Healthcare-Associated Pneumonia and Hospital-Acquired Pneumonia: Bacterial Aetiology, Antibiotic Resistance and Treatment Outcomes: A Study From North India

Sandeep Kumar¹ · Rafi Ahmed Jan¹ · Bashir Ahmad Fomda² · Roohi Rasool³ · Parvaiz Koul¹ · Sonaullah Shah¹ · Umar Hafiz Khan¹ · Syed Mudasir Qadri¹ · Shariq Rashid Masoodi⁴ · Suhail Mantoo¹ · Mudasir Muzamil¹

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Abstract

Background Data regarding the comparative profiling of HCAP and HAP from developing countries like India are scant. We set out to address the microbial aetiology, antibiotic resistance and treatment outcomes in patients with HCAP and HAP. **Methods** 318 consenting patients with HCAP ($n = 165$, aged 16–90 years; median 60 years; 97 males) or HAP ($n = 153$; aged 16–85 years; median 45 years; 92 males) presenting to a tertiary care hospital in North India from 2013 to 2015 were prospectively recruited for the study. Data on patient characteristics, microbial aetiology, APACHE II scores, treatment outcomes and mortality were studied. Clinical outcomes were compared with various possible predictors employing logistic regression analysis.

Results Patients in HCAP had more comorbidity. *Escherichia coli* (30, 18%) and *Acinetobacter baumannii* (62, 41%) were the most commonly isolated bacteria in HCAP and HAP, respectively. Multidrug-resistant bacteria were isolated more frequently in HCAP, only because the incidence of extensively drug-resistant bacteria was markedly high in HAP ($p = 0.00$). The mean APACHE II score was lower in HCAP (17.55 ± 6.406 , range 30) compared to HAP (19.74 ± 8.843 , range 37; $p = 0.013$). The length of stay ≥ 5 days ($p = 0.036$) and in-hospital mortality was higher in HAP group ($p = 0.002$). The most reliable predictors of in-hospital mortality in HCAP and HAP were APACHE II score ≥ 17 (OR = 14, $p = 0.00$; HAP: OR = 10.8, $p = 0.00$), and septic shock (OR = 4.5, $p = 0.00$; HAP: OR = 6.9, $p = 0.00$).

Conclusion The patient characteristics in HCAP, treatment outcomes, bacterial aetiology, and a higher incidence of antibiotic-resistant bacteria, suggest that HCAP although not as severe as HAP, can be grouped as a separate third entity.

Keywords *Acinetobacter baumannii* · Pneumonia · Bacterial · Drug resistance · Microbial · *Escherichia coli* · Ventilator-associated

Introduction

Pneumonia is the third leading cause of years of life lost (YLLs) worldwide. Globally, pneumonia was responsible for 2377.7 thousand death for the year 2016. The mortality varies with the social demographic index, from eighth most common cause in high socio-demographic index (SDI) groups to the most common cause of death in low SDI group of nations [1]. In India, pneumonia was the fourth leading cause of mortality, for the year 2016 [2].

The data on healthcare-associated pneumonia (HCAP) from prospective studies are scant, notably from developing nations like India. Most of the data come from the studies done in Europe [3–6]. These studies did a comparative analysis of HCAP and community-acquired

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✉ Rafi Ahmed Jan
rafiahmedjan@gmail.com

Extended author information available on the last page of the article

pneumonia (CAP) and concluded that microbial aetiology of HCAP was similar to CAP, but with higher morbidity and mortality in HCAP. The studies advocated that HCAP is an entity similar to CAP, despite higher morbidity and mortality. However, these studies excluded immunocompromised patients, and Vales et al. [4] even discussed pneumonia in immunocompromised patients as a separate entity. The immunocompromised state was described as Multidrug-resistant (MDR) risk factor in 2005 ATS/IDSA guidelines, the year in which HCAP was introduced as a new entity because of a large percentage of patients coming from the community were found to be infected with drug-resistant pathogens [7]. The exclusion of these patients can alter the results in studies aiming at determining the microbial etiological profile of HCAP and treatment outcomes in HCAP, as these patients also have a history of frequent hospitalisations and antibiotic use (prophylactic as well as therapeutic). Contrary to the European data, some of the US data suggest a higher prevalence of antibiotic resistance among the isolated organisms from these patients [8]. Against the backdrop of such a difference in the etiological profile between the United States and European data, it is essential to consider the data from developing countries, where pneumonia is more common than in developed nations. Also, the prevalence of MDR pathogens in pneumonia is higher, with alarming resistance to cephalosporins and carbapenems, especially among the isolates of *Acinetobacter* species, *Klebsiella pneumoniae* [9].

