

Adverse Hospital Outcomes Associated With the Choice of Empiric Antibiotics in *Klebsiella pneumoniae* Pneumonia: A Retrospective Observational Study

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Abstract

Introduction: In Malaysia, *Klebsiella pneumoniae* ranks high as a cause of adult pneumonia requiring hospitalisation. **Patients and Methods:** With concern over its rising microbial resistance, we explored the association of empiric antibiotics choices with the hospital outcomes of patients treated for microbial proven *K. pneumoniae* pneumonia in an urban-based teaching hospital. **Results:** In 313 eligible cases reviewed retrospectively, hospital mortality and requirement for ventilation were 14.3% and 10.8% respectively. Empiric regimes that had in vitro resistance to at least one empiric antibiotic (n = 90) were associated with higher hospital mortality (23.3% vs. 10.8%, $P = 0.004$) with risk increased by about two-fold [Odds ratio (OR), 2.5; 95% confidence interval (CI), 1.3 to 4.8]. Regimes (n = 84) other than the commonly recommended “standard” regimes (a β -lactam stable antibiotic with or without a macrolide) were associated with higher ventilation rates (16.7% vs. 8.8%, $P = 0.047$) with similar increased risk [OR, 2.0; 95% CI, 1.0 to 4.3]. **Conclusions:** Our findings reiterate the clinical relevance of in vitro microbial resistance in adult *K. pneumoniae* pneumonia and support empiric regimes that contain β -lactam stable antibiotics.

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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 Thailand⁴ do not always share this finding. Studies from Singapore have shown that *K. pneumoniae* is important in severe CAP requiring hospitalisation,⁵ not in CAP per se.⁶ The morbidity and mortality caused by *K. pneumoniae* infections, and particularly the extended-spectrum β -lactamases (ESBLs) producing organisms, are high,⁷⁻⁹ and appropriate antimicrobial therapy is crucial in determining clinical outcomes.¹⁰

In vitro antibiotic susceptibility has important implications in the surveillance of microbial resistance and clinical treatment. However, the link between in vitro microbial resistance and clinical outcomes has been debated over the years. An example of this is penicillin-resistant *Streptococcus pneumoniae*, where the association between

in vitro resistance and treatment failure has not been consistently demonstrated.^{11,12} In the treatment of adult patients hospitalised with pneumonia, the choice of empiric antibiotics has clearly shown to improve clinical outcomes. Most clinical practice guidelines recommend a β -lactam stable antibiotic such as an extended spectrum cephalosporin as initial empiric choice for patients with pneumonia severe enough to warrant hospitalisation, regardless of whether the pneumonia is community-^{13,14} or hospital-acquired.¹⁵ Such “standard” empiric coverage appears appropriate in the majority of cases of *K. pneumoniae* pneumonia.

In view of the importance of *K. pneumoniae* in hospitalised adults with pneumonia in Malaysia, a retrospective observational study of all patients admitted to our university’s teaching hospital for the treatment of pneumonia associated with *K. pneumoniae* was conducted. The study aimed to examine whether in vitro antibiotic resistance to the choice of initial empiric antibiotics and the generally

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recommended “standard” empiric antibiotics consisting of a β -lactam stable antibiotic were associated with hospital clinical outcomes in terms of hospital mortality, the requirement for mechanical ventilation and the length of hospital stay.

Patients and Methods

Data Collection

Data on all respiratory specimens (i.e. sputum, tracheal aspirates, bronchial washing and bronchoalveolar lavage) that cultured *K. pneumoniae* between January 2003 and December 2004 from our 800-bed urban-based teaching university hospital and patient details were downloaded from the hospital computer. The medical records of these patients were then retrieved and reviewed for eligible cases. Included were adult patients (≥ 12 years of age) who received antibiotic treatment for pneumonia and whose respiratory isolates cultured *K. pneumoniae*. Pneumonia was defined as an acute illness with radiographic pulmonary shadowing that was at least segmental or present in one lobe, or when there was clinical evidence of pneumonia that was not pre-existing and could not be explained otherwise. Cases where other respiratory pathogens were also cultured were excluded from this study in order to meaningfully assess the impact of empiric antibiotics on *K. pneumoniae* alone. For the purpose of this study, we did not seek to make any distinction between community- and hospital-acquired cases.

