# *Klebsiella pneumoniae* respiratory isolates from 2000 to 2004 in a Malaysian hospital: characteristics and relation to hospital antibiotics consumption

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## ABSTRACT

**Introduction: *Klebsiella pneumoniae* ranks high as a cause of community-acquired pneumonia in hospitalised patients in Malaysia.**

**Methods: A retrospective study of 5,990 clinical respiratory specimens in patients, with a mean age of 54 (standard deviation 18.5) years, admitted to an urban-based general hospital between 2000 and 2004, was conducted.**

**Results: The percentages of *K. pneumoniae* isolates during these years were 11, 19.1, 41.4, 27.8 and 16.6 percent, respectively. During this time, the percentage of isolates resistant to ampicillin were consistently in excess of 80 percent, those resistant to cephalosporins were relatively stable between eight and 23 percent, while those resistant to beta-lactam/beta-lactamase inhibitors [amoxicillin clavulanic acid/ ampicillin-sulbactam] and aminoglycosides steadily increased between six and 58 percent. Compared with hospital consumption of these corresponding antibiotic classes, only beta-lactam/beta-lactamase inhibitors and aminoglycosides showed a clear trend of eight- and four-fold increases, respectively. Co-resistance rates in isolates resistant to ampicillin and amoxicillin-clavulanic acid/ ampicillin-sulbactam were generally low to second to third generation cephalosporins (less than 20 percent).**

**Conclusion: Our local findings highlighted the changing trend in respiratory *K. pneumoniae* over a five-year period, and its escalating resistance to beta-lactam/beta-lactamase inhibitors and aminoglycosides that is possibly attributable to the widespread use of these antibiotics in our hospital.**


**Keywords: antibiotic resistence, community-acquired pneumonia, *Klebsiella pneumoniae*, respiratory infection, respiratory isolates**

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## INTRODUCTION

*Klebsiella pneumoniae* ranks high as a cause of community-acquired pneumonia (CAP) in hospitalised patients in Malaysia.[1-3] This appears unique as most reports from other countries, including Thailand, do not always share this finding.[4] An earlier study from Singapore did not show *K. pneumoniae* as being particularly important in CAP requiring hospitalisation,[5] but its presence is commoner in severe pneumonia.[6] *K. pneumoniae,* however, has been a well-recognised nosocomial pathogen for many years, especially now because of the rapidly increasing antibiotic resistance observed in this organism.[7,8] It is, medically, the most important *Klebsiella* species accounting for a significant proportion of worldwide hospital-acquired and healthcare-associated urinary tract infections, pneumonia, septicaemias and soft tissue infections. The same have been reported in intensive care units,[9] and more recently, paediatric wards in Malaysia.[10,11]

To understand the prevalence and potential clinical implications of *K. pneumoniae* respiratory isolates in hospitalised patients, we carried out a retrospective study with the following objectives: Firstly, to study clinico-demographical characteristics of patients in whom the clinical respiratory specimens cultured *K. pneumoniae*, including their antibiotic resistance, between 2000 and 2004. Secondly, to study the trend of *K. pneumoniae* isolates and to identify any associations between their trends of microbial resistance and the

**Table I. Characteristics of patient and bacterial isolates in relation to *Klebsiella pneumoniae* identified in the general ward and intensive therapy unit between 2000 and 2004.**