With hospital-acquired pneumonia (HAP), there is a consensus that Gram-negative bacteria predominate as etiological agents. In the United States, *Acinetobacter* species were the only Gram-negative bacteria that increased significantly as a cause of pneumonia in Intensive Care Units (ICUs) between 1986 and 2003 [10].

The alarming incidence of antibiotic resistance among hospitalised patients, in general, is increasing worldwide, including the USA, [11] European nations, Greece, [12] and India [9]. Reports of infections caused by organisms that are resistant to all currently available antibiotics, including Colistin, [13] are of most significant concern.

There is a scarcity of data on comparative profiling of HCAP and HAP from developing nations like India. With only 36% of the population using improved sanitation, [14] and high antibiotic consumption (Carbapenems in particular), [15] the problem of antibiotic resistance is severe in the Indian setting. A study on etiological profile of CAP at our centre ($n = 225$), found *Streptococcus pneumoniae* (30.5%) and *Legionella pneumoniae* (17.5%) to be the commonest agents, with in-hospital mortality of 8% [16]. We set out to determine the clinical spectrum, etiological profile and treatment outcomes of HCAP and HAP, in our

setting and also assess if HCAP should be considered as an entity distinct from HAP in our setting.

Methods

Setting

A prospective study was conducted at the 800-bedded tertiary care hospital, after getting approval from Sher-I-Kashmir Institute of Medical Sciences - Institutional ethics committee.

Design

The study design, along with HCAP and MDR risk factors, is illustrated in Fig. 1. The 2005 American Thoracic Society/ Infectious Disease Society of America (ATS/IDSA) criteria for clinically defined pneumonia were used to define HCAP, HAP and VAP [7]. Of the total of 554 cases of pneumonia seen over the study period, a total of 318 patients meeting the criteria (excluding CAP, $n = 225$) were grouped in HCAP ($n = 165$, 52%) and HAP ($n = 153$, 48%) including VAP ($n = 63$, 20%). Immunocompromised patients, an important risk factor for MDR pathogens, were also included to cover all the pneumonia groups for MDR pathogens. (Fig. 1) From HCAP, 11 immunocompromised cases were excluded. Data were collected on demographic features, patient characteristics including data on comorbidities, Charlson comorbidity index (CCI), [17] microbiological patterns of isolated organisms, radiological findings and clinical outcomes including in-hospital mortality and the length of hospital stay (LOS). Treatment of the patients was carried out employing standard hospital protocols based on the hospital ecology of microbiologic data.

Microbiological Investigation

Sputum and Endotracheal aspirate (ETA) cultures were done using blood agar, MacConkey agar and chocolate agar. BacT/ALERT® 3D automated system was used for blood cultures. Standard care was taken while processing sputum samples. Sputum was considered microbiologically adequate only if it contained > 10 white blood cells for each epithelial cell at a magnification of $400\times$ [18]. The purulent ETA secretions were defined as lower respiratory tract samples that contained ≥ 25 neutrophils and ≤ 10 squamous epithelial cells per lower power field $100\times$. The threshold values of 10^5 CFU/mL, for ETA, 10^6 for sputum and 10^3 for pleural fluid (obtained during thoracentesis and not from chest tubes) cultures were taken, and values below the threshold were considered as colonisers [19, 20]. Antibiotic susceptibility testing for isolates from sputum and ETA was done by Kirby

Fig. 1 Risk factors for multidrug-resistant pathogens causing pneumonia, and the study design

and Bauer disc diffusion method as per Clinical Laboratory Standard Institute (CLSI) guidelines. Antibiotic susceptibility testing for isolates from blood was done on VITEK® 2. The European Centre for Disease Control (ECDC) definitions for defining multi-, extensively, and pandrug-resistant (MDR, XDR, PDR) strains were used as follows [21]:

MDR strain: non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories,

XDR strain: non-susceptible to ≥ 1 agent in all but 2 or fewer antimicrobial categories,

PDR strain: non-susceptible to all antimicrobial agents listed, for specific organisms.

Statistical Analysis

Standard statistical methods as appropriate were employed. A multivariate regression analysis was performed to identify factors associated with antibiotic-resistant strains and in-hospital mortality. First, univariate relationships were analysed to determine the possible factors related to the treatment outcome. Cox regression analysis was used to calculate the hazard ratio. Data were analysed using 95% confidence

interval (CI) for estimates. SPSS software for Windows, version 21.0, was used (IBM—SPSS, Chicago, IL, USA).

