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Is gentamicin safe and effective for severe community-acquired pneumonia? An 8-year retrospective cohort study

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ABSTRACT

Gram-negative bacilli are the causative organisms in a significant proportion of patients with severe community-acquired pneumonia (CAP) admitted to the intensive care unit (ICU). Clinical guidelines recommend broad-spectrum antimicrobials for empirical treatment despite alarming global trends in antimicrobial resistance. In this study, we aimed to assess the safety and efficacy of gentamicin, an aminoglycoside with potent bactericidal activity, for empirical Gram-negative coverage of severe CAP in patients admitted to the ICU. A retrospective cohort study was performed at a university teaching hospital where the severe CAP guideline recommends penicillin, azithromycin and gentamicin as empirical cover. Ceftriaxone plus azithromycin is used as an alternative. Adults with radiologically-confirmed severe CAP were included, comparing those who received gentamicin in the first 72 h of admission with those who did not. Participants were identified using ICD-10 codes for bacterial pneumonia and data manually extracted from electronic medical records. Of 148 patients admitted with severe pneumonia, 117 were given at least one dose of gentamicin whereas the remaining 31 were not. The two groups were well matched in terms of demographics, co-morbidities and disease severity. There were no significant differences between the gentamicin and no-gentamicin groups in the incidence of acute kidney injury [60/117 (51%) vs. 16/31 (52%), respectively], hospital mortality [20/117 (17%) vs. 7/31 (23%)] and secondary outcomes including relapse and length of hospital stay. In conclusion, gentamicin is safe and has similar outcomes to alternative Gram-negative antimicrobial regimens for empirical coverage in severe CAP patients admitted to the ICU.

1. Introduction

With over 3 million attributable deaths globally per year, community-acquired pneumonia (CAP) is the world's most fatal communicable disease [1]. Antimicrobial therapy for CAP is largely empirical because a causative organism is typically only identified in 30–65% of cases using conventional diagnostic methods [2–4] and is rarely known at presentation. Empirical regimens are designed to cover *Streptococcus pneumoniae* and so-called atypical pathogens such as *Legionella* and *Mycoplasma* spp. Aerobic Gram-negative bacilli are an important but less common group of causative organisms, accounting for ca. 10% of cases of CAP and up to 19% in severe CAP requiring admission to the intensive care unit (ICU) [5–9]. *Haemophilus influenzae*, *Escherichia coli* and *Klebsiella pneumoniae* are the most common Gram-negative causative organisms [6,7].

Current US and Australian guidelines recommend a third-generation cephalosporin plus azithromycin as first-line therapy for severe CAP [10,11]. However, Australian guidelines recommend benzylpenicillin, gentamicin and azithromycin as a suitable alternative regimen, providing excellent Gram-negative cover while avoiding the host and ecological effects of third-generation cephalosporins on antimicrobial resistance and *Clostridium difficile* infection [5,10,11]. Gentamicin penetrates well into alveolar lining fluid [12] and has useful activity against nearly all common community-onset Gram-negative CAP pathogens. Small observational studies [13–15] as well as a single phase 3 randomised controlled trial (RCT) [16], all published over 20 years ago, suggest that aminoglycosides are associated with good clinical outcomes in CAP, however larger and more recent studies are lacking.

The potential for nephrotoxicity is a key concern with the use of empirical gentamicin for CAP, but the risk is minimised if gentamicin is used for ≤48 h [10,17]. Ototoxicity is a significant but rare

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complication and is also usually associated with cumulative dose exposure [18].

In this study, we aimed to examine the safety and efficacy of gentamicin in adults with CAP admitted to the ICU. We hypothesised that the proportion of patients with acute kidney injury (AKI) would be no higher in the group receiving gentamicin compared with the group not receiving gentamicin, and that those receiving gentamicin would have a lower in-hospital mortality and lower chance of relapse than those not receiving gentamicin.

2. Methods

2.1. Study design and setting

A retrospective observational study of patients admitted to a single 650-bed teaching hospital in temperate Australia was performed. This hospital's local antibiotic guideline for severe CAP is benzylpenicillin, gentamicin (4–6 mg/kg in a single daily dose for up to three doses) and azithromycin. Ceftriaxone is an alternative option for those with minor β-lactam allergy or contraindications to aminoglycosides. The routine microbiological workup at the hospital for severe CAP includes: two sets of blood cultures; sputum microscopy and culture if there is purulent sputum; microscopy and culture of endotracheal aspirate if the patient is intubated; urinary antigen assays for *Legionella pneumophila* and *S. pneumoniae*; baseline and convalescent serology for *Mycoplasma*, *Chlamydophila*, *Legionella* and *Coxiella burnetii*; and multiplex PCR on a combined nose and throat swab for 10 respiratory viruses (including influenza, parainfluenza, respiratory syncytial virus and others; AusDiagnostics, Beaconsfield, NSW, Australia). Empirical gentamicin is continued for ca. 48 h (i.e. two or three doses). At this stage, clinical progress and microbiology results are reviewed. If a pathogen is identified, the patient is switched to directed therapy, but further aminoglycosides are avoided. If no organism is identified and the patient is still severely ill and requiring intravenous (i.v.) therapy, then they are switched to ceftriaxone. If no organism is identified and the patient is improving, then penicillin plus azithromycin is continued. Oral step-down is amoxicillin.