| Characteristics | Total | Source of *K. pneumoniae* isolates | | p-value* |
|---|---|---|---|---|
| | | General ward | ITU | |
| n (%) | 1,581 (100) | 1,399 (88.5) | 181 (11.5) | – |
| Mean age (years) (95% CI) | 54 (18.5) | 55 (18.5) | 56 (18.4) | 0.525 |
| Ethnicity | | | | |
| Malays | 51.8 | 52.0 | 50.4 | – |
| Chinese | 18.4 | 18.4 | 18.7 | – |
| Indians | 28.5 | 28.6 | 27.3 | 0.099 |
| Specimen type | | | | |
| Sputum | 80.1 | 89.4 | 8.6 | – |
| Tracheal aspirates | 19.2 | 10.0 | 89.9 | – |
| Bronchoalveolar lavage | 0.7 | 0.7 | 1.4 | < 0.001 |
| Years | | | | |
| 2000–01 | 20.7 | 19.1 | 32.4 | – |
| 2002–04 | 79.0 | 80.6 | 66.9 | 0.001 |
| Resistance to: | | | | |
| Ampicillin | 92.2 | 88.6 | 95.5 | 0.02 |
| Augmentin™/ Unasyn™ | 31.8 | 30.3 | 43.2 | 0.002 |
| 2nd generation cephalosporin | 17.3 | 11.1 | 38.8 | < 0.001 |
| 3rd generation cephalosporins | 14.7 | 7.1 | 36.0 | < 0.001 |
| Aminoglycosides | 24.6 | 21.2 | 42.4 | < 0.001 |
| Resistance to: | | | | |
| 1 antibiotic class | 52.8 | 55.4 | 34.1 | – |
| ≥ 2 antibiotic classes | 47.2 | 44.6 | 65.9 | < 0.001 |

Values shown are in percentage unless otherwise specified.

ITU: intensive therapy unit; CI: confidence interval; Augmentin™: amoxicillin-clavunate acid; Unasyn™: ampicillin-sulbactam; second generation cephalosporin: cefuroxime; third generation cephalosporins: ceftazidime, cefotaxime, ceftriaxone; Aminoglycosides: gentamicin, amikacin.

* indicates significance assessed between those in general ward and ITU.

volume of antibiotics consumed while hospitalised during these years.

## METHODS

Computer-generated data on all respiratory specimens (i.e. sputum, tracheal aspirates, bronchial washing and bronchoalveolar lavage) obtained between 2000 and 2004 in an urban-based, 800-bed, university teaching hospital (Tuanku Jaafar Hospital, Seremban, Malaysia) was retrieved for the purpose of this retrospective study. Data available from the computer included patient details, ward where specimen was sent, types of organism(s) identified, and antibiotics susceptibility. Specimen data could be derived from the same patients as long as they were not based on the same hospital admission. Records of the amount of various antibiotics consumed yearly were obtained from the hospital stock pharmacy record office. Data was analysed for patients' clinico-demographical characteristics, trends over the years, trends of antibiotic in vitro resistance, correlation with volume of annual hospital consumption of different antibiotics, and co-resistance rates among various antibiotic classes.

*K. pneumoniae* was identified by standard microbiological culture technique and nomenclature by Ørskov's classification.[12] All Enterobacteriaceae cultured were tested for susceptibility to a panel of six to nine antibiotics pre-specified by the Ministry of Health, Malaysia (Personal communication from Mr Haji Abdul Jalil Mohamed, Microbiology Unit, Tuanku Jaafar Hospital). To obtain a meaningful comparison between the years, the choice of antibiotics studied was based on the types of common antibiotics used in the hospital during the five years, and analysed according to antibiotic classes. The antibiotic classes consisted of β-lactam antibiotic (ampicillin), β-lactam/β-lactamase inhibitor antibiotics (amoxicillin-clavulanic acid, ampicillin-sulbactam), second generation cephalosporin (cefuroxime), third generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone),

and aminoglycosides (gentamicin, amikacin). The study protocol was approved by the local university research and ethics committee (IMU 065/2004).

For this study, oral and injectable forms of the same antibiotic were considered together to enable a comparison on the impact of individual antibiotic classes, regardless of the route of administration. To be clinically relevant, the comparable volume of intravenous antibiotics to that of oral antibiotics was taken at a ratio of 2:1, this being based on the assumption that the intravenous route has the greater potential of inducing microbial resistance than the oral route. This is due to the faster and higher plasma level achieved with intravenous administration – at least twice that of the oral route during the early distribution phase and with successive dosing.[13] Furthermore, oral antibiotics were commonly prescribed for and nearing hospital discharge, while intravenous antibiotics were confined to hospital ward use only, and therefore had a greater impact than oral antibiotics in the hospital microbial milieu. Similarly, higher doses of the same antibiotics were given higher numerical values in volume compared to lower doses, calculated based on their dose differences. These calculations were decided a priori for the purpose of studying the correlation with trends of resistant isolates.

