompletely neutralized, either because they are released in close proximity to the tissue or in sufficient quantities to overwhelm antiproteinase and antioxidant tissue defences. Neutrophil products increase epithelial permeability, damage epithelial cells and stimulate mucus production [47–50]. The influx of neutrophils is self-perpetuating, in that their activation results in release of further IL-8 and LTB4, and as they move into the airway they degrade connective tissue releasing peptides that may be chemoattractant in their own right. Neutrophil elastase also activates C5, generating C5a, and may also activate epithelial cells to release more IL-8 [51, 52]. Immune complexes with bacterial antigens stimulate other inflammatory processes that escalate the inflammatory reaction [15]. Therefore, chronic inflammation weakens the host defences of the COPD airway, making it more susceptible to bacterial infection, and the inflammatory response is sustained by the presence of bacteria creating a circle of events (fig. 2). Bacterial infection is only one of numerous stimuli causing inflammation in COPD and evidence is lacking that increased inflammation due to bacterial infection alone leads to progression of airflow obstruction. However, when infective exacerbations occur, they have a major impact on the patients overall health status, which may take 6 weeks or more to recover and infection can lead to serious complications requiring hospitalization [1, 4, 6, 15, 53].

Bacterial respiratory pathogens are well equipped to exploit any weakness of the local host defences by employing various mechanisms to avoid clearance by those host defences that remain. These include production of factors that impair mucociliary clearance by paralysing ciliary beat and stimulating mucus production, enzymes that breakdown local immunoglobulin, antigenic heterogeneity to avoid immune surveillance, growth in biofilms, adherence to epithelium, survival within epithelial cells and formation of microcolonies surrounded by polysaccharide gel [2]. The serum and sputum of patients with COPD contain abundant antibodies to antigens of the bacteria that infect them. Studies using homologous isolates show a new antibody response to *H. influenzae* following an exacerbation [54]. However, bacteria can often persist in the airway despite this antibody response. Some of the antibodies may be directed against irrelevant antigens and possibly these antibodies block effective opsonization [15]. *H. influenzae* displays marked antigenic heterogeneity in its outer membrane proteins. The genetic mechanisms underlying these changes involve accumulation of point mutations in genes resulting in amino acid changes in surface exposed regions of major outer membrane proteins, and also transfer of deoxyribonucleic acid (DNA) between strains. There is a strong selection pressure favouring heterogeneity in order that the bacterium can avoid recognition by the host inflammatory response [55]. Lipopolysaccharide (LPS) is the major glycolipid in the outer membrane of *H. influenzae*. *H. influenzae* expresses an LPS molecule that lacks the long repeating polysaccharide side chains that are typical of the LPS of Gramnegative bacteria such as *Escherichia coli*. Therefore, endotoxin of *H. influenzae* is more accurately called lipo-oligosaccharide (LOS). There is marked structural heterogeneity of LOS between strains and even within a clone of bacteria derived from a single strain. The structure is influenced by environmental factors and genetic mechanisms that allow the bacterium to adapt to its environment. LOS components resemble oligosaccharide moieties on the surface of human cells, and this molecular mimicry may be another way that the bacterium avoids recognition by the host [55].

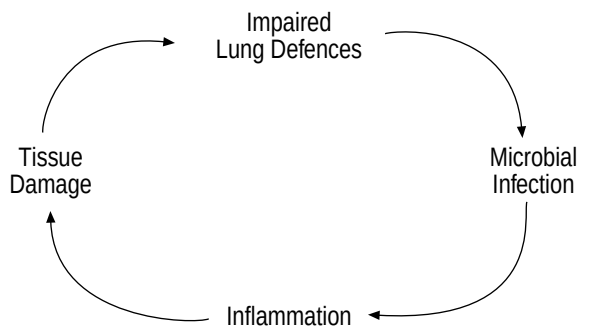

Fig. 2. – A circle of events in which impaired airway defences predispose to bacterial infection. Bacterial products and chronic inflammation cause changes to the mucosa which favour persistent infection.

