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Contributions to an understanding of community-acquired pneumonia

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1 INTRODUCTION

1.1 General Remarks

The works presented here were published by myself and collaborators between 1985 and 2007. All of the publications deal with aspects of respiratory tract infections, in particular community-acquired pneumonia. Most of the clinical studies, and especially the initial ones, were undertaken among patients in Johannesburg, South Africa, and therefore have particular reference to that group of patients. Several of the more recent studies have been multicentre, international collaborations, involving patients from many parts of the world.

There are also laboratory-based research articles that are included, the initial studies having being undertaken in the Host Defence Unit, Department of Thoracic Medicine, Imperial College of Science and Technology, University of London and the Royal Brompton Hospital, London United Kingdom, and the remainder in South Africa in collaboration with Professor Ronald Anderson and the various members of his research unit, the MRC Unit for Inflammation and Immunity, Department of Immunology, Faculty of Health Sciences, University of Pretoria and the Tshwane Academic Division of the National Health Laboratory Services, University of Pretoria, Pretoria, South Africa.

In all the clinical studies, standard diagnostic criteria for community-acquired pneumonia were used and therefore the cases included were patients with a lower respiratory tract infection, acquired in the community, which was associated with radiological evidence of consolidation of part or parts of one or both lungs. In this respect

all the cases of pneumonia, therefore, had been radiologically confirmed. In the early studies, patients with pneumonia were considered to severely ill simply because they required admission to the intensive care unit, although an attempt was also made to assess objectively severity of illness using the various "severity of illness" scoring systems. In the more recent studies severity of illness was quantified on the basis of one or more of the modern "severity of illness" indices or scores.

1.2 Background to the community-acquired pneumonia studies

Community-acquired pneumonia has been defined as a lung infection, acquired in the community, most commonly bacterial in nature, associated with inflammation of the lung parenchyma distal to the terminal bronchiole, with clinical and radiological evidence of consolidation of part or parts of one or both lungs. It is a common infection that causes considerable morbidity and mortality, even in the modern world, especially among the very young, the elderly, and those patients with underlying co-morbid disease (File Jr., 2004). The infection was well known to Hippocrates and the ancient Greek Physicians. Aretaeus was said to have given a remarkable description of the condition, and Morgani and Valsalva contributed valuable clinical and anatomical observations on the condition; however, modern knowledge of the disease is said to date back to Laennec (1819) "whose masterly description of the physical signs and morbid anatomy left very little for subsequent observers to add or modify" (Osler, 1967).

The overall mortality of community-acquired pneumonia varies from < 1% in outpatients to approximately 14% in cases admitted to hospital and to 50% or more in

patients requiring intensive care unit admission (File Jr., 2004; Woodhead et al., 2006). Community-acquired pneumonia puts an enormous burden on medical and economic resources, particularly if patients are hospitalized, since this is associated not only with direct hospital costs but also with intensified laboratory investigation and broader empiric antimicrobial chemotherapy (File Jr., 2004; Lode, 2007). Studies from the United States (File Jr., 2004), Europe (Lode, 2007) and the United Kingdom (Guest and Morris, 1997; Melegaro et al., 2006) attest to the considerable burden of disease that is associated with this infection, even in the developed world.

A number of recent studies have investigated in detail the global and regional burden of diseases in the world (Lopez and Mathers, 2006; Lopez et al., 2006). In 2001 slightly more than 56 million people died (Lopez et al., 2006). Five of the ten leading causes of death in low and middle income countries were infectious diseases including lower respiratory tract infections, which were the commonest infectious cause, being even more common than human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), diarrhoeal diseases, tuberculosis and malaria. In low and middle income countries, lower respiratory tract infections were the third leading cause of death (3.41 million deaths – 7% of total deaths) and in high-income countries the fourth leading cause of death (0.34 million deaths – 4.4% of total deaths) (Lopez et al., 2006). Importantly, lower respiratory tract infections were the second leading cause of burden of disease, as measured by disability-adjusted life years (DALYs) in low and middle income countries of the world (83.61 DALYs (millions of years) – 6.0% of total DALYs) (Lopez et al., 2006).

Similarly, in 2002 it was reported that slightly over 57 million people died in the world of which lower respiratory tract infections were the third leading cause of death (3.94 million deaths – 6.9% of total deaths) (Lopez and Mathers, 2006). Lower respiratory tract infections were the second leading cause of burden of disease in low and middle income countries as measured by DALYs (92.2 DALYs (millions) – 6.7% of total DALYs) (Lopez and Mathers, 2006). In sub-Saharan Africa, lower respiratory tract infections were the second leading cause of disease burden (second only to HIV/AIDS) (37.2 DALYs (millions) – 10.0% of all DALYs) (Lopez and Mathers, 2006).

Several studies have also been undertaken in South Africa investigating the leading causes of death (van Rensburg and Mans, 1982; Bradshaw et al., 2002; Bradshaw et al., 2003; Statistics South Africa, 2007). These studies have investigated not only the cause of death, but also years-of-life-lost (YLL), since the latter takes into account the age at which death occurs, which is particularly important because it focuses on premature loss of life (Bradshaw et al., 2002). Even as early as 1982 it was reported that pneumonia, excluding influenza, was the first to third leading cause of death in all population groups in South Africa for the year 1976 (van Rensburg and Mans, 1982). In 1996, there were reported to be 327,253 deaths in South Africa, including 186,538 males and 140,530 females (Bradshaw et al., 2002). Lower respiratory tract infections accounted for 4.0% and 4.8% of deaths, respectively. Importantly, lower respiratory tract infections accounted for 3.9% and 5.4% of years-of-life-lost for males and females respectively (Bradshaw et al., 2002). Similarly, in 2000 among the top 20 causes of premature mortality burden (YLLs), lower respiratory tract infections were sixth overall (449,010 – 3.8%), being fifth in males (239,770 – 3.7%) and fourth in females (209,240 – 3.8%) (Bradshaw et al., 2003).

Statistics South Africa have released data showing that in 2005, “Influenza and Pneumonia” was the third leading cause of death in the country (45,596 – 7.71% of deaths)(Statistics South Africa, 2007). Most of these cases were described in more detail as being “Pneumonia: organism unspecified”. Further analyses indicated that while in the years 1997-1999 “Influenza and Pneumonia” was the fourth leading cause of death, for the years 2000-2003 “Influenza and Pneumonia” was the second leading cause of death (Statistics South Africa, 2007).

One factor that has contributed significantly to the impact of community-acquired pneumonia, particularly in patients in sub-Saharan Africa, has been the associated epidemic of HIV infection (Merson, 2006). Worldwide more than 40% of new infections have occurred in adults aged 15-24 years, and 95% of these infections and the associated deaths have occurred in developing countries. Sub-Saharan Africa is home to almost 64% of persons living with HIV and this burden is seen particularly among women (Merson, 2006). Pulmonary infections including tuberculosis, opportunistic infections, but also community-acquired pneumonia, occurs much more commonly in HIV-infected persons than in non-immunocompromised individuals and community-acquired pneumonia is second among the pulmonary complications (Murray, 2005). Among the causes of pneumonia, as in non-immunocompromised cases, *Streptococcus pneumoniae* remains the commonest pathogen (Murray, 2005). Interestingly, initial studies, erroneously, suggested that *Pneumocystis carinii* (now called *Pneumocystis jirovecii*) infections were uncommon causes of infection and/or death in African patients infected with HIV (Abouya et al., 1992). This impact of HIV infection on the profile of disease presentation in patients in South Africa has been clearly shown in a study in northern KwaZulu Natal (a province in

South Africa particularly devastated by the HIV epidemic), which indicated that between 1991 and 2002 hospital admissions in the medical wards of a small rural district hospital rose from 228 to a total of 626 patients, in particular due to infectious diseases, among which lower respiratory tract infections featured prominently (Reid et al., 2005).

The outcome of community-acquired pneumonia is influenced by a number of factors, including host factors, bacterial factors and antibiotic factors (Lujan, Gallego and Rello, 2006). Among the host factors, older age, the presence of underlying co-morbid illness and various genetic characteristics of the host are all potentially associated with increased risk of pneumonia as well as a worse outcome (Lujan et al., 2006). Severity of illness on its own may impact negatively on pneumonia outcome, even in the absence of any of these other risk factors (Lujan et al., 2006; Valencia, Sellares and Torres, 2006; Garau and Calbo, 2008). Severity of illness assessment is therefore important not only because it gives an indication as to the likely outcome of the patient with community-acquired pneumonia, but because it dictates the appropriate site of care of these patients, the extent of the microbiological work-up needed and the choice of initial empiric antimicrobial chemotherapy (Lujan et al., 2006; Valencia et al., 2006; Garau and Calbo, 2008). A number of severity-of-illness indices and various scoring systems have been developed to assist in severity assessment, among which the PSI (Pneumonia Severity Index) and the CURB-65 score (derived from the British Thoracic Society rules) are the most commonly used (Valencia et al., 2006). The PSI was developed primarily to identify low-risk patients that could safely be managed at home, whereas the CURB-65 score was developed to identify patients with severe community-acquired pneumonia at high risk of

mortality. While each scoring system has its own individual strengths and weaknesses none of them are able to replace sound clinical judgment of the attending physician.

