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Diagnosis and features of hospital-acquired pneumonia: a retrospective cohort study

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SUMMARY

Background: Hospital-acquired pneumonia (HAP) is defined as radiologically confirmed pneumonia occurring ≥48 h after hospitalization, in non-intubated patients. Empirical treatment regimens use broad-spectrum antimicrobials.

Aim: To evaluate the accuracy of the diagnosis of HAP and to describe the demographic and microbiological features of patients with HAP.

Methods: Medical and surgical inpatients receiving intravenous antimicrobials for a clinical diagnosis of HAP at a UK tertiary care hospital between April 2013 and 2014 were identified. Demographic and clinical details were recorded.

Findings: A total of 166 adult patients with a clinical diagnosis of HAP were identified. Broad-spectrum antimicrobials were prescribed, primarily piperacillin–tazobactam (57.2%) and co-amoxiclav (12.5%). Sputum from 24.7% of patients was obtained for culture. Sixty-five percent of patients had radiological evidence of new/progressive infiltrate at the time of HAP treatment, therefore meeting HAP diagnostic criteria (2005 American Thoracic Society/Infectious Diseases Society of America guidelines). Radiologically confirmed HAP was associated with higher levels of inflammatory markers and sputum culture positivity. Previous surgery and/or endotracheal intubation were associated with radiologically confirmed HAP. A bacterial pathogen was identified from 17/35 sputum samples from radiologically confirmed HAP patients. These were Gram-negative bacilli (N = 11) or Staphylococcus aureus (N = 6). Gram-negative bacteria tended to be resistant to co-amoxiclav, but susceptible to ciprofloxacin, piperacillin–tazobactam and meropenem. Five of the six S. aureus isolates were meticillin susceptible and all were susceptible to doxycycline.

Conclusion: In ward-level hospital practice ‘HAP’ is an over-used diagnosis that may be inaccurate in 35% of cases when objective radiological criteria are applied. Radiologically confirmed HAP represents a distinct clinical and microbiological phenotype. Potential risk factors were identified that could represent targets for preventive interventions.

Introduction

The syndrome of hospital-acquired pneumonia (HAP) is defined as pneumonia occurring in non-intubated patients...
48 h after hospitalization, and therefore not incubating at the time of admission. This is distinct from ventilator-associated pneumonia (VAP), which is defined as pneumonia occurring after 48–72 h of mechanical ventilation in an intubated patient. HAP may be suspected if a patient develops new symptoms and signs consistent with respiratory tract infection (fever, abnormal chest examination, purulent sputum, tachypnoea, impaired oxygenation) and laboratory results consistent with inflammation (raised white cell count and C-reactive protein). However, the diagnosis of HAP also requires radiological demonstration of a new or progressive lung infiltrate. American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines for the management of HAP highlight Gram-negative bacilli as frequently occurring pathogens in HAP and Staphylococcus aureus as an emerging cause.

Empirical treatment of HAP aims to include cover for nosocomial pathogens, especially Gram negative bacteria, therefore it necessitates using broad-spectrum agents such as co-amoxiclav and piperacillin–tazobactam, with the attendant risks of antibiotic-associated diarrhoea, *Clostridium difficile* infection, selection for antimicrobial resistance in patient and environmental flora and also high costs. An accurate diagnosis of HAP is therefore essential to ensure appropriate use of these antimicrobials.

The aim of this study was to retrospectively evaluate the accuracy of the diagnosis of HAP in inpatients on acute internal medicine and general surgical wards receiving intravenous antimicrobials for a clinical diagnosis of HAP made by the patient’s team. The demographic and microbiological features of patients with radiologically confirmed HAP will be described.