LPS is a potent secretagogue for a variety of inflammatory mediators and immunoregulatory cytokines from resident and inflammatory cells in the lung, including tumour necrosis factor-α (TNF-α), prostaglandins, leukotrienes, interleukins, platelet-activating factor, NO, superoxide anion and hydrogen peroxide [41, 42]. The LOS of *H. influenzae* significantly increased the release of IL-6, IL-8 and soluble intracellular adhesion molecule-1 (sICAM-1) by cultured bronchial epithelial cells [56]. There are differences in the potential of LPS from different species to provoke inflammation. For example, *P. aeruginosa* LPS is more potent than *E. coli* LPS in stimulating release of monocyte chemotactic activity from various lung cell lines [57]. Other bacterial products stimulate IL-8 release from epithelial cells [58].

The mechanism by which some respiratory bacterial toxins damage epithelial cells has been elucidated. *Bordetella pertussis* tracheal cytotoxin (TCT), a muramyl peptide fragment secreted during bacterial

growth, is thought to contribute to the respiratory epithelial pathology of whooping cough. A series of elegant experiments by FLAK & GOLDMAN [59] have shown that TCT and LPS trigger the production of IL-1, which in turn stimulates NO production that causes cell damage. The present authors have shown that inhibition of NO synthase reduced the amount of epithelial damage caused by *P. aeruginosa* infection of a respiratory tissue organ culture, suggesting that the mechanism elucidated for TCT might be common to other respiratory pathogens that damage epithelial cells [60]. It is, therefore, of interest that levels of exhaled NO are elevated during exacerbations of COPD, and were not reduced acutely by intravenous corticosteroids, but did return to normal several months later when the patient was clinically stable [61].

The cause of an exacerbation might be multifactorial. Allergic airway fluid, components of air pollution and products of Grampositive and Gramnegative bacteria may all upregulate mucin production. The intracellular signalling and gene regulation mechanisms mediating these effects are being discovered, and to date it seems that the signalling pathways are distinct, although there are some common pathways *e.g.* mucin induction by both Grampositive and Gramnegative bacteria is tyrosine kinase dependent [62]. Viral infections are implicated in about a third of exacerbations [63]. Virus infection impairs mucociliary clearance by causing a loss of ciliated cells and altered mucus rheology [64], and *via* inflammatory mediators such as kinins, viral infections cause increased epithelial permeability which may escalate the inflammatory process [65]. These changes may facilitate subsequent bacterial infection or an increase in the number of bacteria already colonizing the lower airways. Although the viral infection itself may be self-limiting, secondary bacterial infection may prolong the exacerbation. Viruses could also enhance the inflammatory response to subsequent bacterial infection through the activation of transcription factors [66].

Bacterial colonization of the bronchial tree during the stable state

The application of bronchoscopy techniques to study infections in COPD has confirmed the results of earlier sputum studies that stable patients quite often carry bacteria in the lower respiratory tract, and multiple strains of the same species may be present [25, 28–31, 38, 39, 67, 68]. LABC probably represents a balance in which the impaired host defences are able to limit the numbers of bacteria, but not eradicate them. LABC is a dynamic process, so that strains may be carried for variable periods of time before being lost and replaced by others [55]. What is not clear at this stage is whether LABC influences the level of inflammation in the airway or the frequency of infective exacerbations. MONSO *et al.* [25] found that the bacteriology during exacerbations was the same as in the stable state. An exacerbation might occur when a reduction in the host defences follows a viral infection or some other insult allowing the colonizing strain to increase in numbers. However, other workers have suggested that acquisition of a new strain, or a change in the antigenic profile of the strain being carried, allows it to escape the host defences and cause an exacerbation [31].