Among the bacterial factors that may impact on the outcome of pneumonia are the nature of the infecting microorganism, its associated virulence factors and its susceptibility to commonly prescribed antibiotics (Lujan et al., 2006). Overall the commonest microorganism causing community-acquired pneumonia is *Streptococcus pneumoniae.* This bacterium is known to have a number of important virulence determinants that are associated with its pathogenicity, but its cytolytic, thiol-activated, protein toxin, pneumolysin, is thought to be one of its most important virulence factors, playing an pivotal role in microbial colonization, invasion, and dissemination, as well as tissue inflammation (reviewed in Cockeran, Anderson and Feldman, 2002; Cockeran, Anderson and Feldman, 2003; Cockeran, Anderson and Feldman, 2005; Feldman and Anderson, 2007).

Significant consideration also needs to be given to the potential impact of antibiotic resistance, particularly pneumococcal resistance to beta-lactam agents, on the outcome of pneumonia (Metlay, 2002; File, 2004; Lujan et al., 2006; Mufson, Chan and Stanek, 2007). While much has been published on this subject, it does appear, overall, that current levels of beta-lactam resistance among pneumococcal isolates are such that if appropriate beta-lactam agents are used at appropriate dosages, resistance should not impact negatively on the outcome of respiratory tract infections (Metlay, 2002; Mufson et al., 2007). The situation is less clear-cut in the case of macrolide antibiotics, which have received much less attention, but it does appear that when these agents are used on their own, particularly

in the presence of high-level macrolide resistance, breakthrough bacteraemias may well occur (Lujan et al., 2006). One considerable concern internationally is the fact that there are very few new antibiotics in the developmental pipeline that would be available to combat infections due to highly resistant microorganisms, should these become more widespread (Wenzel, 2004; Norrby, Nord and Finch, 2005). While other adjunctive strategies are being studied for use together with antibiotics to improve the outcome of severely ill patients with community-acquired pneumonia (Cazzola, Page and Matera, 2004; Rano et al., 2006; Valencia et al., 2006), it still remains true that the mainstay of therapy of such infections will always be effective antibiotic therapy.

Among the antibiotic factors, choice of agent, dosage and duration of therapy, as well as time to initiation of antibiotics from time of presentation of patients to hospital all potentially play a role in the outcome of pneumonia (Garau and Calbo, 2008). Importantly, new strategies recommended for antibiotic management, for example the use of combination antibiotic therapy in sicker hospitalized cases with pneumonia, including the subset of patients with bacteraemic pneumococcal infections, have been said to have a positive impact on pneumonia outcomes (Waterer, 2005; Lujan et al., 2006). The most commonly used combination therapy for which benefit has been shown has been the addition of a macrolide to standard beta-lactam therapy, although benefit has also been shown with other combinations (Waterer, 2005; Lujan et al., 2006). A number of questions still remain with regard to combination therapy, including an understanding of which combination(s) are best (Waterer and Rello, 2006), as well as the exact mechanism(s) by which combination therapy may have benefit (Waterer, 2005; Lujan et al., 2006). One of the reasons suggested for the benefit of combination therapy is that this is associated with

the addition to the beta-lactam agent of an antibiotic effective against so-called atypical pathogens (i.e. a macrolide, azalide, ketolide, tetracycline, or fluoroquinolone). Interestingly, a recent study investigated the outcome of bacteraemic pneumonia in relationship to initial antibiotic therapy, and although the investigation confirmed that the use of an agent active against atypical pathogens was independently associated with a decreased 30-day mortality, further analysis suggested that this benefit was limited to the use of macrolides and not fluoroquinolones or tetracycline (Metersky et al., 2007). Many believe that the reason for benefit of adding a macrolide to standard beta-lactam therapy resides in the considerable anti-inflammatory, immunomodultaory activities that the macrolide group of antibiotics posses (Kobayashi, 1995; Tamaoki, Kadota, and Takizawa, 2004; Tateda et al., 2004; Amsden, 2005).

As part of the global strategy, a number of national and international guidelines have been developed describing the optimal management of patients with community-acquired pneumonia, with the intention of improving the care and outcome of these patients (Armitage and Woodhead, 2007; Feldman et al., 2007; Mandell et al., 2007). Many of these guidelines are being informed by the various studies of community-acquired pneumonia, and in particular the very large multicentre, international, collaborative studies of community-acquired pneumonia that are being conducted internationally, which are able to recruit large numbers of cases throughout the world. A more detailed description of one of these collaborations that has contributed to a number of the studies described below has been published elsewhere (Ramirez, 2007).

It has been stated that the mortality of community-acquired pneumonia remains substantial in both the developed and developing world, despite all recent advances in medicine, including the availability of potent antimicrobial therapy and even the establishment of intensive care unit facilities. A number of questions and challenges still remain with regard to a full understanding of the nature of community-acquired pneumonia and its optimal management that require continuing ongoing research in this area (Niederman, 2007).

1.3 References

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2 EARLIER STUDIES THAT GUIDED THE DIRECTION OF THE RESEARCH

1 **Feldman C**, Kallenback JM, Levy H, Reinach SG, Hurwitz MD, Thorburn JR, Koornhaof HJ. Community-acquired pneumonia of diverse aetiology: prognostic features in patients admitted to an intensive care unit and a "severity of illness" score. *Intensive Care Medicine* 1989; 15: 302-307.

2 **Feldman C**, Kallenbach JM, Miller SD, Thorburn JR, Koornhof HJ. Community-acquired pneumonia due to penicillin-resistant pneumococci. *N Engl J Med* 1985; 313: 615-617.

In 1981 a new intensive care unit was established at the newly designated Hillbrow Hospital in Johannesburg, South Africa. It soon became apparent that a number of the medical cases that were admitted to the intensive care unit of the Hospital were previously well, young male patients with severe community-acquired pneumonia. The infection was associated with an extremely high mortality, in the region of 50%. The devastating nature of these infections prompted the further investigation of these cases, and the publication of a number of studies, which resulted in the award of a PhD thesis entitled "Aspects of Community-Acquired Pneumonia". All of the studies that contributed to the PhD were undertaken in the pre-HIV era. The advent of the HIV epidemic was associated with significant opportunity for further research among these patients with community-acquired pneumonia.

Among the various studies that contributed to the PhD were two investigations, in particular, that directed the future investigations that were undertaken on the subject of community-acquired pneumonia. The initial study was among the first to have investigated the prognostic features of patients with severe community-acquired pneumonia of diverse aetiology (1). While a number of previous studies had been undertaken investigating negative prognostic factors in patients with pneumococcal pneumonia, documentation of these factors in patients with pneumonia due to micro-organisms other than the pneumococcus was, at that time, lacking. Among the main findings were that a lower white cell count, platelet count, total serum protein and albumin and a higher mean serum creatinine and phosphate level were predictive of a poor prognosis. However the most significant predictor of poor outcome was the presence of bacteraemia. This study encouraged a number of further studies of patients with severe community-acquired pneumonia. Interestingly, even among early studies, such as this, an attempt was made to relate prognostic factors to some of the early "severity of illness" scores (the SAPS – simplified acute physiology score), although these had not yet been comprehensively evaluated.

The second study (2) was the first in the world to describe, in detail, the occurrence of community-acquired pneumonia in adult patients due to penicillin-resistant pneumococcal isolates. This study encouraged several further investigations of patients with pneumococcal infections, as well as studies of the impact of microbial aetiology, as well as antimicrobial resistance, on the outcome of these infections

3 CLINICAL STUDIES OF COMMUNITY-ACQUIRED PNEUMONIA

3.1 Severe community-acquired pneumonia

3 Smith C, Arregui LM, Promnitz DA, **Feldman C**. Septic shock in the intensive care unit, Hillbrow Hospital, Johannesburg. *S Afr Med J* 1991; 80: 181-184.

4 **Feldman C**, Ross S, Goolam Mahomed A, Omar J, Smith C. The aetiology of severe community-acquired pneumonia and its impact on initial, empiric, antimicrobial chemotherapy. *Respiratory Medicine* 1995; 89: 187-192.

5 Baum DR, **Feldman C**, Smith C, Ginsburg P. *Mycoplasma pneumoniae* pneumonia requiring intensive care unit admission. *South Afr J Epidemiol Infect* 1988; 3: 3-4.

6 **Feldman C**, Viljoen E, Morar R, Richards G, Sawyer L, Goolam Mahomed A. Prognostic factors in severe community-acquired pneumonia in patients without co-morbid illness. *Respirology* 2001; 6: 323-330.

7 Seedat MA, **Feldman C**, Skoularigis J, Promnitz DA, Smith C, Zwi S. A study of acute community-acquired pneumonia, including details of cardiac changes. *Q J Med* 1993; 86: 669-675.

8 Puren A, **Feldman C**, Savage N, Becker PJ, Smith C. Patterns of cytokine expression in community-acquired pneumonia. *Chest* 1995; 107: 1342-1349.

9 **Feldman C.** Severe community-acquired pneumonia. *Curr Opin Pulm Med* 1997; 3: 98-104.

10 **Feldman C**. Cytokines and acute respiratory infections. *Sepsis* 1998; 1: 173-179.

Septic shock is an important, potentially reversible cause of admission of patients to an intensive care unit (ICU), but the aetiology of such infections in any ICU, and the particular role played by community-acquired pneumonia in such infections, is frequently not appreciated. One study (3) documented that community-acquired infections (69% of cases) were the most common cause and that the most frequent site of such infection was the respiratory tract (51% of cases), with a mortality of 39%. The overall mortality rate for the group as a whole was very high (40%), higher than that predicted by the APACHE II score, but was very similar to that found in various other international studies, with no difference in the outcome between community- or hospital-acquired infections or infections caused by gram-positive or gram-negative pathogens.