Differences between groups were assessed by chi-square tests for categorical data and unpaired *t*-tests for continuous data. Analyses carried out were based on yearly percentage of respiratory specimens, not patients. In all cases, statistical significance was defined at the 5% level and assessed with two-tailed tests. All computation were made using the Statistical Package for Social Sciences version 11.5 for Windows (SPSS Inc, Chicago, IL, USA).

## RESULTS

The number of respiratory isolates between 2000 and 2004 were 716, 896, 1,688, 1,258 and 1,432, respectively, making up to a total of 5,990 isolates. Overall, 26.4% (1,581) of the isolates cultured were *K. pneumoniae*. The mean age (standard deviation [SD]) of the patients with *K. pneumoniae* isolates was 54 (18.5) years. The majority of patients were Malays and most isolates were from the sputum. Overall, general wards contributed 88.5% of the *Klebsiella* isolates, while intensive care wards contributed the remaining 11.5%. Importantly, the intensive care wards contributed more of the *Klebsiella* isolates than general wards between 2000 and 2001 (32.4% versus 19.1%), while more of the isolates were from the general wards between 2002 and 2004 (80.6% versus 66.9%). There was a significantly greater proportion of resistant *Klebsiella* isolates from the intensive care wards compared to the general wards. This difference was observed for all the antibiotics classes studied. The same held true in terms of the number of antibiotics resistance (Table I).

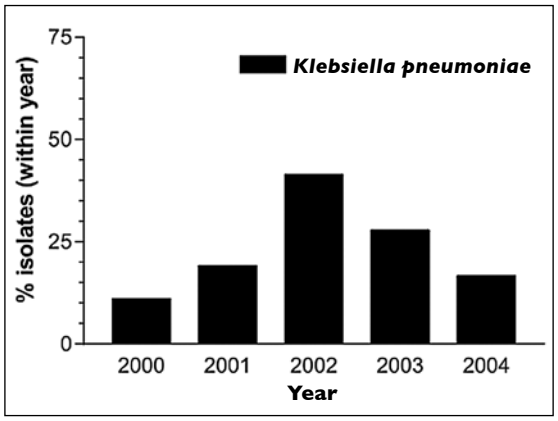


**Fig. 1** Trend in percentage of respiratory isolates of *Klebsiella pneumoniae* in our hospital between 2000 and 2004.

The percentages of *K. pneumoniae* isolates from 2000 to 2004 were 11%, 19.1%, 41.4%, 27.8% and 16.6%, respectively (Fig. 1). Between 2000 and 2004, the percentages of *Klebsiella* isolates that were resistant to ampicillin were 100%, 98.2%, 79.5%, 85.1% and 98.3%, respectively; to combined amoxicillin-clavulanic acid/ampicillin-sulbactam were 6.3%, 19.2%, 27.5%, 51.7% and 58.4%, respectively; to second generation cephalosporin (cefuroxime) were 20.2%, 23.3%, 10.7%, 12.5% and 23.1%, respectively; to third generation cephalosporins (combined cefotaxime, ceftadizime and ceftriaxone) were 20.2%, 18.1%, 7.3%, 8% and 21%, respectively and to aminoglycoside (combined gentamicin and amikacin) were 15.1%, 9.9%, 17.9%, 41.4% and 42.5%, respectively. Clearly, there was a marked increase in the in vitro resistance of *K. pneumoniae* to the amoxicillin-clavulanic acid/ampicillin-sulbactam and aminoglycosides over the years, compared to the rest of the antibiotic classes (Fig. 2a).

Hospital consumption of all five classes of antibiotics had significantly increased between two- and six-fold from 2000 to 2001. From 2001 onwards, ampicillin and cefuroxime consumption had reduced, while consumption of the third generation cephalosporins was relatively stable. However, for amoxicillin-clavulanic acid/ampicillin-sulbactam and aminoglycosides, their consumption continued to escalate, increasing by eight- and four-fold respectively. This trend appeared to mirror the increase of resistant isolates to amoxicillin-clavulanic acid/ampicillin-sulbactam and aminoglycosides from 6% to 58% and from 9% to 42%, respectively, during these years (Fig. 2b). On comparing concurrent resistance rates between the

