

Emerging Pathogens for Pneumonia in Singapore

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"one cannot step twice into the same river" Heraclitus of Ephesus (circa 540-480 BC)

Abstract

The death rate from pneumonia in Singapore has increased steadily over the past decade. The emerging respiratory pathogens may have contributed to this increased mortality. New challenges have arisen from changes in the characteristics of the host and the susceptibilities of the various pathogens to antibiotics. There has been a 60-fold increase in the incidence of penicillin resistance in Streptococcus pneumoniae, the major pathogen for community-acquired pneumonia (CAP). Gram-negative bacilli are the major pathogens in severe CAP with Klebsiella pneumonia being the most frequently isolated organism. There has been a small increase in the number of cases of Legionnaire's disease and a marked increase in the incidence of melioidosis. While the overall incidence of tuberculosis has been unchanged, the number of non-residents with tuberculosis has doubled in the past 5 years. The rising prevalence of human immunodeficiency Virus infection is reflected in an increasing number of apparently healthy young men who present with CAP caused by Pneumocystis carinii. There is increasing resistance to antibiotics among gram-negative bacilli and Staphylococcus aureus, the dominant pathogens in hospital-acquired pneumonia. New strategies are urgently needed to prevent the emergence of pathogens in the hospital environment which may be resistant to all known antibiotics.

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Key words: Antibiotic resistance, Hospital-acquired, Immunocompromised patients

Introduction

Heraclitus commented that every time we re-enter the same river both the water that flow down and we ourselves have changed. Thus the experience never repeats itself. This everchanging complexion of an apparently familiar encounter is a good analogy for the phenomenon of emerging respiratory pathogens which cause pneumonia in Singapore. The emerging pathogens which cause pneumonias in Singapore are more often re-emergent ones and rarely are they brand new entities.

Most of the emerging pneumonias in Singapore are thus associated with pathogens well known to cause lower respiratory tract disease. What is new and challenging is the relative frequency of their occurrence and the changing context in which the infections are acquired both in terms of epidemiological setting and host characteristics. Most important of all, especially with regards to treatment, there has been a gradual decline in the susceptibility of many respiratory pathogens to commonly used antibiotics.

The initial choice of antimicrobial treatment for most infections is an empirical one. This is especially so in the initial treatment of pneumonias. This empirical approach is emphasised in current practice guidelines published by the American Thoracic Society for both community and hospital-acquired pneumonias (HAP).^{1,2} Choosing the correct antimicrobial drug the first time round is likely to have an important impact on outcome. This seems to be the case in severe community-acquired pneumonias (CAP) where the mortality is better related to appropriate initial therapy directed at the known spectrum of likely pathogens than to the ability in identifying the specific pathogen itself.³ Thus, knowledge about the changing prevalence of the pathogens and their likely antimicrobial susceptibilities are key ingredients in the effective management of respiratory infections.

There has been an increase in deaths attributed to pneumonias in Singapore over the past decade. By contrast, over the same period, deaths from acute myocardial infarction have declined with more people dying

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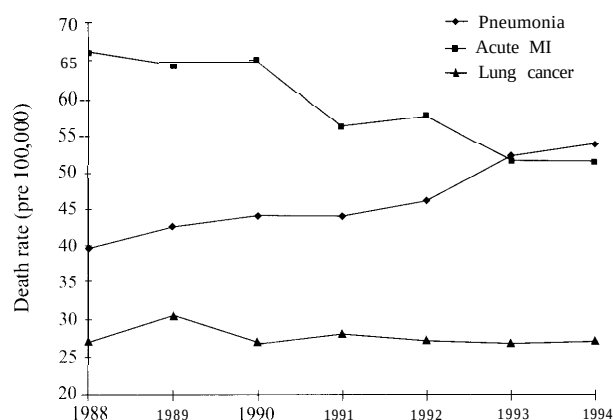


Fig. 1. This figure plots the death rates from pneumonia (solid diamonds), acute myocardial infarction (Acute MI, solid squares) and lung cancer (solid triangles) in Singapore from 1988 to 1994 (Data from the Singapore Register of Births and Deaths).

from pneumonia than heart attacks in Singapore since 1993 (Fig. 1). A recent survey in the United States have shown a similar trend in increasing mortality from respiratory tract infections.⁴ It is not known however if the emerging respiratory pathogens have contributed to this recent increase in mortality associated with pneumonias.

