A sub-group of patients with hospital-acquired pneumonia do not require broad-spectrum gram-negative antimicrobial coverage

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ABSTRACT

Amongst 200 patients developing HAP outwith the ICU, 61% were treated empirically without broad-spectrum gram-negative coverage, with clinical cure in 69.7%. Lower disease severity markers(SIRS, hypoxia, tachypnoea, neutrophilia) and absence of diabetes mellitus and prior doxycycline treatment (but not time to HAP onset) identified patients not requiring broad-spectrum gram-negative coverage.

Key words:

Hospital-acquired pneumonia

Gram-negative bacteria

Doxycycline

Gentamicin

Antimicrobial stewardship

INTRODUCTION

Hospital-acquired pneumonia (HAP) occurring outwith the intensive care unit (ICU) is a relatively under-studied nosocomial infection (non-ICU HAP). Gram-negative bacilli (GNB) such as Enterobacteriaceae and *Pseudomonas aeruginosa* are considered canonical HAP pathogens and international guidelines recommend empiric broad-spectrum gram-negative antimicrobial coverage[1, 2]. However, much of the literature actually describes ventilator-associated pneumonia (VAP) or ICU-HAP. Case ascertainment bias exists in other studies, reporting only on patients able to expectorate sputum or with positive sputum cultures, whereas real-life data demonstrate sputum samples are infrequently available and often culture-negative[3-6]. Therefore, our understanding of the microbial aetiology of non-ICU HAP is incomplete and empiric broad-spectrum gram-negative coverage may not be mandated in all cases. In the U.K., doxycycline is widely recommended for empiric treatment of low-severity HAP, but we are aware of no clinical data supporting this practice[7]. Doxycycline lacks activity against Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter baumanii,* thus its usage provides an opportunity to address the unanswered question of the requirement for broad-spectrum gram-negative coverage in non-ICU HAP. The aims of this study were to ***(i)*** identify and characterise a representative cohort of patients with non-ICU HAP, and ***(ii)*** report treatment outcomes without broad-spectrum gram-negative coverage.

METHODS

Case ascertainment

An electronic search identified all inpatient ward chest x-rays (CXR) performed in two tertiary care hospitals in Edinburgh, U.K. over thirteen months (June 2018–July 2019) where the

request or report included the terms "*consolidation*" or "*pneumonia*" (n=4250). These reports were reviewed to identify cases with radiological evidence of infective consolidation (n=728). The electronic patient records (EPR) for these patients were reviewed to determine if the case definition was met. Non-ICU HAP was defined as ***(i)*** new/progressive CXR consolidation occurring ≥48 hours after hospital admission, ***(ii)*** in a non-intubated adult ***(iii)*** in a non-ICU ward and ≥48h since ICU discharge (ICU defined as capable of providing mechanical ventilation), ***(iv)*** with documentation of consistent symptoms (cough, sputum, pleuritic chest pain, dyspnoea) or chest auscultation findings (crackles, reduced air entry, bronchial breathing), and ***(v)*** a clinical diagnosis of pneumonia. Patients were excluded if pneumonia occurred following a frank aspiration event or a clinical diagnosis of aspiration pneumonia was made.

Data collection

Relevant clinical, laboratory and microbiological details for the first HAP episode were recorded from the EPR. *Clinical cure* was defined as treatment of HAP without requirement for antimicrobial escalation *and* without mortality attributable to HAP (*treatment failure* refers to occurrence of one or both outcomes). Mortality was considered attributable to HAP if pneumonia was recorded on the death certificate.

Statistical analysis

Continuous variables were compared using an unpaired t-test if normally distributed or Mann Whitney test if not. Categorical variables were compared using Fisher's exact test. Following receiver operator characteristic analysis, Youden's J statistic was calculated to determine cut-offs for the association between continuous variables and outcome. Variables identified by univariate analysis were included in multiple logistic regression after assessing

multicollinearity. Two-tailed p-values are reported and $p<0.05$ was considered statistically significant. Statistical analysis was performed using Prism, version 8.0 (GraphPad Software Inc. San Diego, CA).

Ethical approval

A favourable ethical opinion was provided by the West of Scotland Research Ethics Service (19/WS/0152) and Caldicott approval was provided by NHS Lothian R&D (2019/0242).

RESULTS

Characteristics of patients developing non-ICU HAP

Two hundred patients with non-ICU HAP were identified (Table). Patients had a median age of 77 years and 43% were aged ≥80. A median of two (IQR 1–3) medical co-morbidities were present per patient, most commonly chronic lung disease (78%). 57.5% of patients had been hospitalised during the preceding year (median 1 prior admission, IQR 0–2). Common admission events preceding HAP included receipt of antimicrobials (53.5%) and surgery (34%). MRSA carriage was identified in 4/132 screens performed. 11.5% of patients were colonised with other antimicrobial-resistant organisms (vancomycin-resistant enterococci, n=7; multidrug resistant GNB in urine, n=15; carbapenemase-producing organism, n=1).