**Table II. Proportion of concurrent in vitro resistance between antibiotic classes in *Klebsiella pneumoniae* isolates between 2000 and 2003.**

| *K. Pneumonia* isolates resistant to: | Concurrent in vitro resistance to: | | | | |
|---|---|---|---|---|---|
| | Ampicillin | Augmentin™/ Unasyn™ | 2nd generation cephalosporin | 3rd generation cephalosporins | Aminoglycosides |
| Ampicillin (n = 1,336) | – | 35.8 | 15.2 | 11.3 | 25.2 |
| Augmentin™/Unasyn™ (n = 550) | 96.1 | – | 29.0 | 19.7 | 46.5 |
| 2nd generation cephalosporin (n = 230) | 95.4 | 68.0 | – | 56.0 | 58.9 |
| 3rd generation cephalosporins (n = 175) | 98.4 | 64.3 | 77.8 | – | 67.5 |
| Aminoglycosides (n = 405) | 93.0 | 63.9 | 34.4 | 28.4 | – |

Augmentin™: amoxicillin-clavunate acid; Unasyn™: ampicillin-sulbactam; second generation cephalosporin: cefuroxime; third generation cephalosporins: ceftazidime, cefotaxime, ceftriaxone; Aminoglycosides: gentamicin, amikacin.

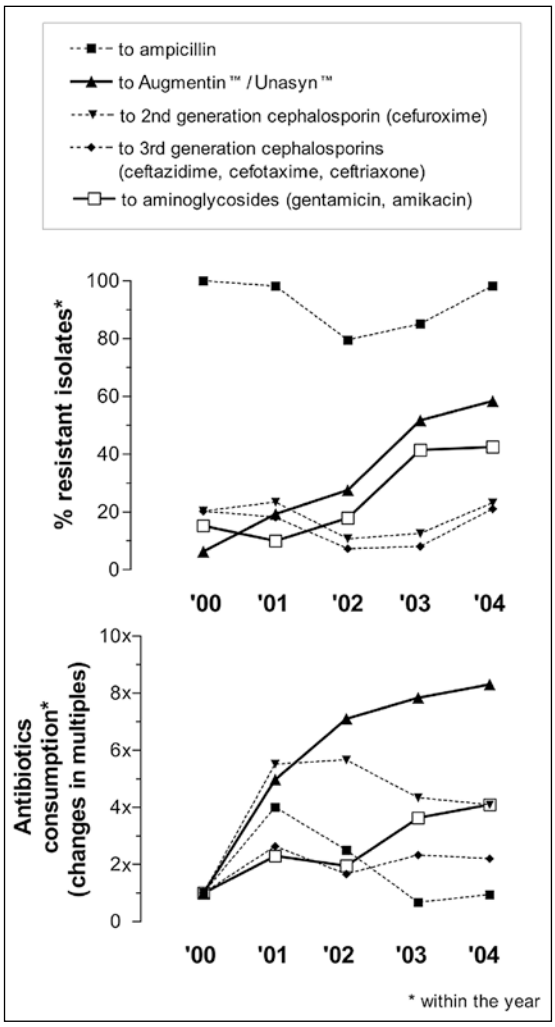


**Fig. 2** Yearly trend in (a) percentage resistant isolates, and (b) changes in multiples in antibiotics consumption among various commonly-prescribed antibiotics classes in hospital. Continuous (–) and dotted (…) lines indicate the increasing and reducing trends, respectively. Augmentin™: amoxicillin-clavunate acid; Unasyn™: ampicillin-sulbactam.

different antibiotic classes, isolates resistant to the broad spectrum antibiotics were generally resistant to the other antibiotic classes of "lower" potency (Table II). Importantly, the co-resistance rates of isolates resistant to ampicillin were still relatively low for second and third generation cephalosporins (15.2% and 11.3%, respectively). Also, for isolates resistant to amoxicillin-clavulanic acid/ampicillin-sulbactam, the co-resistance rate for third generation cephalosporins was relatively low (19.7%).

