Journal of Hospital Infection (2010) **74**, 337–343

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Short course antibiotic therapy for Gram-negative hospital-acquired pneumonia in the critically ill

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Received 14 July 2009; accepted 2 October 2009
Available online 4 March 2010

KEYWORDS
Antimicrobial agent;
Hospital-acquired pneumonia;
Ventilator-associated pneumonia

Summary Hospital-acquired pneumonia (HAP) is a common cause of morbidity and mortality in the critically ill, yet the optimal duration of antibiotic therapy is unknown. Too short a course may lead to treatment failure, whereas too long a course may lead to increased antibiotic resistance, antibiotic-related morbidity and increased costs. Standard duration of antibiotic therapy for Gram-negative (GN-)HAP at our institution is 5 days, significantly shorter than advocated in many current guidelines. We performed a retrospective review of all cases of GN-HAP on our critical care unit fulfilling clinical and microbiological criteria to investigate recurrence rate and mortality following short course antibiotic therapy. Seventy-nine eligible patients with GN-HAP were identified. Of these, 79% were receiving mechanical respiratory support at diagnosis; 42% had GN-HAP due to non-fermenting Gram-negative bacilli (NF-GNB) and 72% were treated with the recommended 5 day course of antibiotics. Two patients had clear evidence of non-resolution of pneumonia after 5 days of therapy. Overall recurrence rate was 14%, with relapse rates significantly higher among patients with NF-GNB when compared to patients with other Gram-negative organisms (17% vs 2%; $P = 0.03$). The overall recurrence rate was no higher than rates reported in earlier studies (17–41%). Critical care mortality (34.2%) was also not in excess of previously reported values (18–57%). In this limited study, use of a 5 day course of appropriate antibiotics for GN-HAP does not appear to increase risk of recurrence or mortality when pneumonia resolution has been achieved prior to the cessation of therapy.

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0195-6701/$ - see front matter
doi:10.1016/j.jhin.2009.10.009

Introduction

Hospital-acquired pneumonia (HAP) is the most common nosocomial infection in the critically ill and has an associated mortality of up to 50%.[1–3] An episode of pneumonia acquired while mechanically ventilated significantly prolongs critical care and hospital stay, and poses a potential additional cost of US $10,000 to $40,000 per patient.[4,5] However, the optimal duration of antibiotic therapy for HAP in the critically ill is not clear. Too short a course risks treatment failure (e.g. in terms of non-resolution, recurrence or death), whereas too long a course may be associated with emergence of potentially resistant organisms, such as *Pseudomonas aeruginosa*, may increase risk of *Clostridium difficile*-associated disease and antibiotic-related toxicity, and will increase pharmacy costs.[6–8]

Use of a 'shorter duration of antibiotic therapy', i.e. 7—8 days, is recommended in current American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for treatment of uncomplicated HAP, when initial antibiotics have been appropriate and there is good clinical response; a longer course, of 2 weeks or more, is recommended when HAP is due to resistant organisms such as *P. aeruginosa*.[3] However, there have to date been very few studies investigating outcomes following short course antibiotic therapy for HAP or ventilator-associated pneumonia (VAP).[6,9]

Standard initial empiric therapy at University Hospital Aintree (UHA) for HAP in critically ill non-MRSA carriers is a short five-day course of piperacillin-tazobactam 4.5 g 8-hourly plus gentamicin 5 mg/kg once daily; this is modified on the basis of respiratory culture results. Short course therapy applies to treatment of all cases of non-staphylococcal HAP, including those due to non-fermenting Gram-negative bacteria (NF-GNB), *P. aeruginosa*, *Stenotrophomonas maltophilia* and *Acinetobacter baumannii*.

The aim of our study was to investigate outcomes following an episode of Gram-negative HAP treated at our institution, primarily in terms of non-resolution and recurrence, and secondarily in terms of mortality.

Methods

Patients were identified from a prospective audit of all critically ill patients with suspected nosocomial pneumonia in the critical care unit (CCU) at UHA from 2004 to 2008. For the purposes of this study, an episode of HAP was defined as the presence of all the following:

- New respiratory illness, occurring at least 48 h after hospital admission and not incubating at time of admission.[3]
- Clinical Pulmonary Infection Score (CPIS) $\geq$6.[10]
- $\geq$2+ pure growth of organism on semiquantitative culture of endotracheal aspirate (ETA), or broncho-alveolar lavage (BAL).
- Administration of antibiotic therapy.

The following patient data were collected: age, sex, admission diagnosis, admission Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score, duration of CCU admission prior to diagnosis, requirement for assisted mechanical ventilation, CPIS and illness severity scores at time of diagnosis [APACHE II score and Multiple Organ Dysfunction Score (MODS)]. We also investigated sensitivity of respiratory pathogen to empiric therapy, delay in administering appropriate antibiotics and duration of antibiotic therapy.

Our primary outcome measure was recurrence of pneumonia. This was defined as an episode of pneumonia (as described above) which recurred more than 48 h after completion of the initial course of antibiotics. Recurrence of pneumonia was further subdivided into relapse (episode due to pathogen of same species with same antibiotic resistance pattern) and re-infection (due to another pathogen). We also sought evidence of non-resolution of pneumonia when CPIS remained $\geq$6 on day 6, there was continued growth of bacterial pathogens ($\geq$2+ growth of organism on semiquantitative culture of respiratory specimen) and antibiotics were continued beyond 5 days.

Our secondary outcome measures were CCU and hospital mortality. Patients were followed up until hospital discharge or death.

Statistical analysis

Data were analysed using SPSS statistics software version 17.0 (SPSS Inc., Chicago, IL, USA). χ^2-Tests were used to assess categorical data. *t*-Tests and Wilcoxon—Mann—Whitney tests were used to assess parametric and non-parametric continuous data respectively.

Results

Clinical characteristics

Eighty patients were identified as having Gram-negative HAP using the above criteria. One was