### Table I

| Characteristics                        | All patients (N = 166) | Radiologically confirmed HAP (N = 108) | Radiology inconsistent with HAP (N = 54) | P-value* |
|----------------------------------------|------------------------|----------------------------------------|-----------------------------------------|----------|
| **Male**                               | 99 (59.6%)             | 67 (62.0%)                             | 31 (57.4%)                             | 0.6      |
| **Age**                                |                        |                                        |                                         |          |
| Median years (IQR)                     | 79.5 (69–87)           | 77 (68–86)                             | 81 (71–88)                             |          |
| ≥65 years                              | 138 (83.1%)            | 88 (81.5%)                             | 46 (85.2%)                             | 0.7      |
| ≥75 years                              | 104 (62.7%)            | 63 (58.3%)                             | 38 (70.4%)                             | 0.2      |
| Admitted by medicine                   | 125 (75.3%)            | 75 (69.4%)                             | 46 (85.2%)                             | 0.04     |
| Admitted by surgery                    | 41 (24.7%)             | 33 (30.6%)                             | 8 (14.8%)                              |          |
| Emergency surgery                      | 24                     | 19                                     | 5                                       | 1.0      |
| Elective surgery                       | 17                     | 14                                     | 3                                       |          |
| Nursing home resident                  | 5 (3.0%)               | 2 (1.9%)                               | 3 (5.6%)                               | 0.3      |
| **Medical history**                    |                        |                                        |                                         |          |
| COPD                                   | 45 (27.1%)             | 32 (29.6%)                             | 12 (22.2%)                             | 0.4      |
| Asthma                                 | 11 (6.6%)              | 10 (9.3%)                              | 1 (1.9%)                               | 0.1      |
| Bronchiectasis                         | 4 (2.4%)               | 3 (2.8%)                               | 1 (1.9%)                               | 1.0      |
| Pulmonary fibrosis                     | 2 (1.2%)               | 2 (1.9%)                               | 0                                       | 0.6      |
| Other lung disease                     | 4 (2.4%)               | 3 (2.8%)                               | 1 (1.9%)                               | 1.0      |
| IHD                                    | 36 (21.7%)             | 22 (20.4%)                             | 13 (24.1%)                             | 0.7      |
| Heart failure                          | 34 (20.5%)             | 22 (20.4%)                             | 11 (20.4%)                             | 1.0      |
| Stroke/TIA                            | 43 (25.9%)             | 26 (24.1%)                             | 17 (31.5%)                             | 0.3      |
| Other neurological disease             | 10 (6.0%)              | 7 (6.5%)                               | 3 (2.7%)                               | 0.7      |
| Cognitive impairment                   | 32 (19.3%)             | 17 (15.7%)                             | 13 (24.1%)                             | 0.2      |
| Chronic liver disease                  | 3 (1.8%)               | 3 (2.8%)                               | 0                                       | 0.6      |
| Chronic kidney disease                 | 15 (9.0%)              | 6 (5.6%)                               | 9 (16.7%)                              | 0.04     |
| Solid malignancy                       | 23 (13.9%)             | 11 (10.2%)                             | 11 (20.4%)                             | 0.09     |
| Haematological malignancy             | 5 (3.0%)               | 3 (2.8%)                               | 2 (3.7%)                               | 1.0      |
| Type 1 DM                              | 3 (1.8%)               | 1 (0.9%)                               | 3 (5.6%)                               | 0.1      |
| Type 2 DM                              | 29 (17.5%)             | 19 (17.6%)                             | 9 (16.7%)                              | 1.0      |
| Imunosuppressive drugs                 | 1 (0.6%)               | 1 (0.9%)                               | 0                                       | 1.0      |
| Dysphagia/GI dysmotility/NG tube fed (new or old) | 33 (19.9%) | 25 (23.1%)                             | 8 (14.8%)                              | 0.3      |

HAP, hospital-acquired pneumonia; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; TIA, transient ischaemic attack; DM, diabetes mellitus; GI, gastrointestinal; NG, nasogastric.