This review only addresses pneumonia in adult patients with a bias towards the more severe clinical presentations which usually require admission to hospital.

Sources of Information

This review article is based on information on respiratory infections in Singapore over the past decade gathered from the following sources:

- mortality statistics from the Annual Register of Births and Deaths,
- the Committee on Epidemic Diseases' monthly publication, the Epidemiologic News Bulletins, 1990 to 1997,
- Communicable Disease Surveillance Report 1994 from the Ministry of Environment,
- Annual Reports of the Singapore General Hospital's Pathology Department,
- a literature search of the Medline database on the Internet and CD-Rom (Medical Library, National University of Singapore) resources from 1985 to 1997 with the key words/MESH headings of "respiratory tract - pneumonia - infection - Singapore",
- abstracts on respiratory infections in Singapore presented at local and regional meetings,
- bacteriological data collated from the Annual Reports of the Microbiology Department of the National University Hospital from 1991 to 1995, and
- where appropriate, individual case examples.

In the interest of brevity, not all sources are cited in the text. A peer-reviewed journal from the National Center

for Infectious Diseases, Centers for Disease Control and Prevention, Georgia, USA—"Emerging Infectious Diseases" (from 1995 to 1997) may be consulted for recent global developments in this area. Full-length articles from this journal are available at the following website: "<http://www.cdc.gov/ncidod/EID/eid.htm>".

Community-acquired Pneumonias

Penicillin-resistant *Pneumococcal Pneumonia*

Streptococcus pneumoniae is the most common causal organism for CAP in Singapore and in the rest of the world.^{5,6} It is also associated with considerable morbidity and mortality. The death rate from bacteraemic pneumococcal pneumonia is about 20%.⁶ There has been a dramatic increase in the incidence of penicillin-resistant *S. pneumoniae* (PRSP) isolated in Singapore over the past decade. In the Singapore General Hospital, the incidence of PRSP was reported to be only 0.5% in a survey conducted from 1977 to 1986.⁷ The same laboratory has noted a greater than 60-fold increase in the incidence of PRSP to above 35% in 1996. This rapid increase in the prevalence of resistant organisms isolated in the community at large has also been noted in many other areas of the world with a high prevalence of PRSP.^{8,9} This acquisition of resistance occurs predominantly in an out-patient and community setting and is especially prevalent among the paediatric population. It is likely that the widespread availability and use of antibiotics for common self-limiting upper respiratory infections is an important causal factor in the acquisition of antibiotic resistance.

Areas with a high prevalence of PRSP have also reported increasing incidence of severe disease caused by invasive PRSP.⁸⁻¹⁰ The most feared manifestations of *S. pneumoniae* are meningitis and bacteremic pneumonia. In July 1996, we encountered the first fatal case of bacteremic penicillin-resistant pneumococcal pneumonia at the National University Hospital. The patient was a 77-year-old man with a history of chronic obstructive pulmonary disease, pulmonary tuberculosis and bleeding peptic ulcer. He presented with an acute community-acquired right lower lobe pneumonia. He was dehydrated, hypotensive (Bp 75/43 mmHg on admission), hypoxic and had renal impairment. He died within 24 hours of hospital admission despite receiving cloxacillin (500 mg qid iv) and ceftriaxone (1g BID iv). Penicillin-resistant *S. pneumoniae* was isolated from blood cultures. The strain of *S. pneumoniae* was susceptible *in vitro* to the cephalosporins and the minimal inhibitory concentration study showed intermediate penicillin resistance. Thus, this patient died from invasive PRSP infection despite receiving appropriate antibiotics.

The current recommendation is to use high dose penicillin G (200 000 u/kg/day) against *S. pneumoniae* with intermediate levels of resistance and a cephalosporin for

high-level resistance.¹⁰ If the *S. pneumoniae* is resistant to both penicillin and cephalosporins then we have to resort to either vancomycin or imipenem.¹⁰

This rapid increase in resistance against penicillin among the pneumococci is a strong argument in favour of the more widespread use of pneumococcal vaccination in individuals at increased risk of acquiring this infection.