MONSO *et al.* [38] and ZALACAIN *et al.* [39] both used PSB to investigate risk factors for LABC in stable COPD patients. The type of patient being studied was with stable chronic bronchitis without reversible airflow obstruction. Twenty-two per cent of patients in the former study and 40% in the latter had LABC. Nontypable *H. influenzae* was the most common isolate in both studies. Both studies found that current cigarette smoking predisposed to LABC. MONSO *et al.* [38] did not find an association between LABC and FEV_1, whereas there was an association with more severe airflow obstruction ($FEV_1 < 50\%$ predicted) in the study performed by ZALACAIN *et al.* [39]. The latter study contained more patients with severe airflow obstruction, which may explain this difference.

The presence of LABC alone does not confirm the importance of bacterial infection in the pathogenesis of COPD or its exacerbations, since LABC could just be a marker of the severity of the airway disease. The study by FAGON *et al.* [27] described earlier, could be interpreted as showing that bacteria are passengers rather than active participants in the inflammatory process. However, a recent study has shown that there were higher neutrophil counts, and elevated IL-8 and TNF-α levels in bronchoalveolar lavage (BAL) performed on stable chronic bronchitic patients with LABC by potential pathogenic bacteria compared to those without [69]. Neutrophil counts were significantly, inversely correlated with FEV_1 in this study. Should this result be confirmed by other studies, and there are no confounding factors such as current cigarette smoking, it will provide us with important evidence that LABC is a stimulus for airway inflammation and by inference it will confirm the importance of bacterial infection during exacerbations when bacterial numbers increase.

MONSO *et al.* [38] and ZALACAIN *et al.* [39] both reported isolation of bacterial species *via* PSB that are not usually regarded as respiratory pathogens *e.g. S. viridans*. Perception of what is a pathogenic species can change, for example *M. catarrhalis* was not regarded as a pathogen for many years, and there is debate at the moment about *H. parainfluenzae* [70]. There is very little information about the propensity of different species to stimulate inflammation, and even different strains of the same species may vary in their ability to elicit an inflammatory response [71]. Consequently, the total bacterial load in the bronchial tree could be an important parameter as well as the species involved [72].

There were three presentations at the American Thoracic Society in Toronto in 2000 concerning LABC. SETHI *et al.* [73] cultured and measured inflammatory mediators in sputum in 35 stable COPD patients. There was a significant ($p = 0.04$) association between LABC by respiratory pathogens and sputum IL-8, TNF-α and neutrophil elastase, which was independent of smoking history and severity of airflow obstruction. In a second study, the same group studied 70 sputum samples from 23 COPD patients in the same way [74]. They compared: 1) stable

COPD with no pathogens in sputum; 2) exacerbation of COPD, but no pathogens cultured; 3) stable COPD with a pathogen in sputum; and 4) exacerbation of COPD and pathogen cultured. Broadly speaking, with respect to the level of inflammation, the results were ranked 4)>3)>2)=1). The third study examined 10 stable COPD patients with chronic LABC by nontypable *H. influenzae* compared to nine noninfected, but otherwise similar COPD patients [75]. There was evidence of an ongoing inflammatory process in the chronically infected patients that caused plasma protein exudation into sputum. These studies all show that LABC stimulates chronic inflammation, and further work is urgently needed to determine how important LABC is in the pathogenesis of COPD. Bronchoscopy techniques are more difficult to justify in stable patients, and despite its limitations, carefully performed sputum examination can provide useful information. Bronchoscopy in smaller numbers of patients might be combined with imaging studies and measurement of surrogate markers of inflammation such as exhaled gases [4, 61, 76].