* Comparing patients with radiologically confirmed HAP and patients with radiology inconsistent with HAP; chi-square test or Fisher’s exact test depending on number of subjects.
Methods

Patients

This was a retrospective observational cohort study of medical and surgical inpatients receiving intravenous antimicrobials for a clinical diagnosis of HAP at a tertiary care hospital in Edinburgh, UK. Data were collected as part of a large prospective audit of antimicrobial prescribing in all inpatients within acute internal medicine and general surgery wards of the Royal Infirmary of Edinburgh (RIE) over 13 months, between April 2013 and April 2014. All patients treated with intravenous antimicrobials for ≥48 h for any indication were identified and reviewed by a consultant infectious disease physician and an antimicrobial pharmacist. To be included in the current study, a patient from this cohort had to be receiving intravenous antimicrobials for a documented clinical diagnosis of HAP, excluding VAP and CAP. Demographic data, medical history, admission details (including death during admission), clinical diagnosis (as deduced by the primary clinical team), microbiological sampling, and radiological investigations were collected. Antimicrobial susceptibility testing was carried out using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology.

Definitions

The presence of signs and/or symptoms consistent with respiratory tract infection was assumed based on the clinical diagnosis of HAP made by the patient’s clinicians ≥48 h after admission to hospital. To be classified as radiologically confirmed HAP in this study, chest X-ray evidence of a new or progressive lung infiltrate was required (reported by a radiologist), consistent with the 2005 ATS/IDSA guidelines.1

Analysis

Fisher’s exact test was used to compare categorical variables if one cell contained five or fewer subjects; chi-square test was used if all cells contained more than five subjects. The Shapiro–Wilk W-test for non-normality was used to assess the distribution of continuous data and the Mann–Whitney U-test was used for data not in a normal distribution. Data were analysed using StatsDirect software version 2.8.0 (StatsDirect, Altrincham, UK). P < 0.05 was considered statistically significant.

Table II

| Admission events                                                                 | All patients (N = 166) | Radiologically confirmed HAP (N = 108) | Radiology inconsistent with HAP (N = 54) | P-valueb |
|---------------------------------------------------------------------------------|------------------------|---------------------------------------|----------------------------------------|----------|
| Surgery pre HAP                                                                 | 39 (23.5%)             | 33 (30.6%)                            | 6 (11.1%)                              | 0.006    |
| ICU admission pre HAP                                                           | 29 (17.5%)             | 23 (21.3%)                            | 6 (11.1%)                              | 0.13     |
| Intubation pre HAPb                                                             | 45 (27.1%)             | 36 (33.3%)                            | 8 (14.8%)                              | 0.01     |
| Clear lung fields                                                               | 103 (62.0%)            | 65 (60.2%)                            | 37 (68.5%)                             | 0.4      |
| Consolidation                                                                   | 15 (9.0%)              | 8 (7.4%)                              | 7 (13.0%)                              | 0.3      |
| Features of heart failure                                                       | 10 (6.0%)              | 6 (5.6%)                              | 4 (7.4%)                               | 0.7      |
| No admission CXR                                                                | 10 (6.0%)              | 7 (6.5%)                              | 2 (3.7%)                               | 0.7      |
| Piperacillin–tazobactam                                                        | 151 (57.2%)            | 107 (60.8%)                           | 44 (50%)                               | 0.1      |
| Co-amoxiclav                                                                    | 33 (12.5%)             | 18 (10.2%)                            | 15 (17.0%)                             | 0.1      |
| Metronidazole                                                                   | 22 (8.3%)              | 10 (5.7%)                             | 12 (13.6%)                             | 0.03     |
| Vancomycin                                                                      | 19 (7.2%)              | 11 (6.3%)                             | 8 (9.1%)                               | 0.5      |
| Ciprofloxacin                                                                   | 13 (4.9%)              | 7 (4.0%)                              | 6 (6.8%)                               | 0.4      |
| Meropenem                                                                       | 13 (4.9%)              | 12 (6.8%)                             | 1 (1.1%)                               | 0.07     |
| Ceftriaxone                                                                     | 4 (1.5%)               | 3 (1.7%)                              | 1 (1.1%)                               | 1.0      |
| Amoxicillin                                                                     | 3 (1.1%)               | 3 (1.7%)                              | 0                                      | 0.6      |
| Gentamicin                                                                      | 2 (0.8%)               | 1 (0.6%)                              | 1 (1.1%)                               | 1.0      |
| Clarithromycin                                                                  | 1 (0.4%)               | 1 (0.6%)                              | 0                                      | 1.0      |
| Linezolid                                                                       | 1 (0.4%)               | 1 (0.6%)                              | 0                                      | 1.0      |
| Minimum antimicrobial duration, median days (IQR)                                | 4 (3–5)                | 4 (3–6)                               | 3.5 (2–5)                              | 0.04     |
| ICU admission                                                                    | 6 (3.6%)               | 6 (5.6%)                              | 0                                      | 0.2      |
| Intubation and ventilation                                                      | 6 (3.6%)               | 6 (5.6%)                              | 0                                      | 0.2      |
| Death during admission                                                          | 32 (19.3%)             | 22 (20.4%)                            | 10 (18.5%)                             | 0.8      |