Klebsiella pneumoniae

There is a regional variation in the incidence of community-acquired gram-negative bacillary pneumonia. It is rarely seen in Northern Europe and England but reported with increasing frequency as we travel from Southern Europe, to the Middle East, South Africa and across East Asia. Hui et al⁵ isolated gram-negative bacteria from 17% of patients admitted to the National University Hospital with acute CAP. Lee et al¹¹ isolated gram-negative bacilli (excluding *Haemophilus pneumoniae*) from 23% of patients with severe CAP managed in the intensive care unit of the same hospital. Thus, gram-negative bacilli appear to be important pathogens of CAP in Singapore. They tend to be more common among elderly patients and those with co-morbid diseases.

Klebsiella pneumoniae is the most common gram-negative bacilli associated with severe lower respiratory infections. It had a tendency to invade the blood stream, complicate with metastatic abscesses and progress to a fulminant necrotising pneumonia despite treatment with appropriate antibiotics."

In our experience at the National University Hospital, *K. pneumoniae* is commonly recovered from the sputum of elderly patients hospitalised with acute medical illnesses. About half of these patients do not present with clinical features of acute lower respiratory tract infection. This most likely represents colonisation of the oropharynx by the gram-negative bacillus.

Colonisation of the upper respiratory tract by *K. pneumoniae* may be a prelude to the development of pneumonia later. Important risk factors for colonisation of the oropharynx by gram-negative bacteria are acute stress, prior broad-spectrum antibiotic usage, invasive instrumentation of the respiratory tract and prior hospitalisation. Patients who do present with pneumonia tend to be older and more sick than those who have been merely colonised.

The initial antibiotic treatment for elderly patients and patients with underlying pre-morbid conditions such as diabetes mellitus and chronic alcoholism who have been admitted to hospital with severe community-acquired pneumonia in Singapore should include cover for *K. pneumoniae*. The antibiotics commonly chosen to treat community-acquired gram-negative bacillary sepsis in-

clude third generation cephalosporins such as ceftriaxone and ceftazidime. The use of either one of these antibiotics would be appropriate since we have found that community-acquired *K. pneumoniae* isolates, whether from blood cultures (20% susceptibility) or from expectorated sputum (13% susceptibility), remain sensitive *in vitro* to either of these antibiotics.

Melioidosis

Burkholderia pseudomallei (previously known as *Pseudomonas pseudomallei*) is a free-living soil bacterium which has been isolated all over Southeast Asia.¹³ It had been shown to cause fatal pneumonia in Singapore from as long ago as 1920.¹³ Over the past decade however there has been a gradual increase in the number of reported cases in Singapore with a doubling in the number of patients from 1994 to 1995 (Fig. 2).^{14,15} The reason for this increase is unknown. The local sero-prevalence of 0.2% is very low in comparison with other countries in the region (over 25% in Thailand) and so is the rate at which *B. pseudomallei* is isolated from the soil (0% to 5.9% in Singapore compared to 60% to 80% in Thailand).^{15,16}

B. pseudomallei is similar to *K. pneumoniae* in its predilection for invading the blood stream, causing metastatic abscesses and fulminant pneumonia. However, it is a more virulent pathogen than *K. pneumoniae*. The mortality rate for all cases of melioidosis (bacteraemic and non bacteraemic) reported in Singapore from 1989 to 1996 was 40% (147/372).¹⁵ By contrast, Lee et al¹² had reported a mortality rate of 26% in 101 patients with bacteraemic *K. pneumoniae* infections. *B. pseudomallei* is an important cause of severe CAP in patients admitted to the intensive care unit of the National University Hospital, accounting for 4% of cases in a recent report by Lee et al.¹¹ Because of its tendency to invade the blood stream, however, it was the most common pathogen to

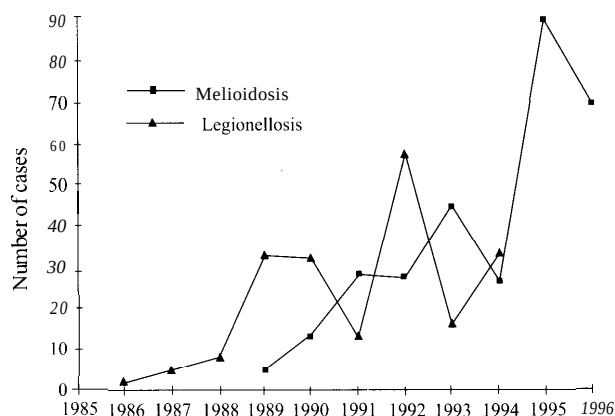


Fig. 2. This figure shows the number of cases of Legionnaire's disease (solid triangles, from 1986 to 1994) and Melioidosis (solid squares, from 1989 to 1996) which had been reported to the Ministry of Environment.

be identified definitively (isolated from blood cultures instead of sputum cultures) as the aetiological agent in severe CAP at the National University Hospital.