Antibiotic resistance and new antibiotics for treatment of lower respiratory tract infection

In recent years, there has been a dramatic rise in antibiotic resistance among common respiratory pathogens. Before 1987, <1% of pneumococci in the USA demonstrated high-level resistance to penicillin [77]. Surveillance during the 1997 respiratory season (autumn and winter) showed that overall penicillin resistance had reached 43.8%, 16% of isolates exhibiting intermediate-level and 27.8% high-level resistance [78]. Penicillin-resistant *S. pneumoniae* (PRSP) were also likely to have reduced susceptibility to other antibiotic classes including macrolides, cephalosporins, tetracyclines and trimethoprim-sulphamethoxazole [78]. Resistance to macrolide antibiotics, including the newer agents clarithromycin and azithromycin, was present in 48% of strains with high penicillin resistance. Risk factors for multidrug resistant *S. pneumoniae* include prior antibiotic use, extremes of age and hospitalization [79]. In two other recent large surveillance studies [80, 81] beta-lactamase production was found in 33.4% of *H. influenzae* and 95% of *M. catarrhalis*. Although most studies have shown considerable geographical variation in resistance patterns, the trend in all areas is towards increased resistance to commonly prescribed antibiotics [82, 83]. Recently, attention has also been drawn to decreased susceptibility of *S. pneumoniae* to fluoroquinolones, perhaps reflecting increased use of this class of antibiotic [84]. The frequency with which antibiotics are used in a community is reflected in the amount of antibiotic resistance in a particular class [85], and probably use of antibiotics in animal husbandry and agriculture is contributing to the problem [86].

Surprisingly, there is little published evidence that the rise in antibiotic resistance has led to a proportional increase in the number of clinical failures in the treatment of LRTI. This might be expected in COPD, given the debate about the importance of antibiotic treatment described earlier, but even in community-acquired pneumonia, there is uncertainty whether a relationship exists, particularly with respect to penicillin treatment [87]. The reason may be partly due to the efficiency of the host defences, which can overcome infection despite suboptimal antibiotic treatment. In addition, particularly for hospitalized patients given intravenous antibiotics, the dosage of antibiotics used *in vivo* can often overcome the *in vitro* resistance. The lack of data should not give a false sense of security, and more studies are required, particularly with respect to strains with high-level penicillin resistance, infections in vulnerable patient groups and in the community where lower dosages are used. In a recently published, very large cohort study of patients with bacteraemic pneumococcal pneumonia, increased mortality was significantly associated with high-level penicillin resistance with mean inhibitory concentrations (MIC) of ≥ 4 $\mu g \cdot mL^{-1}$ [88]. In another study, penicillin resistance was an independent predictor of adverse outcome in a population with high human immunodeficiency virus seroprevalence [89]. Bacteria, because of their promiscuity and rapid generation time, will always develop resistance to antibiotics to which they are regularly exposed. Therefore, there will continue to be a demand for new antibiotics to treat serious LRTI.

The various antibiotic classes have been grouped together on the basis of their mechanism of action: inhibitors of peptidoglycan synthesis *e.g.* beta-lactams; inhibitors of protein synthesis *e.g.* macrolides and tetracyclines; inhibitors of nucleic acid synthesis *e.g.* quinolones; agents interfering with membrane function *e.g.* cationic peptides and lipopeptides. Some new antibiotics have recently become available, and others have reached an advanced stage in clinical development. These antibiotics are summarized in table 1. In terms of COPD, the most useful agents are likely to be the new third-generation quinolones and ketolides.

The new third-generation quinolone agents have antimicrobial activity similar to that of ciprofloxacin against Gramnegative pathogens, but superior activity against Grampositive, atypical and anaerobic organisms. They may be particularly useful in the treatment of PRSP, since penicillin resistance does not influence quinolone sensitivity and, at the present time, a very small percentage of pneumococci have elevated MIC′s to newer quinolones such as moxifloxacin and gatifloxacin [84]. However, it is a concern that wider use of these agents for LRTIs will inevitably lead to increased resistance. This might occur faster if older quinolones with borderline MIC′s against the pneumococcus are used because they cost less. Clinical efficacy of third-generation quinolone agents in registration trials in COPD has largely demonstrated equivalence to commonly prescribed agents [19, 24]. Therefore, their use should be restricted to COPD patients with more serious illness who are at risk for infections with antibiotic-resistant strains (see Guidelines for the use of antibiotics in chronic obstructive pulmonary disease).