Clinical and microbiological features of non-ICU HAP

HAP was diagnosed a median of 9 days after admission. Sepsis (qSOFA ≥2 [8]), was present in 9.5% of patients and systemic inflammatory response syndrome (SIRS, ≥2

criteria) in 51%. Hypoxia necessitating new or increased supplemental oxygen was common (64.5%) but extra-pulmonary organ dysfunction was less common, indicated by low requirement for intravenous fluid resuscitation (19%) and low incidence of altered mentation (20.5%) and acute kidney injury (12%). The median white cell count was in the normal range (10.6 $x10^9$/L) but the median CRP was elevated (94 mg/L) and lymphopenia was common (70%). Microbiological evaluation consisted of a sputum sample in 18.5% of patients, respiratory pathogen PCR throat swab in 27% and blood cultures in 47.5%. It was not known if samples were obtained prior to antimicrobials. Pathogenic bacteria were identified in 19/37 sputum samples and respiratory viruses in 18/54 swabs (Supplementary Table 1). One patient had *E. coli* bacteraemia (1/95 blood cultures). Twelve patients had microbiological evidence of HAP caused by Enterobacteriaceae or *P. aeruginosa*. This was associated with number of co-morbidities (median 3 vs. 2, p=0.035) and specifically COPD (58.3% vs. 23.4%, p=0.013) but not with time to HAP onset, prior hospitalisation or prior antimicrobials.

Management and outcomes

The most common first-line empiric antimicrobial used was doxycycline (59.5%), followed by amoxicillin and gentamicin (14%), vancomycin and gentamicin (6.5%) then piperacillin-tazobactam (5.5%; Supplementary Table 2). Antimicrobial escalation was required in 18% of cases, most commonly from doxycycline to a regimen including broader gram-negative coverage (29/36 instances). The median total duration of antimicrobials was 7 days (IQR 5–7).

Clinical cure was achieved in 70%. Mortality attributable to HAP occurred in 16% of patients. Logistic regression identified new/increased supplemental oxygen requirement (OR 5.5, 95% CI 2.4–13.9, p=0.0002) and urea >5.5mmol/L (OR 4.6, 95% CI 1.9–12.9, p=0.002) as being associated with treatment failure. Undergoing surgery prior to developing HAP was

associated with reduced likelihood of treatment failure (OR 0.4, 95% CI 0.2–1.0, p=0.04). A further episode of HAP during the same admission occurred in 16.5% and there were two cases of *Clostridioides difficile* infection following HAP treatment. HAP diagnosis was recorded on discharge documentation for coding in 42.5% of cases.

Patients treated without empiric broad-spectrum gram-negative coverage

61% of patients were treated without empiric broad-spectrum gram-negative coverage, with clinical cure in 69.7%. These patients had a lower SIRS score compared to patients treated empirically with such coverage (median 1 vs. 2, p<0.0001) consistent with institutional antimicrobial guidelines recommending amoxicillin and gentamicin for HAP with ≥2 SIRS criteria or doxycycline for patients with <2. There was no difference in time to HAP onset or qSOFA score between the groups. Empiric therapy constituted doxycycline (95.9%), amoxicillin (2.5%) or amoxicillin plus clarithromycin (1.6%). In all 29 instances of antimicrobial escalation this represented changing to a regimen with broader gram-negative coverage.

Logistic regression identified new/increased supplemental oxygen requirement (OR 10.9, 95% CI 3.1–51.1, p=0.0007), prior doxycycline treatment (OR 8.2, 95% CI 1.3–73.6, p=0.03), diabetes mellitus (OR 7.5, 95% CI 2.1–33.1, p=0.004), neutrophil count >6.2x10^9/L (OR 3.9, 95% CI 1.1–16.3, p=0.04) and respiratory rate >18/minute (OR 3.5, 95% CI 1.2–11.6, p=0.03) as being associated with treatment failure in patients treated without empiric broad-spectrum gram-negative coverage.

DISCUSSION

In this cohort, patients with non-ICU HAP were elderly, had significant co-morbidities and the overall severity of illness was low. Importantly, a large sub-group were treated successfully without broad-spectrum gram-negative coverage.

Representative case ascertainment is challenging for non-ICU HAP[9]. A strength of this study was patient identification through systematic screening of inpatient CXRs and correlation with clinical data. Relying on submission of sputum cultures, positive sputum cultures or discharge coding would have failed to identify most patients. The lack of a control group with low-severity HAP treated without antimicrobials is a limitation.