The specific microbial aetiology of severe community-acquired pneumonia needed to be adequately documented in the South African setting. In a study investigating the aetiology of severe community-acquired pneumonia in patients both without and with underlying co-morbid illness (designated “primary” and “secondary” infections) it was noted that the commonest cause of infection was *Streptococcus pneumoniae* (51.3% and 36.6%, respectively), while *Klebsiella pneumoniae* was the next most common isolate (31.9% and 29.3%, respectively) (4). This study confirmed the finding that infection with *K. pneumoniae* was extremely common in the intensive care unit setting in South Africa,

even among cases without comorbid illness, who would have had no specific risk factors for gram-negative colonisation, and that these infections contributed to the high mortality rate seen in the patients with community-acquired pneumonia in our intensive care units. Even at that early stage the recommendation was that combination therapy with antimicrobial agents active against *K. pneumoniae* (such as a beta-lactam and an aminoglycoside) should be used routinely in patients with severe community-acquired pneumonia, at least initially. This was carried through as the recommended initial empiric therapy for patients with severe community-acquired pneumonia from the very first guideline on community-acquired pneumonia published by the South African Thoracic Society.

Among the various ICU studies was the description of unusual causes of severe community-acquired pneumonia, including infection with *Mycoplasma pneumoniae,* causing respiratory failure in an adult patient due to acute respiratory distress syndrome, confirmed on Swan-Ganz catheter measurements (5). This study highlighted the need to consider this pathogen as possible cause of severe community-acquired pneumonia and also contributed to the recommendation that a macrolide antibiotic should also be added empirically in patients with severe CAP, not only because of concerns of *Legionella* spp., infection, but also because of occasional infections due to other so-called “atypical pathogens”. This recommendation was also incorporated into the guideline on community-acquired pneumonia published by the South African Thoracic Society.

An attempt was made to determine the prognostic factors among patients with severe community-acquired pneumonia as well as the impact of initial empiric

antimicrobial chemotherapy on the outcome of such patients (6). Markers of disease severity such as multilobar pulmonary consolidation, need for mechanical ventilation, inotropes and dialysis were documented to be independent predictors of mortality, but not empirical antibiotic therapy. Only in the absence of these negative prognostic indicators could different antibiotic regimens be shown to have an apparent impact on outcome. This study suggested that markers of disease severity were the most important predictors of outcome of patients with severe community-acquired pneumonia, but it also revealed that antibiotic treatment regimens that were used by the different clinicians appeared to be dictated, at least in part, by the clinicians' individual perception of the severity of illness of their patients.

An important question is why patients appropriately treated for community-acquired pneumonia still die; one suggestion has been that this may be related to cardiovascular insufficiency. Among the negative prognostic factors documented to be associated with severe pneumonia, this study suggested that changes in the electro-cardiograph (ECG) occurred quite frequently in patient with community-acquired pneumonia (31% of the patients) and especially in moderate to severe infections as apposed to mild infections (7). The study documented that these changes were acute and potentially reversible and that those changes compatible with acute cor pulmonale and accompanied by a cardiac enzyme leak (CK-MB fraction) correlated with severity of illness but not mortality (7). This was the first study in the English language literature documenting ECG changes in patients with pneumonia, although the Russian literature had reported similar findings previously.

With the consideration that aspects of the host response to infection, such as the release of cytokines, may be contributing to morbidity and mortality in severe community-acquired pneumonia a study was undertaken of patients with varying severity of pneumonia compared with appropriate infective and non-infective controls of differing severity (8). The cytokines measured were interleukin (IL)-1β, IL-6, and tumour necrosis factor (TNF-α). The data indicated that IL-1β appeared to be associated with severity of infection, irrespective of whether the infection was respiratory or non-respiratory in origin, IL-6 was associated with severity of stress, whether of infective or non-infective aetiology and TNF-α appeared to be an important indicator of severity of pneumonia.

The last two papers in this section are review articles, which were invited contributions by the editors of that journal edition, possibly based on an appreciation of the studies described above. The first (9) was a review of the literature published in 1996 on the topic of severe community-acquired pneumonia, and the second (10) was a review of all available information of the role of cytokines in respiratory tract infections.

3.2 Severity of illness indices

11 **Feldman C**, Alanee S, Yu V, Richards GA, Ortqvist A, Rello J, Chiou CCC, Chedid MBF, Wagener M, Klugman KP, and the International Pneumococcal Study Group. Severity of illness scores in patients with bacteremic pneumococcal pneumonia: implications for ICU care. (Submitted).

12. Arnold F, LaJoie A, Marrie T, Rossi P, Blasi F, Luna C, Fernandez P, Porras J, Weiss K, **Feldman C**, Rodriquez E, Levy G, Arteta F, Roig J, Rello J, Ramirez J for the Community-Acquired Pneumonia Organization. The pneumonia severity index predeicts time to clinical stability in patients with community-acquired pneumonia. *Int J Tuberc Lung Dis* 2006; 10: 739-743.

13 **Feldman C**. Prognostic scoring systems: which one is best? Curr Opin Infect Dis 2007; 20: 165-169.

A number of recent studies have evaluated various "severity of illness" prognostic indices or scores, aimed at assisting clinicians in their assessment of patients with community-acquired pneumonia, with regard to severity of illness. Assessment of severity of illness is important since it impacts on the appropriate site of care, the extent of microbiological investigation and choice of initial antimicrobial chemotherapy. Although there are a number of indices the two most commonly used are the PSI and the CURB-65. It has become quite clear that although these various scoring systems and indices are useful, each has their own strengths and limitations and they certainly do not replace the individual clinical judgment of the attending physician.

In one study (11), the efficacy of the PSI, CURB-65, modified American Thoracic Society (ATS) score and Pitt Bacteremia score (PBS) were compared in evaluating severity of illness in patients with bacteraemic pneumococcal pneumonia. The PSI was the most sensitive severity of illness score, while the PBS and modified ATS scores were the most specific in predicting mortality. The PBS and modified ATS scores were superior to the

CURB-65 (and CRB-65) with respect to specificity and positive predictive value. The low positive predictive value of the PSI rendered it not useful as a decision making tool for the identification of patients with bacteraemic pneumococcal pneumonia who may best benefit from intensive care unit care.

While most of these scoring systems were developed to predict likely mortality of patients with community-acquired pneumonia, there are no prediction scores that have been developed to estimate the time to clinical stability in hospitalised patients with CAP. This study (12) investigated the relationship between the PSI and time to clinical stability (as assessed by time to switch from intravenous to oral therapy in hospitalized patients with CAP). The main findings were that the PSI was able to accurately predict time to clinical stability in hospitalized patients with CAP.

The last paper in this section (13) was an invited review article by the editor of that journal edition, possibly based on an appreciation of the above studies. This article reviews the published literature from 2006, evaluating the strengths and limitations of the various severity of illness scoring indices with the purpose of providing some indication of the merits, benefits and limitation of the various indices.

3.3 Infections due to *Streptococcus pneumoniae* (the pneumococcus)

14 Yu VL, Chiou CCC, **Feldman C**, Ortqvist A, Rello J, Morris AJ, Baddour LM, Luna CM, Snydman DR, Ip M, Ko WC, Chedid MBF, Adremont A, Klugman KP, for the International Pneumococcal Study Group. An international prospective study of

pneumococcal bacteremia: correlation with *in vitro* resistance, antibiotics administered, and clinical outcome. *Clin Infect Dis* 2003; 37: 230-237.

15 Baddour LM, Yu VL, Klugman KP, **Feldman C**, Ortqvist A, Rello J, Morris AJ, Luna CM, Snydman DR, Ko WC, Chedid MBF, Hul DS, Andremont A, Chiou CCC, and the International Pneumococcal Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med* 2004; 170: 440-444.

16 Alanee SRJ, McGee L, Jackson D, Chiou CCC, **Feldman C**, Morris AJ, Ortqvist A, Rello J, Luna CM, Baddour LM, Ip M, Yu VL, Klugman KP, for the International Pneumococcal Study Group. Association of serotypes of *Streptococcus pneumoniae* with disease severity and outcome in adults: an international study. *Clin Infect Dis* 2007; 45: 46-51.

17 **Feldman C,** Klugman K. Pneumococcal infections. *Curr Opin Infect Dis* 1997; 10: 109-115.

One of the prospective, multicentre, international, studies undertaken was coordinated by Doctor Victor Yu from Pittsburgh, USA. This study admitted 844 hospitalised cases with invasive pneumococcal disease recruited between December 1998 and January 2001. The cases were enrolled in 21 hospitals in 10 countries. By far the largest recruitment was from the one site at Johannesburg Hospital, South Africa, which

admitted overall 29.6% of the cases. A number of publications emanated from this collaboration.

There had been considerable concern that antimicrobial resistance among the various isolates causing community-acquired pneumonia may significantly affect the outcome of such infections, when treated with standard antibiotic therapy. This study investigated the impact of antibiotic resistance of the pneumococcal isolates on disease outcome (14). Overall 15% of the isolates demonstrated intermediate resistance to penicillin (minimum inhibitory concentration (MIC) 0.12-1 μg/ml) while 9.6% were fully resistant (MIC $\geq$ 2 μg/ml). The impact of concordant antibiotic therapy (receipt of a single antibiotic with *in vitro* activity against *S. pneumoniae*) was compared with discordant therapy (use of antimicrobial agents inactive *in vitro*) with regard to outcome at 14 days. Discordant therapy with penicillin, cefotaxime and ceftriaxone did not result in a higher mortality rate, although this was not the case with the use of cefuroxime given at a dose of 750 mg given three times daily. Neither was the time to defervescence, nor frequency of suppurative complications,with the former agents any different. The study concluded that β-lactam antibiotics were still useful for the treatment of lower respiratory tract infections due to the pneumococcus, regardless of the *in vitro* susceptibility as was currently determined by the NCCLS. However this study did suggest that if cefuroxime was the chosen beta-lactam agent for the therapy of patients with CAP, it should be given at a dose of 1500 mg thrice daily. This recommendation was incorporated into the South African pneumonia guideline.