Several new quinolone antibiotics have been withdrawn during their research programme and in four instances this has occurred after launch (or their use has been severely restricted): temafloxacin (haemolysis

Table 1. – New antibiotics for lower respiratory tract infections (LRTI)

Class	Examples	Target of action	Clinical application
Quinolones	Moxifloxacin Gatifloxacin (Gemifloxacin)	Nucleic acid synthesis	Community-acquired LRTI
Ketolides	(Telithromycin)	Protein synthesis	Community-acquired LRTI
New betalactams	New oral third generation cephalosporins (Oral carbapenems) (Tricyclic beta lactam compounds)	Peptidoglycan synthesis	Community-acquired LRTI
Oxazolidinones	(Linezolid) (Eperezolid)	Protein synthesis	Multiresistant Gram-positive cocci including MRSA
Streptogramins	Quinupristin/dalfopristin	Protein synthesis	Multiresistant Gram-positive cocci including MRSA

Antibiotics in parentheses are not yet available, but are in an advanced stage of clinical development. MRSA: multidrug resistant *Staphylacoccus aureus*.

and severe multiorgan dysfunction), trovafloxacin (hepatic toxicity), sparfloxacin (phototoxicity, ventricular tachy-arrhythmias) and grepafloxacin (ventricular tachy-arrhythmias). Quinolone-induced ventricular tachy-arrhythmias have recently received much publicity [90]. The problem is related to prolongation of the electrocardiograph QT interval that is associated with various serious tachy-arrhythmias and specifically torsade de pointes. It is probably a class effect in that it has been described during preclinical animal toxicology assessments of all quinolones adequately investigated. Other drugs are associated with long QT syndromes and these include cisapride, antiarrhythmics *e.g.* amiodarone, antihistamines *e.g.* terfenadine, psychotropics *e.g.* fluoxetine and other antibiotics *e.g.* macrolides. Despite huge exposure of at risk patients to quinolones and macrolides, these agents have very rarely been associated with adverse cardiac events. To date, the three new quinolones mentioned in table 1 have not been reported to have clinical problems related to QT prolongation, although it would be prudent to continue to monitor the situation as they are used in larger numbers of seriously ill patients with associated risk factors, and to avoid co-administration with other drugs known to prolong the QT interval.

Ketolides are semisynthetic derivatives of the 14-membered ring macrolides. They are active against multiresistant penicillin/macrolide resistant pneumococci, and have good activity against other bacterial species involved in LRTI including *H. influenzae*, *M. catarrhalis* and atypical species. They may also retain the anti-inflammatory properties described with macrolide antibiotics [91].

Guidelines for the use of antibiotics in chronic obstructive pulmonary disease

Respiratory tract infections are the most common indication for antibiotic prescription, accounting for ~60% of all scripts (Intercontinental Medical Statistics (IMS) current database). In 1992, ~12 million prescriptions were given for LRTIs in the UK, costing £47.2 million [92]. In Europe, >80% of all LRTIs are treated with antibiotics [93]. Although acute exacerbations of COPD are very common, the pattern of antibiotic prescription varies widely from country to country, and there is no clear rationale for the antibiotic choices. The pharmaceutical industry has not been slow to recognize that increased antibiotic resistance provides a powerful argument in favour of new antibiotics that are active against strains resistant to older agents. Over the last 5 yrs, the number of antibiotic prescriptions has been constant, but newer antibiotics, that would previously have been considered second-line, are now more commonly prescribed [94]. In order to control the rise in antibiotic resistance and conserve the activity of current agents, the volume of antibiotics to which bacteria are exposed should be reduced. The present expectation of patients is that they will receive an antibiotic when visiting a doctor with acute respiratory symptoms, even if they are otherwise fit and the symptoms are relatively trivial. One way of reducing antibiotic consumption would be to educate patients that many LRTIs resolve spontaneously, that viruses are common and do not respond to antibiotics, and that coughing is a normal host defence which fulfils an important role [95].