Melioidosis has a protean clinical and radiological presentation.¹⁷ The acute septicaemic variety is the most common and associated with the highest mortality. The illness runs a fulminant septic course with shock and multi-organ dysfunction as pre-terminal events. Multiple sites of abscess formation may be apparent. The lung is the most common organ affected and multiple splenic abscesses is a characteristic feature. Pulmonary melioidosis may present on the chest radiograph as diffuse nodules (even with a miliary pattern) or segmental consolidations which progress rapidly to a multi-segmental involvement or necrotise to form abscess cavities.¹⁸

There is a strong association between melioidosis and diabetes mellitus. The prevalence of diabetes mellitus in patients with melioidosis was 64%.¹⁵ This was much higher than the overall prevalence of diabetes mellitus in Singapore (<5%) and higher than the prevalence of 36% in patients with *K. pneumoniae* bacteraemia, 29% in patients with severe CAP and 21% in patients with CAP.^{5,11,12} It is thus recommended that the initial antibiotic administered for the treatment of diabetic patients presenting with fulminant pneumonia and/or septic shock in Singapore should be effective against *B. pseudomallei*.

B. pseudomallei is usually susceptible *in vitro* to ceftazidime, tetracyclines, co-trimoxazole (many local strains may be resistant), penicillin combinations with beta-lactamase inhibitors (amoxycillin-clavulanic acid, piperacilin-tazobactam), kanamycin and chloramphenicol. Only kanamycin and ceftazidime are bactericidal. Newer broad spectrum beta-lactams such as imipenem-cilastatin and ticarcillin-clavulanic acid may also be effective. It is resistant to most penicillins, macrolides, aminoglycosides (except kanamycin), quinolones and aztreonam.

The best treatment regimen for melioidosis is not established. Most clinicians use a combination of antibiotics although no evidence of synergy has been demonstrated. Ceftazidime alone may be adequate in most cases. In patients who fail to respond to ceftazidime, oral doxycycline or chloramphenicol is often added to intravenous ceftazidime.¹⁹ After the acute phase, prolonged treatment for 3 to 6 months may be necessary to prevent relapses.

Legionellosis

Legionella pneumophila was first recognised as an aetiological agent for pneumonia in 1976. It has a propensity for infecting elderly subjects with pre-morbid diseases and may cause a severe life-threatening pneumonia needing support in the intensive care unit and prolonged hospitalisation. Since the first description of

Legionnaire's disease in Singapore in 1986, there has been a gradual increase in the number of reported cases (Fig. 2).^{20,21} Despite the increasing incidence however, the number of cases remain small and *L. pneumophila* is not an important causative agent for pneumonia in Singapore. In 1991, Vijayasingham et al²² reported an incidence of Legionnaire's disease in 1.7% of 177 patients admitted to the general wards with chest infections, while Hui et al⁵ did not diagnose even a single case of Legionnaire's disease in a prospective survey of about 100 patients at the National University Hospital in 1993. Lee et al¹¹ reported a similarly low incidence of 2% in 59 patients with severe CAP managed in the intensive care unit of the National University Hospital despite the tendency for *L. pneumophila* to cause severe pneumonia. This contrasts with some centres in Europe and the Middle East, which report a 15% to 20% incidence of Legionnaire's disease in patients with CAP.²³

We should however, not be complacent about the relatively low incidence of Legionnaire's disease in Singapore. Recent epidemiological studies have identified a potential reservoir of Legionnaire's disease in contaminated water distribution systems. Surveillance of legionella bacteria in the environment in Singapore have found it to be ubiquitous in cooling towers (the incidence of contamination ranging from 25% to 100%).¹⁵ The risk of a point-source outbreak from generation of contaminated aerosols especially among susceptible subjects such as immunocompromised patients in hospital should be kept in mind.