A considerable body of literature emerged investigating the outcome of patients with community-acquired pneumonia, including the subset of patients with pneumococcal infection, treated with either single antibiotic therapy or multiple antibiotic agents. Many of these investigations suggested that "combination therapy", most commonly the addition of a macrolide to standard beta-lactam therapy, was associated with a better outcome. This study was the first prospective investigation of bacteraemic pneumococcal infections, which evaluated the effect of antibiotic combination therapy versus monotherapy using univariate analysis and by logistic regression models (15). While the mortality was no different for the 2 groups, in critically ill cases (defined as a Pitt Bacteremia score > 4), combination antibiotic therapy was associated with a lower 14-day mortality (23.4% versus 55.3%; p = 0.0015). This improvement was independent of country of origin, intensive care unit support, class of antibiotics used or even *in vitro* activity of the antibiotics prescribed. The recommendation for combination antibiotic therapy, particularly in hospitalized case with more severe community-acquired pneumonia, including the subset of patient with pneumococcal infections, has been incorporated into the South African pneumonia guideline.

This large database of prospectively collected pneumococcal isolates causing invasive pneumococcal disease from the International Pneumococcal Study Group, allowed the evaluation of whether pneumococcal disease severity in adults may be associated with specific pneumococcal serotypes (16). The data indicated that host factors were more important than isolate serotype in determining the severity and outcome of invasive pneumococcal disease and therefore is unlikely to be affected by either vaccination against pneumococcal infection, such as with the use of the pneumococcal

conjugate vaccine (PCV) or by replacement with non-vaccine serotypes in the post-conjugate vaccine era.

The last paper in this section is an invited review article by the editor of that journal edition, possibly based on an appreciation of the above studies. This paper comprehensively reviews the published literature from 1996 on the topic of pneumococcal infections (17).

3.4 Community-acquired pneumonia in the era of HIV infection

18 **Feldman C**, Glatthaar M, Morar R, Goolam Mahomed A, Kaka S, Cassel M, Klugman KP. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. *Chest* 1999; 116: 107-114.

19 Christensen D, **Feldman C**, Rossi P, Marrie T, Blasi F, Luna C, Fernandez P, Porras J, Martinez J, Weiss K, Levy G, Lode H, Gross P, File T, Ramirez J, and the Community-Acquired Pneumonia Organization (CAPO) Investigators. HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO International Cohort Study. *Clin Infect Dis* 2005; 41: 554-556.

20 **Feldman C**, Klugman KP, Yu Vl, Ortqvist A, Chiou CCC, Chedid MBF, Rello J, Wagener M, the International Pneumococcal Study Group. Bacteraemic pneumococcal

pneumonia: Impact of HIV on clinical presentation and outcome. *J Infect* 2007; 55: 125-135.

21 Buie KA, Klugman KP, von Gottberg A, Perovic O, Karstaedt A, Crewe-Brown H, Madhi S, **Feldman C**. Gender as a risk factor for both antibiotic resistance and infection with pediatric serogroups/serotypes, in HIV-infected and –uninfected adults with pneumococcal bacteremia. *J Infect Dis* 2004; 189: 1996-2000.

22 Schleicher GK, **Feldman C**. Dual infections with *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* in HIV-seropositive patients with community-acquired pneumonia. *Int J Tuberc Lung Dis* 2003; 7: 1207-1208.

23 Schleicher GK, Herbert V, Brink A, Martin S, Maraj R, Galpin J, **Feldman C**. Procalcitonin and C-reactive protein levels in HIV-seropositive subjects with tuberculosis and pneumonia. *Eur Respir J* 2005; 25: 688-692.

24. Schleicher GK, Hopley MJ, **Feldman C**. CD4 Y-lymphocyte counts in HIV-seropositive patients during the course of community-acquired pneumonia caused by *Streptococcus pneumoniae. Clin Micro Infect* 2004; 10: 587-589.

25 Feikin D, **Feldman C**, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. *Lancet Infect Dis* 2004; 4: 445-455.

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26 Goolam Mahomed A, Murray J, Klempman S, Richards G, **Feldman C**, Levy NT, Smith C, Kallenbach J. *Pneumocystis carinii* pneumonia in HIV infected patients from South Africa. *East African Medical Journal* 1999; 76: 80-84.

27 **Feldman C**. Pneumonia associated with HIV infection. *Curr Opin Infect Dis* 2005; 18: 165-170.

The advent of HIV infection afforded a unique opportunity to investigate various aspects of community-acquired pneumonia, and in particular pneumococcal community-acquired pneumonia, in an entirely new setting. In one study (18), the demographic, clinical, laboratory, and microbiological data, the hospital course and outcome were compared in HIV-seropositive and HIV-seronegative patients with bacteraemic pneumococcal pneumonia. This study reported that the clinical features on infection were similar in the 2 groups of patients, and although differences were noted in the laboratory and microbiological data, these were not found to impact on the outcome. A second, case control study of HIV-infected and HIV-uninfected patients with community-acquired pneumonia of all cause (19) also suggested that the time to clinical stability, length of hospitalization and mortality was no different in the 2 groups of patients.

However, a subsequent study of bacteraemic pneumococcal pneumonia, once again comparing HIV-seropositive and HIV-seronegative cases, suggested that these findings may not be correct, based on the results that were generated by more complete statistical analysis (20). The initial evaluation indicated that the mortality for the group as a whole was 14.5%, being 16% in the HIV-seropositive patients and 13.9% in the HIV-

seronegative patients (not significantly different). However, when adjustments were made for age and severity of illness, HIV-infected patients had a significantly higher mortality with a significant trend to increasing mortality (increasing 14-day mortality) in those with lower CD4 counts. Even when adjusting for differences in clinical and laboratory parameters in patients from different parts of the world, and adjusting for regional differences, HIV-infected patients were still noted to have a poorer 14-day prognosis.

It was noted in the early studies of bacteraemic pneumococcal pneumonia (18) that HIV-seropositive patients were more commonly infected with pneumococcal serogroups/serotypes that were more usually found in children (so-called childhood serogroups/serotypes – these being serogroups 6, 19, 23 and serotype 14) than HIV-seronegative patients (48.4% versus 20.8%). The importance of infection with these isolates is that they are more commonly associated with antimicrobial resistance, and therefore, not surprisingly, more HIV-seropositive patients were infected with penicillin-resistant isolates than HIV-seronegative cases. When the same data were analysed according to gender (irrespective of HIV status) women, as compared to the men, were noted to have more infections with penicillin-resistant isolates (15% versus 1%) and co-trimoxazole-resistant isolates (21% versus 5%). In order to confirm these gender differences in a larger cohort of patients, cases with *S. pneumoniae* bacteraemia or meningitis in databases existing at 3 urban hospitals collected between February 1996 and December 2002 were studied (21). This study confirmed that paediatric serogroups/serotypes were more commonly found in women compared to men (OR 1.59 [95% CI 1.18-2.15], who were, therefore, not surprisingly more commonly infected with penicillin resistant strains [OR 1.65 [95% CI 1.06-2.59]. Interestingly, women with these

bacteraemic infections were also more likely to be co-infected with HIV and were younger than the men. These findings suggest that young, mothers, and particularly those that are immuno-compromised by way of HIV infection, are at greater risk of infections with pneumococcal childhood serotypes/serogroups and/or isolates demonstrating antibiotic resistance, because of close contact with their children harbouring such isolates following their contact with hospitals or even day care centres. These observations are similar to that noted in other studies, including some from South Africa. Perhaps more importantly these studies suggest that conjugate pneumococcal vaccination of children may not only be associated with protection of the children from such infections, but also lessen the burden of conjugate vaccine serotype pneumococcal disease in young, HIV-infected women.

As apposed to infections in patients not infected with HIV, pulmonary infections with more than one organism are said to be common in HIV-seropositive cases. One study (22) described the occurrence of simultaneous infections with *S. pneumoniae* and *Mycobacterium tuberculosis* in 9 patients. All pneumococcal infections were confirmed by positive blood culture, and while the diagnosis of tuberculosis was based on positive sputum in 5 of the cases, further invasive diagnostic testing was required for the confirmation of tuberculous infection in the others. The recommendation from this study was that in areas where tuberculosis is endemic, it is essential to exclude pulmonary tuberculosis in HIV-seropositive patients with CAP, particularly in cases who are not responding to initial antibiotic therapy, even if another, apparently appropriate aetiological pathogen, has been isolated.

The concern is how best to differentiate pneumococcal infection from tuberculosis, particularly in HIV-infected patients, since particularly in this setting these infections may have very similar clinical and radiological features. In one study (23) of HIV-infected patients comparing 34 cases with tuberculosis and 33 with pneumococcal community-acquired pneumonia, significantly higher procalcitonin and C-reactive protein levels were found in the latter group. A procalcitonin level > 3ng/ml and C-reactive protein level > 246mg/l were both highly predictive of pneumococcal infection.