HAP, hospital-acquired pneumonia; ICU, intensive care unit; CXR, chest X-ray; IQR, interquartile range.

b Comparing patients with radiologically confirmed HAP and patients with radiology inconsistent with HAP; chi-squared test or Fisher’s exact test depending on number of subjects or two-sample Wilcoxon rank sum (Whitney–Mann) when comparing two medians.

b For emergency airway management, mechanical ventilation or general anaesthesia for surgery.
these continuous variables.

Comparison of inflammatory markers

| Inflammatory marker         | Radiologically confirmed HAP (N = 108) | Radiology inconsistent with HAP (N = 54) | P-valuea |
|-----------------------------|----------------------------------------|-----------------------------------------|-----------|
| White cell count (mean, ×10^9/L) | 14.7                                   | 11.0                                    | 0.0002    |
| Neutrophil count (mean, ×10^9/L)  | 12.5                                   | 8.8                                     | 0.0001    |
| C-reactive protein (mean, mg/L)   | 150.6                                  | 88.1                                    | 0.0003    |

HAP, hospital-acquired pneumonia.

Table III

a The Shapiro–Wilks test demonstrated that the data were not normally distributed, so the Mann–Whitney U-test was used to compare these continuous variables.

Results

Characteristics of patients treated for a clinical diagnosis of HAP

Over the 13-month time-period, a total of 13,096 admissions to eight wards in the RIE were reviewed. Overall 1745 of these adult inpatients received ≥48 h of intravenous antimicrobials (13.3%). Of these, 166 were treated for a clinical diagnosis of HAP (9.51% of patients on intravenous antimicrobials) (Table I).

The cohort of patients was elderly, with a median age of 79.5 years. The majority of patients were aged ≥75 years (62.7%) and were male (59.6%); 75.3% of patients had been admitted to a medical ward, and 24.7% to a surgical ward. Comorbidities, for example chronic obstructive pulmonary disease, heart failure and cardio-/cerebrovascular disease, were widespread in the cohort, reflected in an inpatient mortality of 19.3% (Table II). Median number of comorbidities was 2 with 28.3% of patients having >2.

Of the patients treated for HAP, 23.5% underwent a surgical procedure under general anaesthetic prior to diagnosis and treatment (Table II). A slightly higher percentage (27.1%) had an initial presentation with community-acquired pneumonia or aspiration pneumonia before suspicion of and treatment for HAP arising ≥48 h after admission.

In accordance with local guidelines for the treatment of HAP, piperacillin–tazobactam was the most frequently used antimicrobial, prescribed to 57.2% of included patients (Table II). Co-amoxiclav was the second most widely prescribed antimicrobial, used in 12.5% of cases.

Microbiological sampling in patients treated for a clinical diagnosis of HAP

In our study, blood cultures were drawn in the majority of patients treated for HAP (75.9%). Sputum from 24.7% of patients was sent for culture. Six percent of patients had a throat swab tested by quantitative polymerase chain reaction (qPCR) for influenza A, influenza B, respiratory syncytial virus, parainfluenza virus types 1–3, adenovirus, human coronaviruses 229E, HKU1, NL63 and OC43, human metapneumovirus, rhinovirus, and Mycoplasma pneumoniae. Metillin-resistant Staphylococcus aureus (MRSA) screening was performed in 80.7% of patients during their admission. Following initiation of treatment for suspected HAP, 4.2% of patients had a positive C. difficile toxin assay result and an additional 4.2% had an equivocal result (C. difficile screening test positive but C. difficile toxin not detected) during their hospital admission following treatment for HAP.