Results

Patient Characteristics

Baseline demographic features and clinical characteristics are depicted in Tables 1 and 2, respectively. The age and CCI score of patients in HCAP were more, with higher mean and median values than in HAP ($p=0.00$). In HCAP group, 94% of cases had received antibiotics before the current admission ($p=0.00$). Among the risk factors for antibiotic-resistant pathogens, length of stay (LOS) ≥ 5 days was seen in 68 cases of HCAP, and 81 cases of HAP ($p=0.036$). The mean APACHE II scores were lesser in HCAP compared to HAP group ($F=6.295$, $p=0.013$).

Culture Results

The microbiological profile of the patients is depicted in Table 3. *Escherichia coli* ($n=30$, 18%) and *Acinetobacter baumannii* ($n=62$, 41%) were the most common

Table 1 Patient characteristics

Variables	HCAP (<i>n</i> = 165)	HAP (<i>n</i> = 153)	<i>p</i> value
Age (years)			
Mean $\pm$ SD	55.45 $\pm$ 18.5	45.15 $\pm$ 20.6	0.000
Median	60	45	0.000
Range (years)	16–90	16–85	0.000
Age $\geq$ 60 years	88 (53.3%)	59 (38.6%)	0.010
Age < 60 years	77 (46.7%)	94 (61.4%)	0.010
Gender			
Male	97 (58.8%)	92 (60.1%)	0.807
Comorbidities			
COPD (<i>n</i> = 45)	31 (18.8%)	14 (9.2%)	0.014
ILD (<i>n</i> = 7)	7 (4.2%)	0 (0.0%)	-
Asthma (<i>n</i> = 2)	1 (0.6%)	1 (0.7%)	-
Bronchiectasis (<i>n</i> = 5)	4 (2.4%)	1 (0.7%)	0.205
Chronic lung disease (<i>n</i> = 61)	46 (27.9%)	15 (9.8%)	0.000
Hypertension (<i>n</i> = 186)	115 (69.7%)	71 (46.4%)	0.000
Diabetes (<i>n</i> = 36)	25 (15.2%)	11 (7.2%)	0.025
CAD (<i>n</i> = 24)	11 (6.7%)	13 (8.5%)	0.537
CKD (<i>n</i> = 36)	31 (18.8%)	5 (3.3%)	0.000
Neurological (<i>n</i> = 62)	28 (17.0%)	34 (22.2%)	0.237
Malignancy (<i>n</i> = 39)	26 (15.8%)	13 (8.5%)	0.049
Smoking			
Never	71 (43.0%)	89 (58.2%)	0.026
Ever smoker	94 (57.0%)	74 (48.4%)	
Surgical intervention			
Emergency surgery (<i>n</i> = 22)	2 (1.2%)	20 (13.1%)	-
Elective surgery (<i>n</i> = 9)	0 (0.0%)	9 (6%)	
Trauma + burns (<i>n</i> = 17)	2 (1.2%)	15 (9.8%)	0.004
MDR risk factors			
Chemotherapy (<i>n</i> = 36)	23 (13.9%)	13 (8.5%)	0.126
Steroids—systemic (<i>n</i> = 12)	9 (5.5%)	3 (2.0%)	0.102
Steroids—inhaled (<i>n</i> = 23)	18 (10.9%)	5 (3.3%)	0.009
Immunosuppressant (<i>n</i> = 39)	28 (17.0%)	11 (7.2%)	0.008
Hemodialysis $\leq$ 30 days (<i>n</i> = 33)	30 (18.2%)	3 (2.0%)	0.000
Hospitalisation of > 2 days in last 30 days (<i>n</i> = 148)	145 (87.9%)	3 (2.0%)	0.000
Antibiotic use prior to hospitalisation (<i>n</i> = 159)	155 (93.9%)	4 (2.6%)	0.000
Wound care (<i>n</i> = 14)	9 (5.5%)	5 (3.3%)	0.342
Charlson comorbidity index			
Mean $\pm$ SD	4.04 $\pm$ 2.463	2.44 $\pm$ 2.539	0.000
Range	0–12	0–9	0.000
Median	4	2	0.000
Score > 3	101 (61.2%)	53 (34.6%)	0.000