It has been noted that in both HIV-seronegative and HIV-seropositive patients, that total lymphocyte and CD4 T-lymphocyte counts may decrease considerably in response to stress, inflammation or sepsis. A study was conducted among HIV-seropositive cases, who were anti-retroviral naïve, and considered to have *S. pneumoniae* community-acquired pneumonia (24). There was a significant depression of total lymphocyte count and CD 4 cell count in the acute stages of pneumonia with a subsequent increase in 90% (27/30) of cases after resolution of the infection, treated with antibiotics alone. The median CD 4 cell count was 112 X 10^6 cells/L on admission and 270 X 10^6 cells/L one month later ($p = 0.000009$). The importance of these findings is that measurement of CD 4 cell count during the acute stage of infection with *S. pneumoniae* in HIV-infected patients should not be used to determine the stage of HIV or to prognosticate on the course of HIV infection. A practical recommendation is therefore not to do such testing in the acute situation.

An important question is how best to prevent bacterial pneumonia in patients with HIV disease. One study examined the peer-reviewed literature on the burden of bacterial pneumonia and the effectiveness of the various interventions for their prevention (25). The

rates of bacterial pneumonia were 25-fold higher than in the general community, with rates increasing as the CD4 cell count decreased. In developed countries HAART had the most consistent effect on reducing pneumonia. In sub-Saharan Africa randomized controlled trial indicated that co-trimoxazole prophylaxis decreased rates of bacterial pneumonia but pneumococcal polysaccharide vaccine prevented neither pneumonia nor invasive pneumococcal disease. Although it had not been fully evaluated in Africa, it was considered that based on experience in the developed countries, use of HAART may have substantial potential to prevent bacterial pneumonia.

Contrary to what the early literature reported, it is vitally important to understand that infection with *Pneumocystis carinii* (now called *Pneumocystis jirovecii*) is a significant and important cause of pulmonary infection in HIV-infected patients in Africa, even among indigenous populations (26). The assumptions that such infections were rare or absent in Africa were based on relatively scant data, often obtained in the absence of comprehensive investigative technology, such as fibreoptic bronchoscopy, broncho-alveolar lavage and transbronchial lung biopsy. In this study the overall prevalence of *Pneumocystis* infection in HIV-infected patients was 43.3% and although it was found less frequently in the Black as compared to the White patients, it was still the most frequent diagnosis in the Black group (27.3% of patients). The importance of this is that in patients presenting with severe infection, irrespective of their origin, that may potentially be compatible with *Pneumocystis* infection, should be appropriately treated as such, since these infections are actually common-place and associated, particularly if not appropriately treated, with a poor outcome.

The last paper in this section (27) is an invited review article by the editor of that journal edition, possibly based on an appreciation of the contribution to the literature of the studies described above. This paper comprehensively reviews the published literature from 2004 on the topic of pneumonia in HIV infected patients.

3.4 Less common causes of respiratory tract infections

28 Goolam Mahomed A, **Feldman C**, Smith C, Promnitz DA, Kaka S. Does primary *Streptococcus viridans* pneumonia exist? *S Afr Med J* 1992; 82: 432-434.

29 **Feldman C**, Morar R, Kassel M, Goolam Mahomed A, Kaka S. The occurrence of secondary bacterial infection in patients with newly diagnosed active pulmonary tuberculosis. *South Afr J Epidemiol Infect* 2004; 19: 9-11.

30 Mahida P, Morar R, Goolam Mahomed A, Song E, Tissandie JP, **Feldman C**. Cryptococcosis: an unusual cause of endobronchial obstruction. *Eur Respir J* 1996; 9: 837-839.

31 **Feldman C**, Omar J, Mahida P, Goolam Mahomed A, Morar R, Smith C, Kaka S, Schoeman A. The microbiology and therapy of lung abscess at Hillbrow Hospital. *South Afr J Epidemiol Infect* 1999; 14: 92-96.

A number of diverse microorganisms are known to cause infection of the respiratory tract. Not all of these present with typical features of community-acquired

pneumonia and several may present as a significant clinical diagnostic challenge to the attending Pulmonologist. For example, *S. viridans* is an uncommon but well described cause of community-acquired pneumonia that needs to be considered (28). This microorganism commonly colonises the upper respiratory tract, the gastrointestinal tract, the female genital tract and even sometimes the skin, and is so frequently isolated from sputum specimens that most microbiology laboratories do not report it as a significant pathogen. The clinical features of pneumonia associated with this pathogen is similar to other more common bacterial causes of pneumonia and it also responds to most of the commonly prescribed empiric antibiotics, so that its importance as a cause of pneumonia is frequently overlooked.

It has anecdotally been believed that secondary bacterial infections occur commonly in patients with newly diagnosed active tuberculosis and may actually be responsible for the acute presentation of this infection. Even patients overwhelmingly suspected of having tuberculosis are therefore most commonly treated with standard antimicrobial therapy while awaiting the outcome of further microbiological investigation. While studies, as described above in the section on HIV-associated pneumonia, attest to the fact that in HIV-seropositive patients, polymicrobial and mixed infections are relatively common, the situation in HIV-uninfected cases has not been well investigated. This study documented (29), on the basis of a number of observations, that in a predominantly HIV-seronegative population, secondary bacterial infections are uncommon in patients with newly diagnosed active tuberculosis. This has particular relevance to the empiric management of community-acquired pneumonia in areas where tuberculosis is endemic, since several antibiotics commonly used for the empiric treatment of pneumonia, and in

particular the fluoroquinolones, have activity against *Mycobacterium tuberculosis* and may either delay the diagnosis of tuberculosis or be associated with the subsequent development of drug resistance in patients who actually have tuberculosis but are being treated empirically as community-acquired pneumonia.

Other pulmonary pathogens, such as *Cryptococcus neoformans*, can sometimes present as pneumonia, particularly in immunocompromised patients. However, its mode of presentation in the chest is extremely varied, sometimes being asymptomatic, and occasionally presenting unusually. This study (30) describes a 43-year old male patient with normal immune function, presenting with right middle and lower lobe atelectasis, which was considered by the Pulmonologist to represent a malignant tumour, even on macroscopic appearance of the endobronchial lesion at bronchoscopy, but which subsequently was confirmed to be endobronchial cryptococcosis (30).

Lung abscesses are a relatively common cause of pulmonary infection in the developing world. In general, the pathogenesis is similar to that of community-acquired pneumonia and it is said that the difference between the development of one or the other depends on the ability of the infecting microorganism to cause necrosis of the lung. While anaerobic pathogens are found in most patients with lung abscess, if appropriately investigated for, additional microorganisms are quite commonly encountered. Interestingly, much as was described in patients with severe community-acquired pneumonia, infections with gram-negative pathogens as a cause of lung abscess appear to be a much more common in the South African setting, in particular due to *K. pneumoniae,* and these infections are associated with a more complicated clinical picture and worse outcome (31).

This finding has relevance to the guideline recommendations for the empiric antibiotic management of patients with lung abscess, which in the South African setting, would include the need for adding in empirically an agent that would potentially cover for gram-negative pathogens.

4 PATHOGENESIS OF INFECTION

4.1 Host predisposing factors

32. **Feldman C**, Weltman M, Wadee A, Sussman G, Smith C, Zwi S. A study of immunoglobulin G subclass levels in black and white patients with various forms of obstructive lung disease. *S Afr Med J* 1993; 83: 9-12.

33. **Feldman C**, Goolam Mahomed A, Mahida P, Morar R, Schoeman A, Mpe J, Burgin S, Kuschke RH, Wadee A. IgG subclass levels in previously healthy patients with acute community-acquired pneumonia. *S Afr Med J* 1996; 86: 600-602.

34. **Feldman C**, Wadee A, Smith C, Zwi S. Immunoglobulin G (IgG) subclass levels in respiratory disorders. *Respiratory Medicine* 1992; 86: 3-5.

During a sabbatical undertaken in the United Kingdom, it was noted that a number of patients that were managed in the Unit were cases with recurrent respiratory infections and/or chronic lung disease due to deficiencies of the various immunoglobulin levels that required immunoglobulin replacement therapy. At that time no studies of immunoglobulin deficiencies had been conducted among similar such patients in South Africa. Studies subsequently undertaken (32,33) indicated that abnormal levels of IgG subclasses were quite commonly associated with respiratory tract disorders in South African patients, particularly among cases with recurrent infections, with atopy and with bronchiectasis. In a study of patients with acute community-acquired pneumonia in the community, decreased

immunoglobulin levels were found in a number of cases, but these were relatively infrequent (33). The conclusion of the study was that routine testing for IgG subclass levels in routine patients presenting with acute community-acquired pneumonia would not be recommended, but that such testing would be advocated in cases with recurrent respiratory tract infections.

The last paper in this section was an invited editorial by the editor of the journal (34), possibly based on an appreciation of the contribution to the literature of the studies described above.

4.2 Bacterial pathogenesis, with particular reference to the pneumococcus

35. **Feldman C**, Voorvelt A. A photo-transistor technique for the measurement of ciliary beat frequency of human ciliated epithelium *in vitro*. *S Afr J Sci* 1994; 90: 555-556.

36. **Feldman C**, Read R, Rutman A, Jeffery PK, Brain A, Lund V, Mitchell TJ, Andrew PW, Boulnois GJ, Todd HC, Cole PJ, Wilson R. The interaction of *Streptococus pneumoniae* with intact human respiratory mucosa *in vitro*. *Eur Respir J* 1992; 5: 576-583.

37. **Feldman C**, Kassel M, Cantrell J, Kaka S, Morar R, Goolam Mahomed A, Philips JI. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. *Eur Respir J* 1999; 13: 546-551.

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38. **Feldman C**, Munro NC, Jeffery PK, Mitchell TJ, Andrew PW, Boulnois GJ, Guerreio D, Rohde JAL, Todd HC, Cole PJ, Wilson R. Pneumolysin induces the salient histological features of pneumococcal infection in the rat lung *in vivo. Am J Respir Cell Mol Biol* 1991; 5: 416-423.