Radiologically confirmed diagnosis of HAP

Of all 166 patients treated for a clinical diagnosis of HAP, 65.1% had radiological evidence of a new or progressive lung infiltrate at the time of commencement of HAP treatment. Assuming the presence of consistent clinical signs and/or symptoms in addition, based on the clinical diagnosis of HAP, these patients are considered to have met diagnostic criteria for HAP according to the 2005 ATS/IDSA guidelines. In 32.5%, chest imaging found no evidence of a new or progressive infiltrate. No chest imaging was performed for four patients, and these patients were excluded from the following analyses.

Radiologically confirmed HAP appeared to represent a distinct clinical phenotype, with significantly higher levels of inflammatory markers (white cell count, neutrophils, and C-reactive protein; P < 0.05 for all) in these patients (Table III). Patients with radiologically confirmed HAP were more likely to have a white cell count greater than the upper limit of the local reference range [odds ratio (OR): 3.23; 95% confidence interval (CI): 1.57–6.83; P = 0.0007]. Leucopenia was only observed in one patient from each group. When the total duration of intravenous antimicrobial therapy was considered, patients with radiologically confirmed HAP had a longer median minimum duration of treatment (3.5 days vs 4 days; P = 0.04; Table II) further suggesting that the two groups were clinically different.

There was no significant difference in the use of piperacillin–tazobactam, co-amoxiclav, vancomycin, ciprofloxacin or meropenem between patients with and without radiological confirmation of HAP. The mortality rate during admission for patients with radiologically confirmed HAP was 20.4%, with 5.6% of patients requiring admission to the ICU and mechanical ventilation following HAP diagnosis. In the group without radiological confirmation, no patients went on to require ICU admission and the mortality rate during admission was 18.5% (P = 0.8).

Demographics associated with radiologically confirmed HAP

Patient characteristics and admission details were compared between patients treated for HAP with and without radiological confirmation of a new/progressive infiltrate (Tables I and II). Being admitted to a surgical ward (OR: 2.52, 95% CI: 1.03–6.87; P = 0.04), undergoing surgery (requiring general anaesthesia and intubation) (3.49; 1.31–10.98; P = 0.006) or endotracheal intubation for any indication (2.85;
stream infections, and MRSA and negative bacteria were responsible for two of these blood-tained from any of the patients with bacteraemia). Gram-
logically confirmed HAP and bacteraemia was infrequent,
radiologically confirmed HAP and none of these yielded growth 
Sputum samples were obtained from six patients without
confirmed HAP. In surgical patients, there was no difference
between emergency/elective admissions. Patients from both
compared HAP were similar to the overall population

Table IV

| Sample                          | No.  |
|--------------------------------|------|
| Sputum culture (N = 35)        |      |
| No growth                      | 5    |
| Commensals                     | 5    |
| Yeasts                         | 6    |
| Coliforms                      | 4    |
| Escherichia coli               | 5    |
| Pseudomonas aeruginosa         | 4    |
| Staphylococcus aureus (MSSA)   | 5    |
| Staphylococcus aureus (MRSA)   | 1    |
| Enterobacter cloacae           | 1    |
| Klebsiella oxytoca             | 1    |
| Aspergillus fumigatus\a         | 1    |
| Blood culture (N = 85)\b        |      |
| No growth                      | 81   |
| Klebsiella pneumoniae          | 1    |
| Staphylococcus aureus (MRSA)   | 1    |
| Proteus mirabilis              | 1    |
| Streptococcus pneumoniae       | 1    |
| MRSA screen (N = 90)           |      |
| Positive                       | 5    |
| qPCR for respiratory pathogens\c (N = 6) |      |
| Any positive result            | 0    |