Data of eligible cases were collected using a standard form consisting of patient clinico-demographic details, initial empiric antibiotics, antibiotic in vitro susceptibility data and the clinical outcomes described earlier. The selection of eligible cases and data collection were conducted by 2 investigators only (RM and NIH), while co-morbidity scoring¹⁶ was carried out by a single investigator (LCL) with no knowledge of patients’ details. *K. pneumoniae* was identified by the standard microbiological culture technique to species level and their culture tested for in vitro susceptibility to a panel of 6 to 9 antibiotics pre-specified by the Ministry of Health Malaysia (Personal communication – Hj Abd Jalil Mohd, Microbiology Department). The study protocol was approved by the local university research and ethics committee (International Medical University Research and Ethics Committee, number 065/2004).

“Antibiotic-sensitive” vs “Antibiotic-resistant”

Patients were divided into 2 groups according to whether *K. pneumoniae* was fully sensitive to all the empiric antibiotics administered (antibiotic-sensitive) or resistant to at least one of the empiric antibiotics used (antibiotic-resistant).

“Standard” vs “Non-standard” Empiric Antibiotic Choices

An antibiotic regime consisting of a β -lactam stable antibiotic, used either alone or with a macrolide was categorised as a “standard” recommended initial empiric regime. Any regime other than the standard regime was categorised as “non-standard”.

Statistical Analysis

Patients were analysed according to the “antibiotic-sensitive” vs “antibiotic-resistant” and the “standard” vs “non-standard” groups. Differences between the groups were assessed using chi-square test for categorical, and *t*-test or Mann-Whitney test, depending on the normality of continuous data. Odd ratios (OR) with 95% confidence interval (95% CI) were calculated to determine their relative risks. All computations were made using statistical package SPSS version 11.5 for Windows (Chicago, Illinois, USA). In all the cases, statistical significance was defined at the 5% level and assessed with two-tailed tests.

Results

Of the 441 patients with documented *K. pneumoniae* respiratory isolates, 313 patients (70.9%) met the inclusion criteria. Majority were elderly Malays and males. Over half the patients had moderate to severe diseases of the heart, lungs and gastrointestinal tract. More than 80% of the respiratory specimens were sputum. Almost two-fifths of the patients had no prior antibiotics as clearly stated in their medical records, but there was no clear documentation in over half of them. These characteristics were comparable between the patients with and without antibiotic-sensitive *K. pneumoniae* and between those who received “standard” and “non-standard” empiric antibiotics (Table 1).

Proportionately more patients with antibiotic-resistant *K. pneumoniae* isolates died in hospital, compared to antibiotic-sensitive patients (10.8 vs 23.3%, $P = 0.004$). Compared with the other group, hospital mortality risk associated with antibiotic-resistant *K. pneumoniae* isolates was increased by two-fold [odds ratio (OR), 2.5; 95% confidence interval (CI), 1.3 to 4.8]. There were also proportionately more patients with antibiotic-resistant *K. pneumoniae* isolates requiring ventilation but this increase was not significant compared to the antibiotic-sensitive group (Fig. 1A).

Proportionately more patients who received a “non-standard” empiric antibiotic regime required ventilation, compared to those who had “standard” empiric antibiotics (16.7 vs 8.8%, $P = 0.047$). The risk of ventilation in patients with “non-standard” regimes was also increased by two-fold (OR, 2.0; 95% CI, 1.0 to 4.3). There was also a non-significant trend towards increased hospital deaths in patients treated with “non-standard” antibiotics (Fig. 1B).

Table 1. Clinico-demographic Characteristics of Patients Between Those with *Klebsiella pneumoniae* Respiratory Isolates Sensitive vs Resistant to Empiric Antibiotics and Between Those Treated with “Standard” vs “Non-standard” Antibiotic Regimes