39. **Feldman C**, Anderson R, Kanthakumar K, Vargas A, Cole PJ, Wilson R. Oxidant-mediated ciliary dysfunction in human respiratory epithelium. *Free Rad Biol Med* 1994; 17: 1-10.

40. **Feldman C**, Anderson R, Cockeran R, Mitchell T, Cole PJ, Wilson R. The effects of pneumolysin and hydrogen peroxide, alone and in combination, on human ciliated epithelium *in vitro. Respiratory Medicine* 2002; 96: 580-585.

41. **Feldman C**, Cockeran R, Jedrzejas MJ, Mitchell TJ, Anderson R. Hyaluronidase augments pneumolysin-mediated injury to human ciliated epithelium. *Int J Infect Dis* 2007; 11: 11-15.

42 **Feldman C**. Non-specific Host Defences: Mucocilairy Clearance and Cough. In Niederman MS, Sarosi G, Glassroth (eds). *Respiratory Infections.* 2nd edition. Philadelphia; Lippincott Williams & Wilkins, 2001: 13-26.

43. **Feldman C**, Anderson R, Rutman A, Cole PJ, Wilson R. Human ciliated epithelium *in vitro* – mechanisms of injury and protection. In: Baum GL, Priel Z, Roth Y,

Liron N, Ostfeld E. (eds). *Cilia and Mucus and Mucociliary Interactions*. New York; Marcel Dekker, Inc., 1998: 461-471.

A sabbatical was undertaken at the Royal Brompton Hospital in London, United Kingdom. The studies undertaken during that sabbatical were aimed at understanding the pathogenesis of bacterial infections, in particular those due to *S. pneumoniae*. It was there that I learnt the various laboratory techniques described in the following studies, including the sampling of airway epithelium (nasal brushings, adenoids, nasal turbinates) which were assessed by a specialized phase contrast microscope that also allowed the measurement of ciliary beat frequency (CBF). A number of studies of the pneumococcal toxin, pneumolysin, considered by many to be one of the most important virulence factors of the pneumococcus, were undertaken and published and several of these were incorporated into my PhD thesis and do not appear here.

On returning to South Africa the aim was to continue these various studies and build on the knowledge that had been accumulated in the UK, particularly concentrating on an understanding of various aspects of the pathogenesis of pneumococcal infections. The first step required the acquisition of a phase contrast microscope that also allowed the measurement of ciliary beat frequency. No such units were available in the country and the costs of importation of such a unit were prohibitive. The first study (35) describes the development of a relatively simple and less expensive system for the measurement of CBF, based on the photo-electric principle, that could be used for both diagnostic and research purposes.

It is known that colonization of an epithelial surface is an important initial event in the establishment of an infection and that adherence of microorganisms to the epithelium, or epithelial-associated structures, is an important ecological determinant of colonization, at least in the case of some bacteria. In an organ culture model of nasal turbinate tissue (36) it was demonstrated that when in contact with human ciliated respiratory epithelium, *S. pneumoniae* persists initially, and is able to replicate, in association only with the mucous layer. Both transmission and scanning electron microscopy confirmed that the association of the bacteria was with a thickened gelatinous layer above the epithelial surface. The organism's production of factors such as pneumolysin appeared to be related to the slowing of ciliary beating that was documented as well as the increase in mucus secretion that was noted, thus enhancing this microorganisms' ability to colonise in this way. In the respiratory tract, therefore, it appears that specific adherence of pneumococci, at least initially, to epithelial cells is less important in the establishment of an infection than the organisms' interactions with ciliary motility and epithelial-derived secretions.

The interaction of *S. pneumoniae* with epithelial-derived secretions and the formation of a thickened gelatinous layer almost certainly represented a type of biofilm formation by the microorganism. This appeared to be confirmed by the appearance of the various photomicrographs taken of the organism in organ culture, some of which showed changes that resembled the features of biofilm formation (glycocalyx; slime) produced by *Pseudomonas aeruginosa* (data not shown). We did not evaluate the characteristics of this gelatinous layer any further at that time since it was not within the scope of our current investigations and the formation of biofilm by the pneumococcus had not, at that time, been documented. However a subsequent study investigated the pattern and sequence of

endotracheal tube colonization by various microorganisms in patients undergoing mechanical ventilation and its role in the pathogenesis of ventilator-associated pneumonia (37). The investigation documented that the interior of the endotracheal tubes became rapidly colonized with microrganisms commonly associated with nosocomial pneumonia and therefore potentially represents a persistent source of microrganisms causing such infections. On scanning electron micrograph the presence of endotracheal tube biofilm coating the interior of the endotracheal tube was documented, together with microorganisms adhering within this amorphous matrix. The features of biofilm were not dissimilar to that described in the study of the pneumococus described above. Biofilm formation by the pneumococcus is the subject of current further investigations.

In a number of the studies described previously, it has clearly been shown that pneumolysin slowed ciliary beating, thus enhancing bacterial colonization of the airway, but it appeared important, in addition, to determine whether pneumolysin also contributed directly to the pulmonary infection. In an experimental rat model on pneumococcal infection *in vitro* (38), pneumolysin was able to induce, on its own, the salient histological features of pneumococcal infection *in vitro*, with the conclusion that while toxin may aid initial airway colonization, it was also important in generating pulmonary inflammation with the establishment of pneumonia. An important consideration was what component of the pneumolysin molecule was responsible for this pulmonary inflammation. Injection of a toxin that had been heat-inactivated, not surprisingly, had no such pulmonary inflammatory effect. Modified toxins prepared by site-directed mutagenesis were also studied. Those toxins prepared with reduced haemolytic activity but normal complement activating activity (substituting tryptophan with phenylalanine at position 433), as well as

those with reduced ability to activate complement (tyrosine at position 384 to phenylalanine substitution) were still able to elicit inflammation, suggesting that several of the pro-inflammatory activities of pneumolysin contribute to the pneumonic process.

Although not initially recognized, it was subsequently confirmed that the pneumococcus also produced hydrogen peroxide, which also served as an important virulence factor of this microorganism. This study investigated the effects of reactive oxidants generated or prepared in the laboratory on human ciliates epithelium (39). It documented that reactive oxidants caused significant alterations in ciliary beating with the earliest changes being that of slowing of ciliary beating, progressing to complete ciliary stasis in some areas. Ciliary slowing occurred from as early as 15 minutes after exposure. These detrimental effects were confirmed, by further investigation, to be predominantly due to hydrogen peroxide and hypochlorous acid.

It was therefore appropriate to investigate the effects of pneumolysin and hydrogen peroxide, alone and in combination, on human ciliated epithelium *in vitro* (40). Both recombinant pneumolysin and hydrogen peroxide caused significant ciliary slowing and epithelial damage and the effects of both toxins, when used together, were additive rather than synergistic. The effects of hydrogen peroxide were due to direct oxidative damage to the epithelium, whereas the effects of pneumolysin were a result of its cytolytic, pore forming activity. Neither of these toxins antagonized the effects of the other toxin. These toxins are released at different times during pneumococcal growth and infection and therefore may enhance both early colonization processes, as well as subsequent invasion of the lower respiratory tract.

Another toxin that may play an important role in the pathogenesis of pneumococcal infection is hyaluronidase. This study (41) investigated the effects of hyaluronidase, alone and in combination with pneumolysin, on human ciliated epithelium. Hyaluronidase, *per se,* had no effect on the ciliary beat frequency, or structural integrity, of human ciliated epithelium. However, pre-incubation of the epithelium with hyaluronidase significantly potentiated pneumolysin-mediated ciliary slowing and epithelial damage, which was antagonised by the presence of hyaluronan. This suggests that hyaluronidase by enzymatically dismantling the intracellular matrix and/or hydrolysis of hyluronan in epithelial lining fluid, increases the accessibility of the epithelial cells to pneumolysin. This concept appears to support the suggestions of other studies that hyaluronidase is able to shift mucus off epithelia allowing better access of other toxins, such as pneumolysin, to the epithelium. This study enhances the findings of other investigations in a experimental pneumococcal peritonitis model which suggested that although inactivation of pneumolysin production, but not that of hyaluronidase, was associated with reduced pneumococcal virulence, dual knockout of the genes encoding for both these proteins was associated with an even more pronounced inhibition of pneumococcal virulence.

The last two contributions in this section were invited preparations. The first (42) was an invited contribution to a chapter in a definitive book on respiratory tract infections, being a state of the art review of the role of non-specific host lung defence mechanism, reviewing cilia, mucus, the mucociliary mechanisms and cough. The latter (43) was an invited contribution to a book that emerged from the presentations at a congress on cilia, mucus and mucociliary interactions.

4. 3 Cytoprotective effects of macrolide/macrolide-like antibiotics against airway damage

44. **Feldman C**, Anderson R, Theron AJ, Ramafi G, Cole PJ, Wilson R. Roxithromycin, clarithromycin, and azithromycin attenuate the injurious effects of bioactive phospholipids on human respiratory epithelium in vitro. *Inflammation* 1997; 21: 655-665.

45. Anderson R, Theron AJ, **Feldman C**. Membrane-stabilizing, anti-inflammatory interactions of macrolides with human neutrophils. *Inflammation* 1996; 20: 693-705.

46. **Feldman C**, Anderson R, Theron A, Mokgabu I, Cole PJ, Wilson R. The effects of ketolides on bioactive phospholipid-induced injury to human ciliated epithelium *in vitro*. *Eur Respir J* 1999; 13: 1022-1028.

