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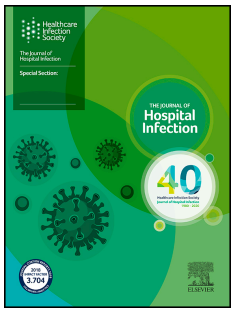


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# Hospital-onset, healthcare-associated (HOHA) gram-negative bloodstream infections (GNBSIs) in patients admitted to a busy district general hospital in England: A retrospective cohort study

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*Sir*,

Gram-negative bacteria are leading causes of healthcare-associated bloodstream infections, with up to 33.9% associated mortality 30 days after an episode of gram-negative bloodstream infection (GNBSIs) [1]. Higher mortality rates from hospital-onset compared with community-onset GNBSIs have also been widely reported [1]. Antimicrobial resistance especially amongst gram-negative bacteria poses a huge global health crisis [2]. As such, the United Kingdom government has set a target to halve incidence of healthcare-associated GNBSIs by 2024/2025 [2]. Identifying avoidable causes of healthcare-associated GNBSIs would inform effective preventive strategies.

We reviewed all cases of GNBSIs in patients admitted to a district general hospital in England between 01/02/2021 and 28/02/2022. Cases were classified into hospital or community-onset and healthcare-association based on nationally accepted criteria [2]. We retrospectively collected data on bacterial species, antimicrobial resistance, and mortality, for all hospital-onset healthcare-associated (HOHA) and community-onset community-associated (COCA) GNBSIs and additional data on infection sources for HOHAs using case notes and laboratory results. Cases that had modifiable risk factors were identified through consensus decision between reviewers. Statistical significance between proportions was estimated using the PR-test; p-value <0.05 was considered statistically significant.

Statistical analyses were performed in Microsoft Excel and STATA 16.0. Ethical approval was not required as this was conducted for clinical audit.

A total of 165 individuals with GNBSIs were identified; 89/165 (54%) female and 76/165 (46%) male, median age 74 (IQR: 63-83). There were 30/165 (18%) deaths within 28 days of diagnosis; 13/89 (14%) female and 17/76 (22%) male - this difference between sex was not statistically significant (p=0.19).

GNBSIs were classed into COCA (64/165, 39%), HOHA (55/165, 33%), community-onset, healthcare-associated (COHA) (34/165, 20%), and community-onset indeterminate association (COIA) (12/165, 7%).

Of 55 HOHA-GNBSIs, median age was 72 (IQR: 65-82), 28 (51%) were female and 27 (49%) were male (Table 1). The predominant causative organism was *Escherichia coli* (35/55, 63%), followed by *Klebsiella* species (14/55, 25%), and *Pseudomonas aeruginosa (*6/55, 11%). Just under half had modifiable risk factors that might have prevented the bacteraemia (24/55, 43%), the remainder had underlying infective aetiologies for the bacteraemia that were not modifiable (31/55, 56%).

Of the HOHA-GNBSIs that had modifiable risk factors, half were due to hospital-acquired or ventilator-associated pneumonias (HAP/VAP) (12/24), one-third were from catheter-associated UTIs (CA-UTI) (8/24), and one-sixth were attributed to central venous catheters (CVCs) (4/24). HOHA-GNBSIs with unmodifiable risk factors were attributed to hepato-pancreatobiliary (20.0%), intra-abdominal (10.9%), urinary (12.7%), and unknown focus (12.7%) (Table 1).

Amongst the HOHA-GNBSIs, 15/55 (27%) died within 28 days of culture. The distribution of causative organisms was similar when compared with the overall HOHA-GNBSIs, although slightly lower proportion of *E. Coli* (6/15, 40%) and higher proportion of *P. aeruginosa* (4/15, 27%) were observed. Of the 15 causative species, all were sensitive to meropenem and 2/15 (13%) were gentamicin resistant. All of the non-pseudomonas isolates were sensitive to temocillin, 4/11 (36%) were ampicillin-resistant, and 2/11 (18%) were resistant to co-amoxiclav. 20% (3/15) of HOHA-GNBSIs who died did not have modifiable risk factors identified (unknown focus). 12/15 (80%) deaths followed HOHA-GNBSIs that had modifiable risk factors: 75% (9/12) HAPs/VAPs, 17% (2/12) CA-UTIs, and 8% (1/12) CVCs.