HAP, hospital-acquired pneumonia; MRSA, meticillin-resistant
S. aureus; MSSA, meticillin-susceptible S. aureus.
\a Single isolate, likely contaminant.
\b All patients with positive blood cultures at time of HAP diag-
nosis had negative blood cultures earlier in admission.
\c Influenza A, influenza B, respiratory syncytial virus, para-
influenza virus types 1–3, adenovirus, human coronaviruses 229E, HKU1, NL63 and OC43, human metapneumovirus, rhinovirus, and Mycoplasma pneumoniae.

1.17–7.76; P = 0.01) were all associated with radiologically confirmed HAP. In surgical patients, there was no difference between emergency/elective admissions. Patients from both groups had a median of two medical comorbidities, and aside from CKD no comorbidity was associated with radiologically confirmed HAP.

Microbiology of radiologically confirmed HAP

Rates of microbiological sampling in patients with radiologically confirmed HAP were similar to the overall population of patients treated for clinical suspicion of HAP. A bacterial pathogen was identified from 17 of 35 sputum samples from patients with radiologically confirmed HAP (48.6%; Table IV). The majority of bacterial species identified in sputum samples were Gram-negative bacilli (N = 11) and S. aureus (N = 6). Sputum samples were obtained from six patients without radiologically confirmed HAP and none of these yielded growth of a bacterial pathogen.

Blood cultures were drawn in 78.7% of patients with radiologically confirmed HAP and bacteraemia was infrequent, occurring in only four patients (sputum cultures were not obtained from any of the patients with bacteraemia). Gram-negative bacteria were responsible for two of these bloodstream infections, and MRSA and S. pneumoniae accounted for one each. The patient with S. pneumoniae bacteraemia associated with HAP had clear lung fields on admission chest X-ray. A throat swab for qPCR testing for respiratory pathogens was obtained from 5.6% of patients and was negative in all cases. MRSA was found in only five of 90 MRSA screens (taken any time during admission) and was identified from one sputum sample and one blood culture (from different patients). Both of these patients had a positive MRSA screen.

An antibiogram of the antimicrobial susceptibilities of bac-
teria isolated from sputum samples is shown in Supplementary Table I. Overall, Gram-negative bacteria tended to be resistant to amoxicillin and co-amoxiclav, but susceptible to ciproflo-
acin, gentamicin, piperacillin–tazobactam, and meropenem. Five out of six S. aureus isolates were susceptible to fluclox-
acin and all six were susceptible to doxycycline (including the one MRSA isolate). The MRSA sputum isolate was susceptible to vancomycin.

Discussion

We have retrospectively evaluated a cohort of 166 medical and surgical inpatients treated for a clinical diagnosis of HAP. Applying the 2005 ATS/IDSA HAP guidelines to these patients, we identified that only 65.1% of patients had radiologically confirmed HAP; therefore it appears that in ward-level hospital practice at our institution ‘HAP’ is an over-used diagnosis that may be inaccurate in more than one-third of cases. Surgical ward admission, undergoing surgery with general anaesthesia, or endotracheal intubation for any indication were associated with radiologically confirmed HAP.