42.5% of all patients had clinical cure without broad-spectrum gram-negative coverage, representing 69.7% of patients treated empirically without such coverage. Amongst patients treated without such coverage, treatment failure was associated with diabetes, prior doxycycline treatment during the same admission, new/increased oxygen requirement, neutrophil count and respiratory rate. Hypoxia, tachypnoea and neutrophilia likely relate to disease severity. Diabetes has been associated with increased pharyngeal colonisation by GNB and therefore could be a risk factor for GNB HAP[10]. Similarly, prior doxycycline treatment could deplete the respiratory tract of doxycycline-susceptible organisms, influencing the aetiology of subsequent HAP. Importantly, time from admission to HAP onset was not associated with treatment failure without broad-spectrum gram-negative coverage. Five days of hospital admission is often used as a cut-off to define ‘late-onset’ HAP and risk of hospital-acquired GNB infection, based on ICU studies and expert opinion[1, 2]. Amongst patients in this cohort with clinical cure without broad-spectrum gram-negative coverage, the

median onset of HAP was 10 days after admission (IQR 5–21), suggesting the currently recommended 5-day cut-off is not applicable to non-ICU HAP.

In conclusion, using a representative cohort of patients with non-ICU HAP, we report that a large sub-group of patients do not require broad-spectrum gram-negative coverage. Lower disease severity markers (SIRS, hypoxia, tachypnoea, neutrophilia) and absence of diabetes mellitus and prior doxycycline treatment (but not time to HAP onset) identify this sub-group.

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POTENTIAL CONFLICTS OF INTEREST

None

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TABLE

Table: Clinical, laboratory and outcome data for included patients with non-ICU hospital-acquired pneumonia (n=200)

Variable	**N (%)**
Patient characteristics	
Age, median (IQR) years	77 (62–87)
Male	110 (55)
Co-morbidities	
Chronic lung disease	78 (39)
Ischaemic heart disease or heart failure	74 (37)
Cerebrovascular disease	57 (28.5)
Diabetes mellitus	49 (24.5)
Chronic kidney disease	46 (23)[a]
Solid cancer	45 (22.5)
Immunosuppression[b]	19 (9.5)
Liver cirrhosis	15 (7.5)
Haematological malignancy	10 (5)
Current smoker	35 (17.5)
Time to onset of HAP, median (IQR) days	9 (5–21)
Admitting speciality	
Medicine	(59.5)
Surgery	(40.5)
Admission events preceding HAP	
Prior antimicrobials	107 (53.5)
Surgery	68 (34)
Other infection	66 (33)
Endotracheal intubation[c]	50 (25)
Bone fracture	38 (19)

Intensive care unit admission	30 (15)
Community-acquired LRTI or pneumonia	42 (21)
HAP episode[d]	
Physiological parameters	
Sepsis (qSOFA ≥2)	19 (9.5)
SIRS (SIRS ≥2)	102 (51)
New/increased supplemental O_2 requirement	129 (64.5)
Altered mentation	41 (20.5)
Temperature ≥38.0°C or <36°C	80 (40)
Heart rate, mean (SD) beats/minute	95 (±22)
Systolic blood pressure, median (IQR) mmHg	119 (107–132)
Respiratory rate, median (IQR) breaths/minute	20 (17–24)
Intravenous fluid resuscitation	38 (19)
ICU admission	9 (4.5)
Laboratory parameters	
New acute kidney injury[e]	24 (12)
Total white cell count, $x10^9$ L^{-1}, median (IQR)	10.6 (7.7–14.7)
Neutrophil count, $x10^9$ L^{-1}, median (IQR)	8.4 (5.7–11.8)
Lymphocyte count, $x10^9$ L^{-1}, median (IQR)	1.0 (0.7–1.6)
C-reactive protein, mg L^{-1}, median (IQR)	94 (38–190)
Outcomes	
Clinical cure	140 (70)
HAP antimicrobial escalation	36 (18)
Mortality attributable to HAP	32 (16)
Further episode of HAP	33 (16.5)

[a] requiring haemodialysis in 5 cases

[b] therapeutic immunosuppression (n=13), anti-neoplastic chemotherapy (n=3), HIV infection (n=2), IgG2 & 3 deficiency (n=1).

[c] for general anaesthesia or mechanical ventilation.

[d] physiological and laboratory parameters obtained within 24 hours of HAP diagnosis were recorded

[e] increase in creatinine of ≥26.5 μmol/L from last measurement.

IQR: interquartile range; LRTI: lower respiratory tract infection; SIRS: systemic inflammatory response syndrome; SD: standard deviation; ICU: intensive care unit