HCAP healthcare-associated pneumonia, HAP hospital-acquired pneumonia, SD standard deviation, COPD chronic obstructive pulmonary diseases, ILD interstitial lung diseases, CAD coronary artery disease, CKD chronic kidney disease, MDR multidrug-resistant

microorganisms isolated in HCAP and HAP groups, respectively. Bacteria belonging to *Enterobacteriaceae* family were more frequently isolated in HCAP (*n* = 49, 30%) than in HAP group (*n* = 40, 26%). Details of culture methods used and organisms isolated are given in Table S1. *ESKAPE* group of

bacteria were isolated in 94 cases (104 isolates) in HCAP and 104 cases (144 isolates) in HAP group (*p* = 0.001). Among patients with chronic lung conditions (*n* = 61), *A. baumannii* (*n* = 13, HCAP = 7, HAP = 6, *p* = 0.067) and *E. coli* (*n* = 12, 22%, HCAP = 10, HAP = 2, *p* = 0.712) were the

Table 2 Patient clinical characteristics and disease severity

Variable	HCAP (n = 165)	HAP (n = 153)	p value
APACHE II score (≥ 17) (n = 165)	82 (49.7%)	83 (54%)	0.000
Mean APACHE II score $\pm$ SD	17.55 $\pm$ 6.406	19.74 $\pm$ 8.843	0.013
	95% CI 16.57–18.54	95% CI 18.33–21.15	
APACHE II score—range	7–37	7–44	0.013
Acute kidney injury (n = 151)	73 (44.24%)	78 (51%)	0.208
Coagulopathy (n = 98)	45 (27%)	53 (34.6%)	0.155
Septic shock (n = 174)	77 (46.7%)	97 (63.3%)	0.002
Encephalopathy (n = 150)	64 (38.8%)	86 (56.2%)	0.002
Congestive cardiac failure (CCF) (n = 31)	23 (14%)	8 (5.2%)	0.009
Pleural effusion (n = 95)	57 (34.5%)	38 (24.8%)	0.059
Empyema (n = 19)	14 (8.5%)	5 (3.3%)	0.050
Multilobar consolidation (n = 106)	43 (26.1%)	63 (41.2%)	0.004

HCAP healthcare-associated pneumonia, HAP hospital-acquired pneumonia, SD standard deviation, APACHE II acute physiology and chronic health evaluation-II

Table 3 Culture results in HCAP and HAP

Etiological agent	HCAP (n = 165)	HAP + VAP (n = 153)	p value	Etiological agent	HCAP (n = 165)	HAP + VAP (n = 153)	p value
<i>Escherichia coli</i>	30 (18%)	17 (11%)	0.083	<i>Proteus mirabilis</i>	0	1 (0.7%)	
<i>Acinetobacter baumannii</i>	23 (14%)	62 (41%)	0.000	<i>Mycobacterium tuberculosis</i>	3 (1.8%)	0	0.100
<i>Klebsiella pneumoniae</i>	18 (11%)	16 (10%)	1.000	<i>Serratia marcescens</i>	0	2 (1.3%)	0.100
<i>Pseudomonas aeruginosa</i>	11 (7%)	21 (14%)	0.012	<i>Serratia liquefaciens</i>	0	1 (0.7%)	
<i>Pseudomonas fluorescens</i>	0	1 (0.7%)		<i>Alcaligenes faecalis</i>	0	2 (1.3%)	0.250
<i>Pseudomonas putida</i>	0	1 (0.7%)		<i>Aerococcus viridans</i>	1 (0.6%)	1 (0.7%)	0.975
<i>Pseudomonas stutzeri</i>	0	1 (0.7%)		<i>Stenotrophomonas maltophilia</i>	0	2 (1.3%)	0.250
<i>Enterococcus faecium</i>	8 (4.8%)	7 (4.6%)	0.750	<i>Listeria monocytogenes</i>	1 (0.6%)	1 (0.7%)	0.975
<i>Enterococcus faecalis</i>	0	2 (1.3%)		<i>Achromobacter denitrificans</i>	0	1 (0.7%)	0.500
<i>Staphylococcus aureus</i>	7 (4.2%)	5 (3.3%)	0.772	<i>Chryseobacterium indologenes</i>	0	1 (0.7%)	0.500
<i>Staphylococcus hominis</i> (MRSH)	5 (3%)	7 (4.6%)	0.500	<i>Kluyvera cryocrescens</i>	0	1 (0.7%)	0.500
<i>Enterobacter cloacae</i>	2 (1.2%)	3 (2%)	0.750	<i>Leuconostoc mesenteroides</i>	0	1 (0.7%)	0.500
<i>Burkholderia cepacia</i>	3 (1.8%)	2 (1.3%)	0.750	<i>Moraxella catarrhalis</i>	0	1 (0.7%)	0.500
<i>Sphingomonas paucimobilis</i>	1 (0.6%)	3 (2%)	0.500	<i>Providencia stuartii</i>	0	1 (0.7%)	0.500
<i>Citrobacter freundii</i>	1 (0.6%)	2 (1.3%)	0.750	Sterile	64 (38.8%)	32 (21%)	0.001
<i>Proteus vulgaris</i>	1 (0.6%)	2 (1.3%)	0.500	Polymicrobial	13 (8%)	39 (25.5%)	0.010