There were 64 COCA-GNBSIs, of which 37/64 (57.8%) were female and 27/64 (42.2%) were male, median age 76 (IQR: 68-86). The proportion who died within 28 days of culture (7/64, 10.9%) was lower than from HOHA-GNBSI (15/55, 27.3%); this was statistically significant (p=0.0096).

Within our cohort, the most common source of HOHA-GNBSI that was likely to be modifiable was HAPs/VAP, followed by CA-UTI, and CVC-associated infection; with a similar distribution amongst those who died within 28 days of culture. Current nationally-recommended interventions champion urinary catheter care to reduce in-hospital GNBSIs [3,4]. Although these strategies remain important, our data have demonstrated the burden of healthcare-associated pneumonias as a cause of HOHA-GNBSIs, highlighting the need for local and national policies targeting VAP/HAP prevention. Strategies reported as effective include oral care, early mobilisation, swift diagnosis of dysphagia for HAPs; prevention of aspiration, and minimising ventilator-days for VAPs [5,6].

The higher 28-day mortality rate amongst HOHA-GNBSIs compared with COCA-GNBSIs amongst our cohort has also been reported by other cohorts, supporting the need to target interventions against in-hospital infection acquisition [7,8].

Our study has potential limitations. This is a retrospective, single-centre study with a relatively small sample size. Moreover, the hospital catchment has one of the highest nursing home and elderly populations in the country; this may result in higher rates of mortality and aspiration pneumonia or HAP compared to national averages.

GNBSIs remain an important source of healthcare-associated infection with worse outcomes when acquired in-hospital. Preventive strategies should target appropriate management of healthcare devices and risk factors for HAPs/VAPs.

**Conflict of interest statement**

None declared.

**Funding statement**

None.

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*Table 1: Patient demographics, species and sources of HOHA-GNBSIs*

| | **Total HOHA** | **Death within 28-days of diagnosis** |
|---|---|---|
| **Total** | 55 | 15 |
| **Age (median, IQR)** | 72 (65-82) | 76 (67-78) |
| **Sex**<br>Male<br>Female | <br>27 (49%)<br>28 (60%) | <br>8 (29%)<br>7 (25%) |
| **SPECIES** | | |
| ***E Coli*** | 35 | 6 |
| ***Klebsiella spp*** | 14 | 5 |
| ***Klebsiella aerogenes*** | 4 | 2 |
| ***Klebsiella oxytoca*** | 3 | 0 |
| ***Klebsiella pneumoniae*** | 7 | 3 |
| ***Klebsiella variicola*** | 0 | 0 |
| ***P aeruginosa*** | 6 | 4 |
| **RESISTANCE** | | |
| **Temocillin** | 3 (5.5%) | 0 |
| **Co-amoxiclav** | 20 (36%) | 6/15 (40%) |
| **Gentamicin** | 6 (11%) | 2/15 (13%) |
| **Meropenem** | 0 | 0 |
| **Ampicillin** | 28(60%) | 8/15 (53%) |
| **SOURCE** | | |
| **Potentially Modifiable Risk Factors** | | |
| **HAP/VAP** | 12 (22%) | 9 (60%) |
| **CA-UTI** | 8 (14%) | 2 (13%) |
| **CVC** | 4 (7%) | 1 (6.7%) |
| **Unlikely Modifiable Risk Factors** | | |
| **HPB** | 11 (20%) | 0 |
| **Unknown** | 7 (13%) | 3 (20%) |
| **Intra-abdominal** | 6 (11%) | 0 |
| **Urinary** | 7 (13%) | 0 |

*Abbreviations: HAP: Hospital-acquired Pneumonia; VAP: Ventilator-associated Pneumonia; CA-UTI, Catheter-associated Urinary Tract Infection; CVC: central venous catheter; HPB: Hepato-pancreatobiliary;*