The guidelines of learned societies have differed in what they advise about antibiotics and COPD. The European Respiratory Society [96] and American Thoracic Society [97] have paid scant attention to the importance of antibiotic treatment in the overall management of COPD. The American guidelines state that antibiotics are not of proven value unless there is evidence of infection. Rather surprisingly, they cite fever, leukocytosis and changes in the chest radiograph as evidence of infection. Fever is unusual in bacterial infections of the airway mucosa and is more common in viral infections [92], and most LRTIs are treated in the community without the benefit of further investigations. The European guidelines acknowledge that most antibiotic treatment is empirical, and emphasize the importance of sputum purulence as an indicator of bacterial infection. Both sets of guidelines

recommend that knowledge of local resistance patterns should influence choice of antibiotic, but emphasize that older inexpensive antibiotics are usually effective.

More recently, the European Respiratory Society have published guidelines in the management of adult community-acquired LRTI [98, 99]. They emphasize that the main goal of the initial clinical evaluation is to determine whether the patient can be managed at home or whether there is evidence that suggests potential or immediate severity, or that the illness will follow a complicated course which requires admission to hospital. This involves an assessment of clinical criteria of more severe illness and consideration of risk factors for poor outcome. These guidelines and those of the British Thoracic Society [100] lean heavily on the study by ANTHONISEN *et al.* [17] described earlier, and advise that antibiotics should be used if the patient has two or more of: increased breathlessness, increased sputum volume and development of purulent sputum. Once again they recommend that local guidelines should be derived from sensitivity data, and the British Thoracic Society [100] add that new "brands" of antibiotic are not appropriate. The European Respiratory Society [98] recommends amoxycillin (500 mg or 1 g three times daily) as first-line, and lists alternatives to be used where the frequency of beta-lactamase producing *H. influenzae* or penicillin-resistant *S. pneumoniae* justifies it. Unfortunately, it is not clear how widely this local knowledge is available to primary care physicians, nor the level of resistance that should lead to a change in antibiotic policy.

The Canadian [101], Asia-Pacific [102] and Latin American [103] guidelines have taken a different approach. They have each, in broadly similar ways, stratified patients according to likely pathogen and risk factors for poor outcome. The Canadian guidelines were the first to adopt this approach, although it had been suggested elsewhere several years earlier [104]. Their scheme is summarized in table 2 [99]. The concept which is common to each of these guidelines is to differentiate patients who do not require antibiotic treatment, from patients in whom antibiotic treatment is indicated, but it is unlikely to be critical to their recovery, and finally a third group in which inadequate treatment will lead to increased morbidity and mortality. The guidelines include acute bronchitis because they recognize that many antibiotics are prescribed inappropriately in this condition.

There is broad agreement in the guidelines on several key issues. There are differences in the likely pathogens in acute bronchitis, mild-to-moderate COPD and severe COPD. Acute bronchitis is predominantly a viral illness that is self-limiting and antibiotics should not be used. If symptoms persist, other conditions such as bronchial hyperreactivity and asthma should be considered first, but likely bacterial pathogens are *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *S. pneumoniae*, so a macrolide antibiotic would be most appropriate. In mild-to-moderate COPD ($FEV_1 > 50\%$ pred), viral infections are again common, and *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* are the likely bacterial pathogens. The ANTHONISEN *et al.* [17] criteria adopted by the European Respiratory Society [98] and the British Thoracic Society [100] would seem reasonable evidence based guidelines that are easy to apply to decide which patients require an antibiotic. In most areas, the levels of antibiotic resistance in the three main species would not be sufficient to recommend anything other than older antibiotic agents *e.g.* amoxycillin or doxycycline, in this low risk group. Erythromycin is not thought appropriate because of poor activity against *H. influenzae*. Sputum culture and other investigations should be reserved for those patients who fail empiric therapy.