Bold values indicate the most commonly isolated bacteria in each group

HCAP healthcare-associated pneumonia, HAP hospital-acquired pneumonia, MRSH methicillin-Resistant *Staphylococcus hominis*

most commonly isolated microorganisms. A total of 13 cases in HCAP and 39 cases in HAP had a polymicrobial aetiology

($p=0.00$), out of which 5 cases in HCAP and 4 cases in HAP group had a chronic lung condition ($p=0.204$).

Antibiotic Resistance

From 87 (53%) cases in HCAP group and 134 (87%) cases in HAP group, antibiotic-resistant bacteria were isolated. In HAP group, three PDR bacteria were isolated. In HCAP, among patients who had received antibiotics before hospitalisation, MDR and XDR bacteria were isolated from 21% and 32% of cases, respectively. ($p=0.349$). Multidrug-resistant bacteria were isolated more among patients with HCAP ($p=0.495$), only because the incidence of extensively drug-resistant bacteria was markedly high in HAP ($p=0.00$). The antibiotic susceptibility of the most common bacteria is shown in e-Table 2. *Vancomycin-resistant Enterococcus* (VRE) was isolated from 2 (1%) cases in HCAP and 4 (3%) cases in HAP. Also, *Methicillin-Resistant Staphylococcus aureus* was seen in 4 (2%) cases in HCAP and 5 (3%) cases in HAP group. All *Methicillin Sensitive Staphylococcus aureus* (MSSA), 3 (1.8%) were isolated from HCAP. In this study, among all 318 cases, out of total 476 isolates and from 254 positive cultures, 91 (40%) isolates in HCAP and 145 (59%) in HAP ($p=0.000$) isolates were resistant to at

least one category of antibiotics used in the empirical antibiotic regimen [7]. (Table S2) Details of MDR and XDR isolates are shown in Table 4. Using multivariate regression analysis, chronic lung diseases were the strongest predictor of MDR bacteria (OR 2.73, 95% CI 1.26–5.915, $p=0.011$). Isolation of *A. baumannii* (OR 35.503, 95% CI 14.688–85.817, $p=0.000$), *Pseudomonas* spp. (OR 8.913, 95% CI 2.762–28.76, $p=0.000$) and bacteria belonging to the *Enterobacteriaceae* family collectively (OR 9.533, 95% CI 2.62–34.688, $p=0.001$) along with immunocompromised state (OR 4.050, 95% CI 1.39–11.796, $p=0.010$) were the strongest predictors for XDR pathogens. The probability of isolating bacteria sensitive only to Polymyxin/Colistin ($n=70$ (22%); HCAP-22, HAP-48) was strongly associated with isolation of *A. baumannii* (OR 8.386, 95% CI 3.698–19.015, $p=0.000$) and *Pseudomonas* spp. (OR 6.063, 95% CI 1.965–18.705, $p=0.002$).

Table 4 Distribution of drug-resistant isolates among HCAP and HAP groups

Isolate	Pneumonia	MDR (n)	XDR (n)	PDR (n)	Sensitive only to colistin/polymyxin (n)
Number of cases (number of isolates)	HCAP	38 (40)	49 (54)	0 (0)	22 (22)
	HAP	30 (33)	84 (110)	3 (3)	48 (53)
<i>Acinetobacter baumannii</i> (n)	HCAP	4	16	0	10
	HAP	7	60	0	33
<i>Escherichia coli</i> (n)	HCAP	13	13	0	3
	HAP	7	7	0	3
<i>Pseudomonas</i> spp. (n)	HCAP	5	6	0	2
	HAP	1	20	1	13
<i>Klebsiella pneumoniae</i> (n)	HCAP	2	12	0	6
	HAP	2	13	0	7
<i>Staphylococcus aureus</i> (n)	HCAP	4	0	0	-
	HAP	4	1	0	-
Others (n)	HCAP	12	8	0	1
	HAP	12	16	2	4
Death [number of cases (number of isolates)]	HCAP	15 (17)	12 (13)	0	5 (5)
	HAP	13 (14)	38 (53)	1 (1)	26 (29)
XDR	HCAP	<i>Citrobacter freundii</i> —1, <i>Enterobacter cloacae</i> —2, <i>Enterococcus faecium</i> —4, <i>Burkholderia cepacia</i> —1			
	HAP	<i>Alcaligenes faecalis</i> —2, <i>Citrobacter freundii</i> —1, <i>Enterobacter cloacae</i> —2, <i>Enterococcus faecium</i> —5, <i>Burkholderia cepacia</i> —1, <i>Proteus vulgaris</i> —1, <i>Sphingomonas paucimobilis</i> —2, MRSH—1, <i>Chryseobacterium indologenes</i> —1			
MDR	HCAP	<i>Citrobacter freundii</i> —1, <i>Enterococcus faecium</i> —4, MRSH—4, <i>Burkholderia cepacia</i> —2, <i>Sphingomonas paucimobilis</i> —1			
	HAP	<i>Providencia stuartii</i> —1, <i>Achromobacter denitrificans</i> —1, <i>Enterococcus faecium</i> —2, <i>Leuconostoc mesenteroides</i> —1, MRSH—4, <i>Kluyvera cryocrescens</i> —1, <i>Burkholderia cepacia</i> —1, <i>Proteus vulgaris</i> —1			