Moraxella (Branhamella) catarrhalis

Moraxella catarrhalis used to be considered a harmless commensal of the upper respiratory tract. Over the past decade, however, many reports have described its pathogenicity in sinusitis, pneumonia and in infective exacerbations of chronic obstructive pulmonary disease and bronchiectasis.²⁴ Chin et al²⁵ have reported that, in Singapore, *Moraxella catarrhalis* causes a pattern of respiratory disease which is very similar to that reported in the West. It is usually associated with infective exacerbations in elderly patients with underlying chronic broncho-pulmonary diseases such as chronic obstructive pulmonary disease and bronchiectasis. It is however a rare cause of pneumonia in a previously healthy host. The organism is generally sensitive to the extended spectrum beta-lactams and newer macrolides usually prescribed for infective exacerbations of pulmonary disease and the overall prognosis is good.

Tuberculosis

Over the past ten years, there has been a global resurgence of tuberculosis.²⁶⁻²⁸ This is particularly striking among the countries of Southeast Asia where the World Health Organization reported that the average rate of

disease notification has increased from an average of 90 per 100 000 population between 1983 and 1987 to 194 per 100 000 population in 1990.²⁸ In contrast, the annual reported incidence of new cases in Singapore have declined from 100 per 100 000 in 1980 to around 50 per 100 000 in 1990.²⁹ Thus, during the 1980s, while the incidence of tuberculosis doubled in the other countries of Southeast Asia, it halved in Singapore.

There are no grounds for complacency, however, regarding the relatively low incidence of tuberculosis in Singapore when compared to that in neighbouring countries. The incidence is still much higher than in most developed countries. Moreover, the reported incidence of new cases of tuberculosis had not declined over the past 5 years. This is partly due to an increase in the number of new cases of tuberculosis among foreigners of non-resident status employed in Singapore from 165 (10% of new cases) in 1989 to 402 (22% of new cases) in 1994.³⁰ Most of these non-residents have come from neighbouring countries where there has been a resurgence of the disease and, most alarming of all, where the prevalence of drug-resistant tuberculosis is also higher than in Singapore. While there is also great concern about the potential for increase in the incidence of multidrug-resistant cases of tuberculosis, this appears not to be a major problem in Singapore at present.³⁰ Comprehensive screening for the disease in foreigners who apply for employment in Singapore and close surveillance of these workers after they have started working in Singapore are two measures which may help control the emergence of tuberculosis among this subgroup.

Infection with the human immunodeficiency virus (HIV) is the greatest risk factor ever identified which favours the progression of tuberculous infection to disease. The acquired immunodeficiency syndrome (AIDS) epidemic, which has been spreading rapidly in some Southeast Asian countries, is probably an important causal factor in the resurgence of tuberculosis in this region. HIV infection has yet to reach its most severe proportions in Singapore.³¹ It is very likely, with the steady increase in the prevalence of HIV infection among the local population in Singapore, tuberculosis will also re-emerge as an important complicating disease.

Since 1987 however, even among local residents, the incidence of new cases of tuberculosis has not changed and is a cause for concern. The commencement of the Singapore Tuberculosis Elimination Programme in 1997 with its emphasis on directly observed treatment and close contact tracing is an important step in the long-term control of this ancient disease.

Pneumocystis carinii

P. carinii, recently reclassified as a fungi, has for a long time been considered a sentinel infection indicative of an

underlying immunodeficient state. The key host defence mechanism against this opportunistic pathogen is cell-mediated immunity, especially the CD4+ lymphocytes. Infection with *P. carinii* is almost always limited to the lungs where it causes an alveolar filling process which, if untreated, may progress to respiratory failure.

In recent years we have seen a steady increase in the incidence of *P. carinii* pneumonia among patients admitted with CAP at the various hospitals in Singapore. This is a result of changes in the patient population. There has been an increase in the number of patients with immunosuppression caused by treatment of lymphoreticular malignancies and organ transplants. An even more important factor is the impact of HIV infection on the risk of developing *P. carinii* pneumonia. *P. carinii* is the most common AIDS-defining illness in Singapore and the most frequent cause of life-threatening infection in patients with AIDS.³²

Raghuram et al (unpublished data) from the Singapore General Hospital recently highlighted the problem of *P. carinii* pneumonia presenting as CAP in young patients (mean age 30 years) with no pre-morbid disease and who were not previously known to be HIV positive. The incidence of patients with HIV infection presenting as CAP is likely to increase in the future in parallel with the prevalence of HIV infection in Singapore. Bartlett and his colleagues³³ in a paper from the Johns Hopkins Hospital, where 57% of their patients admitted with CAP were immunocompromised, illustrate the extent of this problem in some parts of the United States. They found that *P. carinii* was the second most common causative organism in CAP after *S. pneumoniae*. A high index of suspicion is necessary to diagnose this infection in its early stages before it progresses to frank respiratory failure.