The guidelines differ in the recommendations that they make for patients with severe COPD ($FEV_1 < 50\%$ pred) and patients with conditions that have been associated with poor outcomes. These conditions have been reviewed elsewhere and include cardiopulmonary disease, hypoxia, hypercapnia, long duration and severity of disease, mucus hypersecretion, frequent exacerbations and requirement for oral corticosteroid therapy [4, 99, 105, 106]. The current American, European and British guidelines do not recommend any change in antibiotic policy, whereas the other three sets recommend first-line empirical therapy with an antibiotic that is active against resistant strains such as those producing beta-lactamase enzyme, and in some patients who have received frequent courses of antibiotics or also have chronic bronchial suppuration Gram-negative bacilli. The former bacteria would be covered by a quinolone, co-amoxyclavulanate, which contains a beta-lactamase inhibitor, some oral second

Table 2. – The Canadian guidelines for stratification of patients with acute and chronic bronchitis

Group	Title	Characteristics
1	Acute bronchitis	Healthy people No previous respiratory problems
2	Simple chronic bronchitis	Cough plus sputum for 3 months of 2 consecutive yrs Age < 65 yrs Moderate or no respiratory impaiment < 4 exacerbations$\cdot yr^{-1}$
3	Complicated chronic bronchitis	Cough plus sputum for 3 months of 2 consecutive yrs Age > 65 yrs or $FEV_1 < 50\%$ or > 4 exacerbations$\cdot yr^{-1}$
4	Chronic bronchitis with other risk factors	Group 2 or 3 with risk factors for poor outcomes *e.g.* comorbid illness
5	Bronchiectasis	Chronic purulent sputum production

Data from [101].

and third generation cephalosporins and the azalide antibiotic azithromycin; whereas the latter group would only be covered by ciprofloxacin because of the risk of *P. aeruginosa* [34–36]. Sputum culture should be more readily performed in this group. None of the guidelines advise whether the dosage or length of treatment should be adjusted depending on the severity of underlying disease, since there is almost no published information on this topic. The logic for treating severe COPD patients with risk factors differently, is that these patients are more likely to carry resistant pathogens [107], and if their infection is inadequately treated, they are more likely (than patients with mild-to-moderate COPD and no risk factors) to have a complication either of their respiratory condition *e.g.* respiratory failure, or a comorbid illness *e.g.* congestive cardiac failure. It is important to emphasize that this approach of identifying an at risk group for different antibiotic therapy has never been prospectively studied or validated.

A small number of studies have compared different classes of antibiotic in at risk patient groups. In a retrospective study in a Veterans Administration clinic population, COPD patients were treated mainly with older "standard" antibiotics. There was a 14.7% failure rate within 4 weeks, and more than half of these failures required hospitalization. The choice of antibiotic did not affect the outcome [108]. In a prospective study, chronic bronchitis patients who had $\geqslant 3$ treated exacerbations in the past year, were randomized to receive ciprofloxacin or their physicians (non-quinolone) choice of antibiotic, at each exacerbation during one full year of observation [94]. Clinical endpoints (days of illness, hospitalization, time to next exacerbation), quality of life measures and an assessment of healthcare costs, showed no difference between the two treatment arms. However, a *post hoc* analysis showed trends in favour of ciprofloxacin with respect to clinical outcome, higher quality of life and less overall cost in patients with risk factors. A recently published retrospective study examined 224 exacerbations in 60 outpatients. Therapy was divided into first-line (amoxycillin, tetracycline, erythromycin, trimethoprim-sulphamethoxazole), second-line (cephalosporins) and third-line (amoxycillin-clavulanate, azithromycin, ciprofloxacin). Patients who received first-line agents failed more often than those who received third-line agents (19% *versus* 7%, $p < 0.05$). In addition, those given first-line agents were hospitalized more often than those given third-line agents, and the time between exacerbations was significantly longer for those given third-line agents [109].

Further studies are needed to determine whether differences in bacteriology among the different populations of chronic obstructive pulmonary disease patients, necessitates different choices of antibiotic, and whether this influences clinical outcomes.

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