Fig. 2 Outcomes and complications of HCAP and HAP groups, with comparison of main complications in all three categories—HCAP, non-ventilator-associated HAP (nvHAP) and VAP separately

Clinical Outcomes

The overall incidence of in-hospital mortality, acute kidney injury/worsening of renal functions, coagulopathy, septic shock and encephalopathy was higher in HAP group. The other complications like the congestive cardiac failure (CCF), pleural effusion and empyema were higher in HCAP group. When clinical outcomes were compared between HCAP and non-ventilator-associated HAP, septic shock, coagulopathy, worsening of renal functions (Fig. 2) were comparable, but still more severe in non-ventilator-associated HAP. The LOS ≥ 5 days was more among in HAP group, with mean $\pm$ SD = 17.85 ± 12.212 (range 2–85 days), compared to mean $\pm$ SD = 14.23 ± 10.158 (range 1–61 days) in HCAP group. The Levene's test for equality of variance for LOS value was found significant ($F = 4.341$, $p = 0.038$), and non-parametric test (Mann–Whitney test) was applied for the lack of homogeneity (Overall Mean $\pm$ SD = 15.97 ± 11.321 , Mean rank: HCAP = 144.99, HAP = 175.15). The length of stay in HAP group was more than that of HCAP group, and the relation was statistically significant ($p = 0.003$). There were 98 deaths during the study [HCAP: 38 (23%); HAP: 60 (39%) including VAP: 28 (44%); $p = 0.002$]. Comparison of various parameters to in-hospital mortality is depicted in Table 5. The *ESKAPE* group (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, *Enterobacter species* and *E. coli*) [22] of bacteria were responsible for more deaths in HAP ($p = 0.005$).

Using multivariate regression analysis, various factors were analysed for predictability of in-hospital mortality. (Table S3) In HCAP and HAP group, APACHE II score ≥ 17 and septic shock were the most reliable predictors of in-hospital mortality. (Table 5) In addition to these factors, the presence of consolidation was also a strong predictor

of mortality in HCAP, but not in HAP. (Table S3) Various factors were analysed, using Cox Regression analysis for in-hospital mortality as an outcome. It was found that APACHE II score (HR 6.439, 95% CI 3.591–11.549, $p = 0.000$), septic shock (3.229, 95% CI 1.931–5.4, $p = 0.000$), and CCI score > 3 (HR 1.576, 95% CI 1.051–2.364, $p = 0.028$) were the significant causes of in-hospital mortality in our study population. Comparison of both groups is given in Table 5.

Discussion

Our data reflect the problem of antibiotic resistance, and adverse treatment outcomes in HCAP are as severe as in HAP in our setting, contrary to the European data [3–6]. To the best of our knowledge, this is the first prospective study of its kind where HCAP and HAP were studied, and results analysed, notably from India. We found an alarming incidence of MDR and XDR bacteria in both groups. The status of HCAP is still uncertain after its removal from HAP, [23] and treating HCAP as a separate entity needs to be addressed, also considering data from developing nations. CAP and HAP lie on two extremes of the pneumonia spectrum, and HCAP is in the grey area where some of the recent studies have advocated keeping HCAP in the CAP group [3–6]. The grounds for the debate over HCAP status have been the rising concerns regarding resistance to antibiotics including antibiotics used in empirical antibiotic regimens recommended [7]. There is a consensus among various studies, over higher morbidity or mortality in HCAP [3–6, 8]. Although the higher mortality and morbidity in HCAP needs to be addressed separately, the controversy in HCAP is somewhat over microbiological aetiology, [3–6, 8] and the spectrum of antibiotic resistance (non-MDR [3–6] vs MDR [8]).