47. Mokgabu I, Theron AJ, Anderson R, **Feldman C**. The ketolide antimicrobial agent HMR-3004 inhibits neutrophil superoxide production by a membrane-stabilizing mechanism. *In J Immunopharmacol* 1999; 21: 365-377.

48. Theron AJ, **Feldman C**, Anderson R. Investigation of the anti-inflammatory and membrane-stabilizing potential of spiramycin *in vitro. J Antimicrob Chemother* 2000; 46: 269-271.

49. **Feldman C**, Anderson R, Theron AJ, Steel HC, van Rensburg CEJ, Cole PJ, Wilson R. Vitamin E attenuates the injurious effects of bioactive phospholipids on human ciliated epithelium *in vitro. Eur Respir J* 2001; 18: 122-129.

50. **Feldman C**, Anderson R, Theron AJ, Cole P, Wilson R. The cytoprotective effects of macrolides, azalides, and ketolides on human ciliated epithelium *in vitro*. In: Salathe M. *Cilia and Mucus. From Development to Respiratory Defense.* New York; Marcel Dekker, Inc., 2001: 145-153.

51. **Feldman C**, Anderson R. The cytoprotective interactions of antibiotics with human ciliated airway epithelium. In: Rubin B, Tamaoki J (eds). *Antibiotics as anti-inflammatory and immunomodulatory agents.* Basel; Birkhauser Verlag, 2005: 49-63.

For many years it had been known that when patients with asthma were treated with a macrolide-type of antibiotic there was an improvement in the overall control of their asthma. While initially it was suggested the mechanism(s) may be related to interactions of the macrolides with theophylline levels in the blood, or with various aspects of corticosteroid metabolism, it clearly became evident through these studies that the improvement in asthma control occurred even in the absence of such interactions, and that this seemed to occur through mechanisms that were not clearly defined. Subsequently it also became apparent that patients with severe community-acquired pneumonia requiring admission to hospital, including the subset of patients with bacteraemic pneumococcal pneumonia, had a better outcome if they were treated with a combination of antibiotics rather than a single agent. The most common combination noted in the various studies was

the addition of a macrolide to standard beta-lactam therapy, although other combinations also appeared to have benefit. There were significant discussions as to the mechanism(s) by which combination therapy, especially the addition of the macrolide to standard therapy, may be of benefit to patients with pneumonia. Possible mechanisms described included potential cover for atypical pathogens, potential cover for polymicrobial infections, or potential cover for antibiotic resistant infections (including the concept of antibiotic tolerance), as well as the possibility of synergism of the antibiotics, particularly in immunocompromised patients. Another mechanism described, which had considerable support was the so-called anti-inflammatory immunomodulatory activities of the macrolide-group of antibiotics.

While a number of investigations had clearly indicated that the macrolide group of antibiotics possessed a range of anti-inflammatory and immunomodulatory activities, the logical next study would be to determine whether macrolide antibiotics interacted, either directly or indirectly, with virulence factors of the pneumococcus, such as pneumolysin, its thiol-activated, protein toxin considered by many to be its most important virulence factor. Unfortunately, initial studies (data not shown) clearly indicated that macrolides had no direct effects on the pro-inflammatory interactions of pneumolysin with neutrophils, erythrocytes or human ciliated epithelium. An alternative model of airway inflammation was therefore developed to investigate the anti-inflammatory effects of macrolides/ macrolide-like agents with human ciliated epithelium.

The effects of bioactive phospholipids (PL), platelet-activating factor (PAF), lyso-PAF and lysophophatidylcholine (LPC) on ciliary beat frequency and structural integrity of

human ciliated epithelium *in* vitro was studied, in the absence and/or presence of human polymorphonuclear leukocytes (PMNL), the macrolide antibiotics roxithromycin, clarithromycin, and azithromycin, and antioxidative enzymes catalase and superoxide dismutase (SOD)(44). All three PL caused dose related slowing of cilairy beat frequency and progressive epithelial damage which was unaffected by the inclusion of the antibiotics or antioxidative enzymes. When the epithelium was exposed to PL, in the presence of PMNL, the extent of ciliary slowing and epithelial damage was enhanced and that these effects were attenuated by pretreatment of the PMNL with the macrolide antibiotics or catalase, but not SOD. These findings suggest that macrolide/azalide type of antibiotics may have beneficial effects on airway inflammation in asthma and microbial infections due to their ability to protect ciliated epithelium from oxidative damage inflicted by activated phagocytes. Confirming the findings of this study, further *in vitro* investigations (45) demonstrated that while PL have a membrane-disruptive pro-oxidative, pro-inflammatory activity in association with PMNL, macrolides have a membrane-stabilizing activity, which is associated with a dose-related inhibition of superoxide production by activated PMNL, which counteract these PL effects. Very similar findings were documented with the ketolide agents (46,47), a newer subgroup of macrolide antibiotics. However, in this model these agents appear to have anti-inflammatory properties that are greater than that of the older macrolide agents, and therefore were demonstrated to be able to antagonize both the direct and PMNL-mediated injurious effects on human ciliated epithelium.

Interestingly, a number of the studies documenting the anti-inflammatory, immunomodulatory effects of the macrolide group of antibiotics confirm that these occur with the 14-member macrolides (e.g. erythromycin, clarithromycin, roxithromycin), and

the 15-member macrolides (e.g. azithromycin), but not with the 16-member macrolides (e.g. spiramycin, josamycin). This study (48) confirmed that with regard to superoxide production by activated neutrophils, clarithromycin (14-member macrolide) but not spiramycin (16-member macrolide) caused dose-related inhibition and that as apposed to clarithromycin, spiramycin had only very weak membrane-stabilizing activity. Another agent that was shown to have similar activity was vitamin E (49). In addition to antagonizing membrane-destabilizing and pro-oxidative actions of all three PL, spectrophotometric analysis of mixtures of vitamin E with PAF, lyso-PAF and LPC demonstrated alterations in peak intensity and peak shifts, indicative of physicochemical interactions between PL and the vitamin. The implications of this study are that vitamin E status may be a determinant of susceptibility to PL-mediated airway inflammation and damage.

The last two papers were invited contributions by the editors of the publications, the first one (50) being a conference proceeding that arose out of personal studies presented at a conference and the second (51) being a stand alone book on the alternative activity of antimicrobial agents, being a review of the anti-inflammatory and immunomodulatory effects of the macrolide group of antibiotics.

4.4 The effect of macrolide/macrolide antibiotics on bacterial pathogenic mechanisms

52. Rutman A, Dowling R, Wills P, **Feldman C**, Cole PJ, Wilson R. Effect of dirithromycin on *Haemophilus influenzae* infection on respiratory mucosa. *Antimicrob Agents Chemother* 1998; 42: 772-778.

53. Anderson R, Steel HC, Cockeran R, Smith A, von Gottberg A, de Gouveia L, Brink A, Klugman K, Mitchell TJ, **Feldman C**. Clarithromycin alone and in combination with ceftriaxone inhibited the production of pneumolysin by macrolide-susceptible and macrolide-resistant strains of *Streptococcus pneumoniae. J Antimicrob Chemother* 2007; 59: 224-229.

54. Anderson R, Steel HC, Cockeran R, von Gottberg A, de Gouveia L, Klugman K, Mitchell T, **Feldman C.** Comparison of the effect of macrolides, amoxicillin, ceftriaxone, doxycycline, tobramycin and fluoroquinolones on the production of pneumolysin by *Streptococcus pneumoniae in vitro. J Antimicrob Chemother* 2007; 60: 1155-1158.

However studies still needed to be undertaken to determine whether there were any interactions of the macrolide group of antibiotics with bacteria commonly causing community-acquired pneumonia and their pathogenic mechanisms. In one study (52) dirithromycin, another 14-member macrolide, but not amoxicillin, was shown to reduce the slowing of ciliary beating and damage to nasal epithelium induced by broth culture filtrates of *Haemophilus influenzae.* Furthermore prior incubation of an adenoid organ culture model with dirithromycin lessened the mucosal damage induced by *H. influenzae* by as much as 50%. The study confirmed that at concentrations likely to be achieved *in vivo* dirithromycin was able to reduce the mucosal damage cause by this microorganism.

While macrolides could not be demonstrated to have any direct effects against the activity of pneumolysin, clarithromycin, at sub-MIC (minimum inhibitory concentrations) concentrations and both in macrolide-susceptible, and even more remarkably in macrolide-

resistant strains (even isolates with extremely high-level resistance with MICs > 256 μg/ml) was shown to attenuate, significantly, the production of pneumolysin, considered by many to be one of the most important virulence factors of the pneumococcus (53). Only macrolide, or macrolide-like antibiotics, but not other antimicrobial agents commonly used in the treatment of pneumonia, such as beta-lactams or fluoroquinolones, subverted the production of pneumolysin (54). These studies may explain the reason(s) why combination antibiotic therapy, and in particular the addition of a macrolide to standard beta-lactam therapy may be associated with a better outcome in hospitalized patients with severe community-acquired pneumonia, including the subset of cases with bacteraemic pneumococcal infection treated with beta-lactam therapy alone.

5 THE VALUE OF SPUTUM INVESTIGATION IN THE DIAGNOSIS OF CAP

55. **Feldman C**, Smith C, Kaka S, de Jong P. Analysis of routine sputum specimens at Hillbrow Hopital. *S Afr Med J* 1992; 81: 42-43.

56. **Feldman C**, Kaka S, Goolam Mahomed A, Frankel A, Smith C, de Jong P, Koornhof HJ. Factors influencing the sensitivity of the Gram stain of sputum samples in pnumococcal pneumonia. *South Afr J Epidemiol Infect* 1994; 9: 72-75.