## DISCUSSION

We have shown that the percentage of respiratory isolates with *K. pneumoniae* was high (over a quarter); initially increasing and later decreasing over a five-year period in our hospital. Overall, most *K. pneumoniae* were isolated from the general wards. Interestingly, the intensive care wards contributed to more of the *Klebsiella* isolates in the earlier years while general wards contributed more in the latter years. Intensive care units, not surprisingly, had more resistant organisms. Importantly, there was a noticeable trend of increasing in vitro resistance of these isolates to β-lactam/β-lactamase inhibitor antibiotics and aminoglycosides that paralleled with the increased annual hospital consumption of these antibiotics. Otherwise, co-resistance rates to β-lactam antibiotics, with or without β-lactamase inhibitors, and to the other "broader spectrum" antibiotics remained low.

Our results indicate an important trend in hospitalised patients with *K. pneumoniae* and its escalating antibiotic resistance to β-lactam/β-lactamase inhibitors and aminoglycosides that mirrored closely the steep increase of the hospital consumption of these antibiotics.

It is well established that widespread and prolonged use of potent antibiotics predispose to microbial resistance,[10,14] and in the case of *Klebsiella* species, they are intrinsically resistant to penicillins and they can acquire resistance to extended spectrum cephalosporins and aminoglycosides due to the production of plasmid-mediated extended spectrum β-lactamases (ESBLs) and aminoglycoside-modifying enzymes.[7,15] Our finding of the close correlation between the escalating consumption of certain antibiotics and the increasing microbial resistance to them provides important circumstantial evidence that this has occurred and might be due to the widespread use of these antibiotics in our hospital over these years. The reason for such a dramatic increase in the usage of these antibiotics in our hospital is unclear. It is probably a reflection of the switching in prescribing patterns among our hospital doctors from ampicillin and cefuroxime to β-lactam/β-lactamase inhibitor antibiotics and aminoglycosides during these past few years.

It is noteworthy that the concurrent resistance rate of β-lactam antibiotics to third-generation cephalosporins in our respiratory isolates remained low (≤ 20%) throughout these years, and by inference, the incidence of ESBL-producing *K. pneumoniae* is probably low. The absence of definitive ESBL data was because specific testing for ESBL-producing isolates in our hospital did not commenc until 2003 (Personal communication with Mr Haji Abdul Jalil Mohamed). The lack of a parallel between the yearly prevalence of resistant organisms and annual hospital consumption of third-generation cephalosporins suggests that there had probably not been any significant widespread use of these antibiotics that had caused any escalation of ESBL-producing strains. ESBLs have a problematic resistance mechanism that is now reported worldwide and is commonly associated with *K. pneumoniae*.[14,16] In a recent study that assessed microbial susceptibility to β-lactam antibiotics of 570 clinical isolates in four Malaysian medical centres and two Singaporean medical centres, Biedenbach et al showed that ESBL-producing *Klebsiella* species was worryingly prevalent between 36% and 38%.[17] The reason for this discrepancy is unclear but it illustrates, as found in the United Kingdom,[7] there is a potential for large variance even in the same region due to differences in hospitals, locations and patient cohorts.

While our finding of a higher degree of antibiotic resistance of respiratory isolates from the intensive care unit is not surprising,[10,15] the reversal of the pattern between the early and latter years, implies a worrying shift of the dominance of *K. pneumoniae* infection from the intensive care unit to the general wards. One plausible explanation is that over the years, the *K. pneumoniae* load in the community has increased and contributes to their continual increase in the respiratory isolates in patients admitted to the general wards. The Malaysian data that *K. pneumoniae* is a high ranking cause for community-acquired pneumonia,[1-3] lends support to this notion.

The knowledge of local microbial epidemiology is crucial to enable the clinician to select the appropriate antibiotics.[18] There is now compelling evidence which indicates that appropriate empirical antibiotic therapy can save lives of patients with severe infections including pneumonia.[19,20] Our data not only contributes to this knowledge for local practising clinicians, but also adds to the existing published literature pertaining to the worldwide concern on multi-drug resistance of Enterobacteriaceae in the likes of *K. pneumoniae*. Our findings also have important clinical implications for hospital infection control and antibiotic prescribing policies in the effort to reduce the spread of infection and to mitigate the emergence of resistant microbial strains by judicious use of extended broad-spectrum antibiotics.[18]

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