Table 5 In-hospital mortality: comparison of microbiological and clinical parameters

Variable	HCAP (n)	HAP (n)	p value
Total deaths = 98	n = 38	n = 60	
Microbiological parameters			
MDR bacteria (n = 28, 28.6%)	15	13	NS
XDR bacteria (n = 49, 50%)	11	38	0.009
Bacteria sensitive only to polymyxin (n = 31, 44%)	5	26	0.002
ESKAPE (n = 71, 72%)	24	47	0.005
Positive bacterial culture (n = 77, 78.5%)	26	51	0.011
Clinical parameters			
APACHE II score ≥ 17 (n = 85, 87%)	34	51	0.000
Multivariate regression analysis. OR; 95% CI	13.99; 4.674–47.874	10.802; 4.721–24.717	0.000
Cox regression analysis. HR; 95% CI	6.088; 3.381–10.963	6.454; 3.595–11.585	0.000
Septic shock (n = 80, 82%)	28	52	0.000
Multivariate regression analysis. OR; 95% CI	4.457; 1.992–9.975	6.933; 2.969–16.192	0.000
Cox regression. HR; 95% CI	3.140; 1.866–5.285	3.274; 1.956–5.481	0.000
Charlson comorbidity index (CCI) score > 3 (n = 48, 49%)	25	23	0.027
Multivariate regression analysis. OR; 95% CI	2.318; 1.394–3.854	0.738; 0.440–1.239	–
	p = 0.001	p = 0.251	
Cox regression. HR; 95% CI	1.796; 1.175–2.745	1.629; 1.081–2.456, p = 0.020	–
	p = 0.007		
Length of stay (LOS) ≥ 5 Days (n = 71, 72%)	25	46	0.202
Multivariate regression analysis. OR; 95% CI	2.221; 1.360–3.627	0.725; 0.431–1.220, p = 0.226	–
	p = 0.001		
Cox regression. HR; 95% CI	0.258; 0.154–0.433	0.257; 0.153–0.432	0.000

HCAP healthcare-associated pneumonia, HAP hospital-acquired pneumonia, MDR multidrug-resistant, XDR extensively drug resistant, ESKAPE *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species and *E. coli* [19], OR odd's ratio, HR hazard ratio; APACHE II acute physiology and chronic health evaluation-II, CI confidence interval

The most frequent cause of HCAP varies with *S. pneumoniae* in Spain, [3–5] Iceland [6] and UK, [24] and as per some studies from the USA—*Staphylococcus aureus* (47%) and *P. aeruginosa* (25%) [8, 25]. The other question to be addressed is, which antibiotics can be used in empirical management [7] of HCAP, which as per the European studies has *non-MDR* aetiology [3–6]. A study from the USA showed a higher incidence of antibiotic-resistant pathogens [8]. In our study, we found an alarming rate of Carbapenem-resistant *Enterobacteriaceae* (CDC-urgent threat) [26] and XDR *Acinetobacter*, and *Pseudomonas species* (CDC-Serious threat) [26]. The data from 50 nations reported the *P. aeruginosa* as the most frequent pathogen, followed by *A. baumannii*, with resistance percentage of 40% and 90% [27]. In our study, bacteria sensitive only to Polymyxin/Colistin were isolated from a large number of cases—more frequently in HAP, but also in HCAP. ESKAPE bacteria in our study were associated with poorer clinical outcomes and increased mortality. Since ESKAPE bacteria are commonly isolated from HCAP and HAP, the group can be targeted in empirical antibiotic treatment. As far as bacteriology is considered, our study shows a higher incidence of antibiotic resistance in HCAP (n = 83) and HAP (n = 95), differing mainly in the

severity of resistance. Also, the debate on initial empirical treatment [7] has another aspect to it. Most of the isolates in our studies were resistant to antibiotics used in empirical treatment, which could have influenced the high mortality in our study population. The high microbiological yield in our study population (70%) (HCAP-61%, HAP-79%) is another perilous factor, which is more than the overall rate of pathogen detection among patients with CAP (30–40%) [28].

The mortality in our study was high, with 23% mortality in HCAP group, which was in consonance with other previous studies, where it ranged from 10 to 24.4% [3–6, 8, 24, 29–32]. In our study, the mortality rate of 39% was seen in HAP group and was also in consonance with other previous studies, where the mortality rates ranged from 9 to 43.5% [8, 29, 30, 32].