The 2005 ATS/IDSA guidelines describe intubation and me-
chanical ventilation as a risk factor for developing nosocomial pneumonia, but the literature cited to support this statement describes VAP, i.e. the development of pneumonia in patients during mechanical ventilation.\1 Hypothesis-generating univariate analysis on our data suggests that intubation and ventil-
tation, especially when associated with surgery, may be a
continuing risk factor for pneumonia even following extubation 
and is therefore a relevant factor when assessing non-
intubated patients with new respiratory signs and symptoms 
in hospital. The pathogenesis of HAP may therefore often be 
related to microaspiration of oropharyngeal contents around 
the cuff of an endotracheal (ET) tube in paralysed intubated 
patients during surgery, without necessarily a prolonged period 
of mechanical ventilation such as during critical illness (i.e. 
VAP). In a systematic literature review of airway management 
strategies to reduce the incidence of VAP in critically ill 
vентilated patients in the ICU, interventions including contin-
uous aspiration of subglottic secretions using a special ET tube 
(vs standard ET tubes) and the use of heat and moisture ex-
changers have been shown to lower VAP rates.\8 In a separate 
study, persistent ET tube cuff pressure of <20 cmH2O was also 
associated with risk of VAP.\9 Such interventions could also be 
evaluated in intubated patients undergoing surgery. Similarly, 
in critically ill ventilated patients, oral hygiene with chlor-
hexidine mouthwash has been shown to reduce rates of VAP, 
and has been included as a component of a successfully evalu-
ed ‘VAP care bundle’.\7 Chlorhexidine mouthwash would be 
an inexpensive measure for use in the immediate pre- 
and postoperative period for surgical patients. Oral care (chlor-
hexidine mouthwash or mechanical cleaning) was shown to be
associated with a reduced relative risk of pneumonia in a meta-analysis incorporating non-ventilated hospital inpatients and nursing home residents (though there was a high risk of bias in included studies).11 Other postoperative factors likely to be important in development of HAP include being bed-bound, having reduced chest wall movement (and therefore reduced clearance of secretions) due to pain or being drowsy secondary to opiate analgesics.

In approximately one-third of patients treated for suspected HAP in this study, a chest X-ray or computed tomography (CT) excluded a pneumatic infiltrate, therefore an alternative diagnosis may have been missed. A phenotype has been described in ventilated ICU patients with respiratory signs but no infiltrate on chest imaging, labelled nosocomial tracheobronchitis.12 This has been associated with longer ICU admission and ventilation times but prospective data describing the necessity for antimicrobials are lacking.12 Further study of this phenotype in non-intubated patients may be valuable and it may account for some of the cases in this study without radiological changes consistent with HAP. Non-infective alternatives include atelectasis, pulmonary embolism, and underlying lung disease, such as chronic obstructive pulmonary disease (present in 27.1% of patients treated for HAP in this study) and asthma. Unwell patients labelled as ‘HAP’ may have a subdiaphragmatic cause of sepsis resulting in the clinical findings. Given the demonstrated difficulty in reaching a reliable clinical diagnosis of HAP, microbiological testing to confirm an infective aetiology becomes even more important, but a sputum sample was obtained from only 24.7% of patients treated for HAP. This low rate may reflect the difficulty in obtaining a suitable deep specimen from non-intubated patients with a degree of respiratory distress or weakness. In such patients biomarkers of pulmonary infection would be helpful in establishing the likelihood of an infective aetiology and justifying the use of empirical antimicrobials prior to culture results.

In comparison to community-acquired pneumonia, where the culture-positive rate of sputum samples at our institution has been reported as 30%, a bacterial pathogen was identified from 17 of 35 (48.6%) samples from patients with radiologically confirmed HAP and therefore has greater potential to influence management.13 In our study, Gram-negative bacilli (11/17) and S. aureus (6/17) were the identified pathogens, with no frequently occurring CAP pathogens isolated. In the remainder of cases where a sputum sample was obtained, the result was ‘no growth’, ‘respiratory commensals’ or ‘yeasts’. Antimicrobial resistance was significant, with most Gram-negative isolates displaying resistance to amoxicillin and co-amoxiclav, but susceptibility to piperacillin–tazobactam. However, the overall number of sputum cultures obtained from patients was low, reducing the utility of these data in describing the microbiology of HAP. In addition, we recognize the potential for contamination of sputum samples with oropharyngeal colonizers. This is an important issue, especially considering the prescription of broad-spectrum antimicrobials to cover the susceptibility pattern of these pathogens, but pragmatically one would aim to cover these species if they were identified in a sputum sample from a patient with HAP. As discussed above, the inability to routinely obtain deep respiratory tract specimens (e.g. BAL) from non-intubated patients hinders microbiological diagnosis in HAP. The largest report on the microbiology of HAP comes from a retrospective cohort study of a US inpatient database of patients with culture-positive pneumonia, including 835 patients with HAP.14 Here, S. aureus accounted for 47.1% of cases, Pseudomonas spp. 18.4%, Klebsiella spp. 7.1%, Haemophilus spp. 5.6%, E. coli 4.7%, Enterobacter spp. 4.3%, and Acinetobacter spp. 2.0%. Overall, Gram-negative pathogens were isolated from 45.8% of HAP cases. A complicating factor in conventional culture-based testing of samples from patients with suspected HAP is the fact they will most likely already have received antimicrobials prior to sampling, impairing sensitivity of pathogen detection using culture-based techniques. A qPCR test for detection and quantification of eight key bacterial causes of pneumonia (including S. aureus, E. coli and P. aeruginosa) from sputum samples has recently been described and could represent a useful tool for the investigation of suspected HAP.