The recent experience with *P. carinii* pneumonia at the National University Hospital serves both to characterise the patients who are at risk and to illustrate the clinical spectrum of the illness (Table I). The HIV-associated disease was usually diagnosed in heterosexual men while non-HIV associated disease was induced either by chemotherapy for lymphoma or immunosuppressive treatment for organ transplants. Patients on corticosteroid treatment (with or without cyclophosphamide) for autoimmune disorders such as systemic lupus erythematosus or Wegener's Granulomatosis are also at risk.

The commonly held notion that when *P. carinii* pneumonia develops in a patient with HIV infection, it usually presents as an acute febrile illness with extensive bilateral lung infiltrates and respiratory failure is not correct. HIV-related *P. carinii* pneumonia may be an indolent illness with the patients presenting to hospital after they had experienced intermittent low grade fever, cough, progressive effort dyspnoea and weight loss for 4 to 6 weeks.³⁴ The chest radiographs were normal or

borderline abnormal at presentation in nearly half the cases (Table I). In two patients, the illness was so mild that they could be sent home with oral medication soon after diagnosis had been made. A high index of suspicion accounts for the relatively high proportion of patients diagnosed with early disease in this series. At the other end of the spectrum were 3 patients who developed acute respiratory distress syndrome and needed ventilatory support in the intensive care. Thus, it is important to recognise the subtle signs of early disease and where appropriate, to perform simple screen tests for *P. carinii* pneumonia.

The trophozoite forms of *P. carinii* selectively attach to and damage type I alveolar epithelial cells but elicit little inflammatory response. This results in increased thickness of the alveolar-capillary interface (not detected on plain chest films) and impairment of oxygen transfer especially during exercise well before the development of extensive alveolar consolidation. Pulmonary disease may be demonstrated by high-resolution computer tomography in early stages of the illness when the plain chest film is normal. The resting diffusing capacity is also abnormal in almost 100% of patients with *P. carinii* pneumonia.³⁴ A simple method to screen high risk symptomatic patients is to monitor the pulse oximetry during exercise.³⁴ A normal oxygen saturation during exercise testing essentially rules out the diagnosis. Pulse oximetry is more widely available and cheaper than either pulmonary function testing or computer tomography and is the screen test of choice for early disease.

The definitive diagnosis of *P. carinii* pneumonia is made by identifying the organisms using toluidine blue or Gomori methenamine silver ' stains in pulmonary

TABLE I: ADULT *Pneumocystis carinii* PNEUMONIA AT THE NATIONAL UNIVERSITY HOSPITAL FROM 1994 TO 1996

Age: Mean (SD): 48 (18) years

Age: Range: 18 to 77 years

	Number of Patients	%
Total	14	100
Males	11	78
HIV +ve	8 (6 heterosexual)	57
Lymphoma	5 (2 HIV +ve also)	36
Renal transplant	3	21
Treated with oral bactrim	2	14
Clear chest radiograph	6	43
Needed prednisolone*	6	43
ARDS	2	14

Bactrim: trimethoprim-sulfamethoxazole

Clear chest radiograph: normal or borderline abnormalities

HIV: Human immunodeficiency virus

ARDS: Acute respiratory distress syndrome

* Prednisolone adjuvant therapy was administered as for patients with hypoxia ($\text{PaO}_2 < 70 \text{ mmHg}$ or Oxygen saturation $< 92\%$) at rest.

secretions usually obtained by fiberoptic bronchoscopy. A lung biopsy is rarely indicated.

Hospital-Acquired Pneumonia (HAP)

The main pathogens associated with HAP are aerobic enteric gram-negative bacilli of the group *Enterobacteriaceae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.³⁵ Additional risk factors can predispose hospitalised patients to infections by specific pathogens. There are associations between aspiration and anaerobes, diabetes mellitus and *S. aureus* and prolonged ICU stay and *P. aeruginosa*. In HAP not associated with such risk factors, the *Enterobacteriaceae* are the most likely pathogens. *K. pneumoniae* is the most common (non-*Pseudomonas*) *Enterobacteriaceae* causing HAP.³⁵

In Singapore, the most important trend in the microbiology of HAP over the past decade is the rapid emergence of resistance to multiple antibiotics among the gram-negative bacilli. This is most evident in the loss of susceptibility of *K. pneumoniae* to the broad spectrum cephalosporins which are the antibiotics most commonly prescribed for HAP at the National University Hospital (Fig. 3).³⁶ The prevalence of antibiotics resistance to "third generation" cephalosporins had increased in parallel with the widespread usage of these drugs. It is very likely that the resistant strains arose in response to the selective pressure caused by the use of these broad-spectrum antibiotics. The mechanism for resistance of *K. pneumoniae* to beta-lactam agents is the production of extended spectrum beta-lactamase enzymes.