The growing medical tourism industry [33] and the risk of acquisition of MDR strains among travellers [34] make our findings more relevant. The spread of New Delhi Metallo- β -lactamases which was mostly found among *E. coli* and *Klebsiella pneumoniae* is a notable example [35]. In a study from our centre, out of 100 Imipenem-resistant isolates, 55% were Carbapenemase positive, and of the 15 class B Metallo-beta-lactamase producers, nine

carried the bla(NDM1) gene. The gene was isolated not only from *K. pneumoniae* but also from *A. baumannii*, *P. aeruginosa*, *Citrobacter freundii* and *E. coli* [36]. The emergence of plasmid-mediated Colistin resistance mechanism (MCR-1) in animals and humans has already indicated that bacteria are becoming resistant to even the last resort antibiotic—the Colistin [37]. In a recently published study, from the USA, 32% of *P. aeruginosa* isolates were MDR, even in cases of CAP [38].

Limitations: This is a single-centre based study. In the state of Jammu and Kashmir, SKIMS is an apex tertiary care hospital offering advanced healthcare with proper laboratory support and gets referrals from other hospitals and parts of the state. Also, we did not test for viruses and atypical pathogens, which may have further decreased the number of cases with no microbial aetiology. *Candida* species were isolated from 9 cases, but were not included in final analysis, as per the guidelines [19]. None were isolated from pleural fluid and no biopsies were performed. Out of 9, two were isolated from sputum and one was isolated from ETA. No BAL or post-mortem histopathological biopsy was done to confirm our findings. The study excluded CAP, which has been studied separately at our centre ($n=225$) [16].

Conclusions

HCAP needs to be categorised separately as a third category, if not in HAP spectrum, because the patient characteristics, bacterial etiological profiling, antibiotic susceptibility and outcomes are unique to HCAP, and can be better addressed when categorised separately. The high mortality in HCAP is multifactorial, clinical (increasing age, comorbidities, pneumonia severity and complications) and microbiological (the type of bacteria and antibiotic susceptibility) and use of empirical antibiotic therapy is justified, but emphasising the need of early aggressive approach and supportive care in HCAP can improve patient outcome.

Author Contributions SK—Study design, patient selection, sample collection, data collection, data entry and analysis, main manuscript writer, manuscript review, editing and main manuscript approval. RAJ—Concept, study design, patient selection, team leader, co-ordination between various teams and departments, manuscript review and main manuscript approval. BAF—Headed the microbiology team for blood and respiratory culture, culture result reporting and manuscript editing. RR—Microbiological aspects, culture results and marker collection. PK—Diagnosing pneumonia, radiological confirmation, patient selection in Department of Internal medicine and facilitating co-ordination with other departments. SS—Diagnosing pneumonia, radiological confirmation, patient selection. UHK—Patient selection and data collection. SMQ—patient selection and data collection. SRM—Data analysis and manuscript editing. SM—Data collection and data entry.

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Compliance with Ethical Standards

Conflict of interest All the authors in study have nothing to disclose.

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Affiliations

Sandeep Kumar¹ · Rafi Ahmed Jan¹ · Bashir Ahmad Fomda² · Roohi Rasool³ · Parvaiz Koul¹ · Sonaullah Shah¹ · Umar Hafiz Khan¹ · Syed Mudasir Qadri¹ · Shariq Rashid Masoodi⁴ · Suhail Mantoo¹ · Mudasir Muzamil¹

Sandeep Kumar
drsandeep.neph@gmail.com;
drsandeep_kumar@hotmail.com

Bashir Ahmad Fomda
bashirfomda@yahoo.com

Roohi Rasool
roohi_wani@yahoo.com

Parvaiz Koul
parvaizk@gmail.com

Sonaullah Shah
sonaullah_shah@yahoo.co.in

Umar Hafiz Khan
drumarhafiz@gmail.com

Syed Mudasir Qadri
drsmudasir@yahoo.co.in

Shariq Rashid Masoodi
shariq.masoodi@skims.ac.in

Suhail Mantoo
mantoosuhail@yahoo.com

Mudasir Muzamil
drmmuzamil@gmail.com

¹ Department of Internal Medicine (Pulmonary Medicine), Sher I Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir 190001, India

² Department of Microbiology, Sher I Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir 190001, India

³ Department of Immunology and Molecular Biology, Sher I Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir 190001, India

⁴ Department of Endocrinology, Sher I Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir 190001, India