2.2. Participants

Following approval from the local Human Research Ethics Committee, hospital discharge coding was used to identify patients who had been admitted between January 2008 and December 2015 with a primary diagnosis of bacterial pneumonia [International Classification of Diseases (ICD)-10 codes J13–16 and J18].

Patients had to meet all three of the following criteria to be included: (i) at least two clinical features of pneumonia among fever (body temperature >38 °C), cough, purulent sputum, pleuritic chest pain, and bronchial breathing or crepitations on examination; (ii) radiological evidence of new alveolar opacity within 48 h of hospital admission on either chest radiography or pulmonary computed tomography (CT) scan; and (iii) admitted to the ICU within 72 h of hospital admission. ICU admission was used as a surrogate for severe pneumonia.

Exclusion criteria were: (i) an alternative diagnosis was deemed more likely than CAP (e.g. pulmonary embolism, acute pulmonary oedema); (ii) death or hospital discharge within 24 h of presentation; (iii) a clinically recorded diagnosis of aspiration pneumonia; and (iv) medical records unavailable or incomplete.

2.3. Definitions

Patients were included in the 'gentamicin' cohort if they received one or more doses of i.v. gentamicin within the first 72 h of hospital admission.

For each patient, we selected what we judged to be the single most important causative organism. To be considered a causative organism in this study, the following criteria had to be met: (i) the same organism grown both from blood and sputum, excluding organisms likely to be skin contaminants; or (ii) an organism grown from sputum or endotracheal aspirate only if the growth was pure and moderate or heavy and the sputum was purulent; or (iii) a positive urinary antigen, serological test or viral PCR was considered significant if it fitted the clinical presentation and there was no other likely pathogen identified.

Antibiotics with Gram-negative activity, apart from gentamicin, were defined as any antibiotic with clinically relevant activity against common community-acquired Gram-negative pathogens. This included ceftriaxone, cefepime, ceftazidime, piperacillin/tazobactam, ticarcillin/clavulanic acid, ciprofloxacin, meropenem and moxifloxacin.

Renal function was analysed using serum creatinine and included baseline creatinine (lowest of the three most recent creatinine levels within the 3 months prior to hospital admission), creatinine on presentation (±24 h), peak creatinine between Days 3 and 14 of admission, and creatinine on discharge (±24 h). AKI was defined as a 1.5-fold increase in the serum creatinine from baseline (stage 1 or greater of the modified RIFLE criteria) [19]. Creatinine on presentation to hospital was used if no baseline creatinine was available.

The primary efficacy outcome was in-hospital mortality. The key secondary outcome was relapse, defined as at least one of: readmission to hospital within the subsequent 6 weeks attributable to CAP; or a new diagnosis of lung abscess or parapneumonic effusion after Day 7 of admission but before hospital discharge.

2.4. Data management and statistical methods

Data were collected by hand review of medical records as well as hospital pathology and radiology databases using purpose-built paper case report forms.

Data were compiled using EpiData v.4.2 (EpiData foreningen, Odense, Denmark) and were analysed using Stata v.12 (StataCorp, College Station, TX). Continuous variables were summarised as mean ± standard deviation (S.D.) and were compared by Student's *t*-test if normally distributed, or were summarised by median [interquartile range (IQR)] and were compared by Mann–Whitney *U*-test if non-normally distributed. Categorical variables were compared using Fisher's exact test. To adjust for disease severity, a logistic regression model was built with in-hospital mortality as the dependant variable and gentamicin use and Acute Physiology and Chronic Health Evaluation (APACHE) II score as the independent variables. To adjust for receipt of other antibiotics active against Gram-negative bacteria, APACHE II score in the above model was replaced with a categorical variable coding for receipt of other antibiotics active against Gram-negative organisms. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Participants

A total of 225 patients were identified by discharge coding as being admitted to the hospital's ICU between January 2008 and December 2015 with a primary diagnosis of community-onset bacterial pneumonia. After application of the eligibility criteria, 148 participants were included in the study (Fig. 1). The mean ± S.D patient age was 64.1 ± 17.6 years and 63% of patients were male. It was a severely ill cohort, with a median APACHE II score of 21 (IQR 16–27) and with 43% of patients having septic shock (Table 1).

The majority of the cohort ($n = 117$) received at least one dose of gentamicin in the first 72 h of hospital admission, with 31 patients

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