| Variables | Entire group | <i>K. pneumoniae</i> isolates | | Empiric antibiotics* | |
|-------------------|--------------|--------------------------------------|-------------------------------------|----------------------|----------------|
| | | Sensitive to all empiric antibiotics | Resistant to at least 1 antibiotic† | “Standard” | “Non-standard” |
| N (%) | 313 (100) | 223 (71.2) | 90 (28.7) | 228 (72.8) | 84 (26.8) |
| Age, mean (SD) | 57 (18.0) | 58 (16.9) | 54 (20.2) | 58 (17.9) | 54 (17.8) |
| Ethnicity | | | | | |
| Malay | 52.7 | 49.8 | 60.0 | 53.1 | 52.4 |
| Chinese | 18.5 | 21.1 | 12.2 | 19.7 | 15.5 |
| Indian | 27.8 | 27.8 | 27.8 | 26.3 | 31.0 |
| Gender | | | | | |
| Male | 68.1 | 66.8 | 71.1 | 68.9 | 65.5 |
| Female | 31.9 | 33.2 | 28.9 | 31.1 | 34.5 |
| Comorbidity‡ | | | | | |
| 1 | 29.1 | 27.8 | 32.2 | 28.9 | 29.8 |
| 2 | 56.5 | 56.5 | 56.7 | 58.8 | 51.2 |
| 3 | 14.4 | 15.7 | 11.1 | 12.3 | 19.0 |
| Specimen type | | | | | |
| Sputum | 83.4 | 83.9 | 82.2 | 89.0 | 80.2 |
| Tracheal aspirate | 15.3 | 15.2 | 15.6 | 9.6 | 10.6 |
| Bronchial washing | 1.3 | 0.9 | 2.2 | 1.3 | 1.2 |
| Prior antibiotics | | | | | |
| Yes | 4.8 | 5.8 | 2.2 | 4.8 | 4.8 |
| No | 39.0 | 36.8 | 44.4 | 42.8 | 29.8 |
| Unknown | 56.2 | 57.4 | 53.3 | 52.6 | 65.5 |

Values are in percentage unless otherwise specified; SD: standard deviation

* “standard” regime consisting of a β -lactam stable antibiotic with or without a macrolide; “non-standard” constitutes regimes other than this.

† by in vitro susceptibility testing.

‡ co-morbidity score¹⁶

1: no important chronic illness; 2: moderate/severe disease of the heart, lungs, GI tract; 3: any cancer (except skin), end stage renal/liver disease.

Note: $P > 0.05$ between groups under both categories

There were no significant differences in the length of hospital stay between the antibiotic-sensitive and antibiotic-resistant groups [median (IQR²⁵⁻⁷⁵): 6 (4-15) vs 7 (4-11) days] and between the “standard” and “non-standard” groups [6 (4-11) vs 8 (5-16) days].

The most commonly prescribed β -lactam stable antibiotics were ampicillin-sulbactam and amoxicillin-clavunate acid, and the most commonly used macrolide was erythromycin. Other antibiotics used included cefuroxime, ceftazidime, cefotaxime, ceftriaxone and azithromycin, ciprofloxacin, cloxacillin, erythromycin, metronidazole, gentamicin, amikacin and doxycyclin, which were administered either alone or in various combinations.

Discussion

We have shown that in vitro resistance to any one of the empiric antibiotics and a “non-standard” empiric regime lacking β -lactam stable antibiotic are associated with adverse hospital clinical outcomes in hospitalised patients with *K. pneumoniae* pneumonia.

In our pragmatic approach of simply looking at isolates showing in vitro resistance to just one of the administered antibiotics, we could already demonstrate a difference in hospital clinical outcomes compared to the other group whose isolates showed full sensitivity to all administered antibiotics. The findings support the argument that the impact of in vitro resistance on outcomes can only be