57. **Feldman C**, Smith C, Kaka S, de Jong P, Promnitz DA. The clinical significance of *Haemophilus influenzae* and *H. parainfluenzae* isolated from the sputum of adult patients at an urban general hospital. *S Afr Med J* 1992; 81: 495-511.

58. **Feldman C**, Smith C, Kaka S, deJong P. The isolation of *Moraxella (Branhamella) catharrhalis* from the sputum of adult patients at an urban general hospital. *South Afr J Epidemiol Infect* 1992; 7: 76-78.

59. **Feldman C**, Smith C, Kaka S, de Jong P, Goolam Mahomed A, Frankel A, Koornhof HJ. Factors associated with airway colonization and invasion due to *Klebsiella* spp. *S Afr Med J* 1993; 83: 643-646.

One of the difficulties in the management of patients with community-acquired pneumonia has been the ability to rapidly identify the causative pathogen. As such several studies have suggested that even with extensive microbiological investigation the causative

pathogen is identified in somewhat less than 50% of cases, particularly in less severely ill patients. While the sputum Gram stain and culture has been a time honoured technique there has been significant controversy and discussion about its accuracy and value. Studies have clearly indicated that various, potentially correctible, factors are associated with its poor performance (55). Grading of the "quality" of sputum specimens using criteria such as the Bartlett system are helpful, since this helps identify those specimens that are of "good quality" and therefore more likely to be representative of lower respiratory tract secretions, whereas poor quality specimens are likely to be misleading.

Furthermore, sputum specimens collected as part of usual hospital routine are often poor in comparison to those that are collected by trained physiotherapists, although even the latter is not infallible. Lastly, delay in submission of specimens to the laboratory, particularly when these are taken after the initiation of antimicrobial chemotherapy, decrease the accuracy of these investigations. However, in the ideal circumstances with the submission of a "good quality" specimen, prior to the administration of antibiotics, and particularly with participation or regular scrutiny by a trained microbiologist, the sputum Gram stain is able to achieve acceptable accuracy, missing fewer than 10% of cases of pneumococcal pneumonia (56).

Several organisms, although identified a number of years ago, were only recently recognized to be important causes or both upper and lower respiratory tract infections, including community-acquired pneumonia. Among the reasons for this are that these pathogens are of relatively low virulence, infrequently associated with bacteraemia and therefore only isolated from careful sputum examination or invasive diagnostic techniques.

Among these are *Haemophilus influenzae* and *Haemophilus parainfluenzae* and *Moraxella (Branhamella) catarrhalis,* which were studied further (57, 58). Most of the patients with these infections have underlying predisposing factors to chest infection, in particular chronic obstructive pulmonary disease (COPD) and bronchiectasis. All the *H. influenzae* isolates were non-typeable, with a wide range of biotypes, and there was a low incidence of beta-lactamase production (only 3 of 49 isolates). Two of the 4 isolates of *M. catarrhalis* produced beta-lactamases.

Given that respiratory tract infections due to *Klebsiella pneumoniae* were found to be so common in patients with severe community-acquired pneumonia and lung abscess in the South African setting (described above), it appeared important to study the clinical significance of the isolation of these microorganisms from sputum cultures and to determine associated underlying medical conditions that could serve as risk factors for these infections (59). Risk factors for airway colonization and invasive disease were similar. Patients with community-acquired infections were more likely to have underlying chronic respiratory diseases, while prior antibiotic use was a risk factor for nosocomial infections, particularly with antibiotic-resistant microorganisms. The sensitivity and specificity of the sputum Gram stain in suggesting the presence of invasive disease due to *Klebsiella* spp., was 42% and 69%, respectively.

6 TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

6.1 Antibiotic treatment

60. **Feldman C**, White H, O'Grady J, Flitcroft A, Briggs A, Richards G. An open, randomized, multi-centre study comparing the safety of sitafloxacin and imipenem/cilastatin in the intravenous treatment of hospitalised patients with pneumonia. *Int J Antimicrob Agents* 2001; 17: 177-188.

61. Leophonte P, File T, **Feldman C**. Gemifloxacin once daily for 7 days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumcocccal origin. *Respiratory Medicine* 2004; 98: 708-720.

62. Tamm M, Todisco T, **Feldman C**, Garbino J, Blasi F, Hogan P, de Caprariis PJ, Hoepelman IM. Clinical and bacteriological outcomes in hospitalized patients with community-acquired pneumonia treated with azithromycin plus ceftriaxone, or ceftriaxone plus clarithromycin or erythromycin: a prospective, randomized, multicentre study. *Clin Microbiol Infect* 2007; 13: 162-171.

A number of clinical drug trials were conducted in the Pulmonology Unit under my direction, mostly of new antibiotics that required regulatory studies by the Medicines Control Council of South Africa for registration and licensing of new agents, but also occasionally as part of post-marketing surveillance.

In the first study (60), a new fluoroquinolone antibiotic was shown to be as safe and as tolerable, and probably as effective, as an already licenced comparator agent. The second (61) was another study of a new fluoroquinolone demonstrating it to be clinically, bacteriologically and radiologically as effective as a standard agent, recommended as a suitable alternative in the South African pneumonia guideline. The third study (62) documented that combination therapy with ceftriaxone and azithromycin was at least equivalent to appropriate comparator regimens and a suitable alternative in hospitalized patients with CAP. This is one of the recommended alternative regimens recommended in several pneumonia guidelines, including those in South Africa.

6.2 Experimental therapy

63. Smith C, **Feldman C**, Seftel HC. A pilot study of pyridoxal in severe pneumonia. *S Afr J Epidemiol Infect* 1993; 8: 77-80.

Given the extremely high mortality among patients with severe community-acquired pneumonia, the last study conducted was a pilot study (63), aimed at documenting whether serum pyridoxal levels were low in severely ill patients with pneumonia, and furthermore whether supplementation of such patients with pyridoxal phosphate would be associated with a better outcome. The rational behind this study is as follows. Vitamin B_6 exists in three forms *in vivo,* pyridoxine being the form found in vitamin supplements and plants. It has no vitamin B_6 activity and needs to be converted in the liver to pyridoxal (PL) and pyridoxal phosphate (PLP), the active metabolites of pyridoxine. PLP depletion has been shown to occur in a number of disease states, including infections, through a number

of possible mechanisms. Depletion of PLP may have a number of significant consequences that could impact negatively on the outcome of an infection, such as being associated with impaired protein synthesis, compromisation of energy-dependent pathways and impaired immune competence. In this study pyridoxal levels were found to be lower in non-survivors with severe community-acquired pneumonia (73 $\pm$ 89 ng/ml versus 141 $\pm$ 224 ng/ml), but this did not reach statistical significance. However, as a pilot study, patient numbers were small and may have adversely affected statistical analyses. Furthermore pyridoxal phosphate supplementation had no effect on patient outcome.

7. GUIDELINES AND REVIEWS

7.1 South African guideline documents

64. **Feldman C**, Brink AJ, Richards GA, Maartens G, Bateman ED. Management of community-acquired pneumonia in adults. Working Group of the South African Thoracic Society. *S Afr Med J* 2007; 97: 1295-1306.

65. **Feldman C**, Klugman KP. Adult Influenza vaccination guideline. SAMA-SA Pulmonology Society Working Group. *S Afr Med J* 1999; 89: 1216-1222.

66. **Feldman C**, Klugman KP. Adult pneumococcal vaccination guideline. SAMA-SA Pulmonology Society Working Group. *S Afr Med J* 1999; 89: 1222-1230.

This last section contains guideline papers and review articles that represent important management recommendations and decisions in patients with community-acquired pneumonia. The first (64) is the recently updated guideline for the management of community-acquired pneumonia in adults in South Africa. This is the third edition of this guideline, the first being published in 1996 and having recommendations that are informed not only by international publications, but also by studies undertaken in South Africa, including those undertaken by this author. Guidelines on the appropriate use of influenza and pneumococcal vaccination have also been published (65, 66). The former has recently been updated.

7.2 "State-of-the-Art" management guideline articles

67. **Feldman C**. Appropriate management of lower respiratory tract infections in primary care. *Primary Care Respiratory Journal* 2004; 13: 159-166.

68. **Feldman C**. Clinical relevance of antimicrobial resistance in the management of pneumococcal community-acquired pneumonia. *J Lab Clin Med* 2004; 143: 269-283.

69 **Feldman C**, Anderson R. Controversies in the treatment of community-acquired pneumonia. *Future Microbiol* 2006; 1: 11-15.

These additional publications are all invited reviews by journal editors, possibly based on an appreciation of the various studies that have been described previously. The first (67) is a definitive description of the appropriate management of lower respiratory tract infections in primary care. The importance of this publication is that these are the "front-line" medical practitioners that most commonly are responsible for the management of patients with respiratory tract infections, such as pneumonia, rather than the private, hospital based and/or academic physicians, and one criticism that has been leveled against guidelines for the management of pneumonia is that they are heavily weighted towards the specialist practitioner. The second paper (68) puts clearly into perspective the true prevalence and likely impact of antimicrobial resistance among the various pathogens that cause pneumonia and give firm recommendations as to the appropriate empiric management of pneumonia, in this era of antimicrobial resistance, as well as the appropriate treatment resistant infections, should these be documented. The last paper (69),

perhaps most appropriately, highlights the considerable remaining controversies that still exist with regard to our full understanding of all the various aspects of community-acquired pneumonia, and in particular pneumococcal infections, describing the various issues related to antimicrobial therapy as well as adjunctive treatments that are available, hoping to achieve the most effective outcome for patients with community-acquired pneumonia.