Only six (5.6%) patients with HAP had throat swabs obtained for qPCR respiratory virus and M. pneumoniae testing and in all cases these were negative. Nosocomial influenza can account for a significant proportion of influenza cases (17.3% in a Canadian surveillance programme).16 Using admission to critical care wards as a marker, the 2013/14 influenza season in Scotland was similar to the preceding year with no significant increase in cases.17 However, the lack of consistent testing for influenza virus in patients with HAP precludes any conclusions regarding the incidence of nosocomial influenza causing HAP during the study period, or the utility of respiratory virus/mycoplasma testing in the work-up of suspected HAP.

A limitation of this study is that radiological confirmation of HAP is primarily derived from the results of chest X-rays (only 10 of the 166 patients underwent CT) which may lead to under-detection of pulmonary infiltrates compared to CT.18–22 In a study of 3423 patients presenting to the emergency department with respiratory symptoms who underwent both chest X-ray and CT, it has been demonstrated that X-ray has poor sensitivity in detecting pulmonary infiltrates in comparison to CT (sensitivity 43.5%).20 The timing of CT scan was not specified in this study, therefore a confounding factor may be that a possible delay between X-ray and CT allows development of a detectable infiltrate. In cases where HAP is suspected clinically but the chest X-ray does not show a new/progressive lung infiltrate, there may be a role for CT scanning. In addition, there is emerging evidence for the role of lung ultrasound for the detection of pulmonary infiltrates in CAP, with some data suggesting superiority over chest X-ray when compared to CT as a gold standard.21,22 A further limitation lies in the case—control analysis performed, which should be repeated in the future with a control cohort of hospital inpatients with no clinical suspicion of HAP. Furthermore, this study only identified patients receiving intravenous antimicrobials, thereby selecting for patients perceived to have more severe illness.

When cases were identified during the antimicrobial prescribing audit, a recommendation was made to the parent team regarding further antimicrobial management. Whereas this occurred after the clinical diagnosis of HAP had been made by the patient’s team and would have had no influence on this, it may have altered subsequent management. This could therefore confound the mortality data presented here, although no significant difference was observed between patients with and without radiologically confirmed HAP.

This study has described the features of radiologically confirmed HAP in a cohort of UK inpatients. Potential risk factors have been identified through a hypothesis-generating
case—control analysis using patients treated for suspicion of HAP but without consistent radiology. Previous surgery and/or endotracheal intubation were found to be associated with radiologically confirmed HAP. Significantly, the clinical diagnosis of HAP may have been inaccurate in more than one-third of cases, where there were no consistent changes on chest imaging. We have also highlighted a lack of microbiological sampling in patients receiving broad-spectrum antimicrobials for a clinical diagnosis of HAP. Directions for further work on HAP are highlighted in Supplementary Table II. Improved accuracy of HAP diagnosis is essential, since around one-third of cases, where there were no consistent changes on chest imaging. We have also highlighted a lack of microbiological sampling in patients receiving broad-spectrum antimicrobials potentially unnecessarily and may have had an alternative diagnosis requiring different investigation and management.

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Conflict of interest statement
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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jhiny.2015.11.013.

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