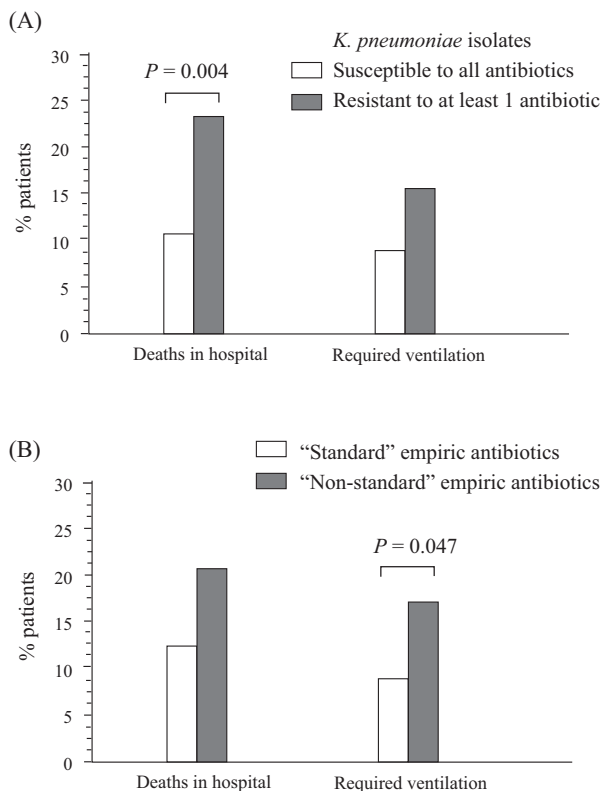


Fig. 1. Hospital mortality and the requirement of ventilation in patients (A) with *Klebsiella pneumoniae* respiratory isolates fully susceptible to all empiric antibiotics vs those resistant to at least 1 antibiotic, and (B) treated with a "standard" (consisted of β -lactam stable antibiotic +/- macrolide) vs "non-standard" empiric antibiotic regimens. $P < 0.05$ is considered significant.

presumed if the drug found to have reduced in vitro activity is the drug actually administered to the patients.¹⁷ The question on why in vitro resistance to a single empiric antibiotic is sufficient to affect clinical outcomes is unclear from our study. This probably relates to the fact that a large proportion of the patients studied (31%) had only a single antibiotic for initial empiric treatment.

In support of most clinical practice guidelines that recommend using a β -lactam stable antibiotic to treat pneumonia in hospitalised patients,¹³⁻¹⁵ our findings showed that such empiric regime is superior to one without a β -lactam stable antibiotic. This is perhaps not surprising given the general susceptibility of *K. pneumoniae* to most β -lactam stable antibiotics. The failure of the "non-standard" regime group to demonstrate equal or better outcomes is likely due to the marked heterogeneity of antibiotic classes used, some of which were clearly inappropriate (e.g. erythromycin alone), while others whose anti-microbial efficacy towards *K. pneumoniae* was known to be reduced in our local hospital data (e.g. gentamicin).

Our findings reiterate the importance of appropriate

empiric antibiotics in the treatment of *K. pneumoniae* pneumonia. Early institution of appropriate empiric antibiotic in pneumonia per se improves survival.^{18,19} Of particular importance in *K. pneumoniae* is the development of ESBL, a problematic resistance mechanism adversely associated with clinical outcomes. ESBL-producing *Escherichia coli* and *K. pneumoniae* has been shown to be significantly associated with longer hospital stay and higher hospital charges.²⁰ A recent international prospective study⁸ of ESBL bacteraemic patients showed that failure to use an antibiotic active against ESBL-producing *K. pneumoniae* can lead to high mortality and that appropriate antibiotics, even if delayed, can prevent deaths.⁹ A study²¹ of all 570 clinical isolates from 4 medical centres in Malaysia and 2 medical centres in Singapore showed a prevalence of ESBL-producing *K. pneumoniae* at a worryingly high of between 36.7% and 38%. In our study, about 10% of *K. pneumoniae* cases were ESBL-producing.

Apart from the inherent weakness of a retrospective study, our study protocol had not included clinical parameters such as oxygenation status, blood urea, the presence of confusion, and the radiological extent of pneumonia, which are known to influence pneumonia outcomes, in addition to the choice of empiric antibiotics. Nevertheless, our data have considered the 2 key parameters of age and co-morbidity in assessing the severity of any pneumonia. Studying all *K. pneumoniae* pneumonia regardless of their source of acquisition (community or hospital) is intentional because it does not conflict with our study objectives and also because of the difficulty of confidently separating one from the other in such a retrospective study as ours. Nevertheless, it is well recognised that hospital-acquired pneumonias are generally more severe than community-acquired pneumonias and have a higher prevalence of drug-resistant organisms.¹⁵ The absence of separation between these 2 in our study can potentially bias our findings and is a study weakness.

In the context of *K. pneumoniae*, which is an important cause of hospitalised pneumonia in Malaysia,²⁻⁴ our findings provide important evidence for the crucial need to initiate empiric antibiotics that are appropriate. Our findings also support the clinical relevance of in vitro antibiotic susceptibility for *K. pneumoniae* and support empiric regimes that contain β -lactam stable antibiotics. More research is necessary to explore the local epidemiology and its antibiotic resistance pattern, and to validate the appropriateness of existing recommendations on the various choices of empiric antibiotics in our local context of treating pneumonia.

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