The strategy for overcoming resistance due to beta-lactamases is by combining labile antibiotics with beta-lactamase inhibitors such as sulbactam, clavulinate and tazobactam. This option has been compromised in recent years by the emergence of *Enterobacteriaceae* which produce mutant beta-lactamases with reduced affinity

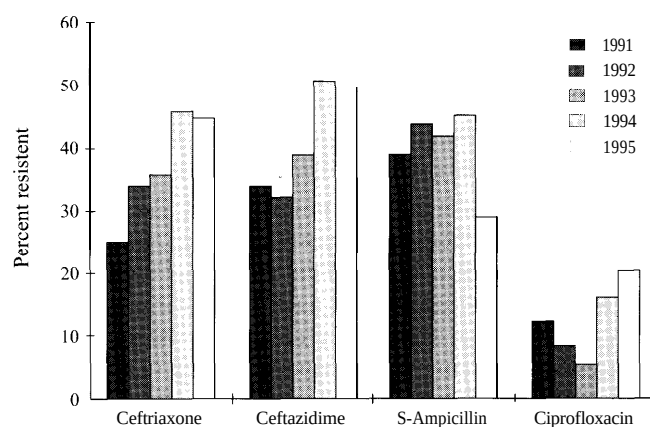


Fig. 3. This figure shows the resistance patterns of *Klebsiella pneumoniae* isolated from the respiratory tract secretions at the National University Hospital against ceftriaxone, ceftazidime, sulbactam-ampicillin (s-ampicillin) and ciprofloxacin from 1991 to 1995 (data from Annual Reports of the National University Hospital Microbiology Department).

to the inhibitors. In 1995, 25% to 30% of *K. pneumoniae* isolates from the respiratory tract at the University Hospital were resistant to amoxycillin-sulbactam and amoxycillin-clavulinate combinations. The *in vitro* resistance of *K. pneumoniae* to aminoglycosides is of the same order. Moreover, the local inactivation and poor penetrance of aminoglycosides in respiratory secretions limit their role as single agents in both CAP and HAP. Only the flouroquinolones and imipenem have retained an acceptable level of activity against such multi-resistant gram-negative bacilli.

At the National University Hospital, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolated from respiratory secretions had remained about 40% in recent years. It is ubiquitous in the hospital environment and has high prevalence in long staying diabetics, patients with neurological diseases and with renal failure. The most disturbing trend with regards to MRSA in recent years is the loss of susceptibility to clindamycin. This limits the choice of drugs against MRSA to vancomycin.

The increasing use of vancomycin against MRSA in many hospitals around the world has set the stage for the emergence of yet another pathogen—vancomycin-resistant enterococci. This organism has emerged as an important cause of nosocomial infections in the United States. The American National Nosocomial Infection Study has reported a 20-fold increase in the incidence of infections associated with this organism from 1989 to 1993.³⁷ It is intrinsically resistant to many commonly used antibiotics and has the ability to rapidly acquire resistance to all known antibiotics. Thus, we may witness, in the near future, the emergence of this virtually incurable “super-bug” in Singapore.

The problem of widespread bacterial resistance to antibiotics has been fuelled rather than dampened by the prescription of newer, more “potent” and more broad-spectrum antibiotics in hospitals. Current strategies of infection control, including strict antibiotic restriction policies, have not worked and new approaches are urgently needed. These may include utilising molecular techniques to rapidly identify the pathogens and their antibiotic susceptibilities in order to facilitate the use of specific narrow spectrum antibiotics, computer-assisted practice guidelines to rationalise prescribing habits, specific infection preventive policies and immunoenhancing therapies.

Conclusion

New challenges have emerged in the management of lower respiratory tract infections in Singapore despite the absence of really new pathogens. This is the result of changes in patient and pathogen populations which involve both community and hospital environments.

These changes have important implications for the diagnosis, empiric first-line treatment and the prevention of respiratory infections in Singapore.

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