Original Article

Incidence, Risk Factors and Clinical Outcomes of Patients with Hypermucoviscoid *Klebsiella* in a Tertiary Intensive Care Unit

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Abstract

Background and Objectives: Hypermucoviscoid *Klebsiella* (hvKP), a dreaded variant of Klebsiella, so far, fewer cases were reported from the community. This study was designed to evaluate the incidence of hvKP isolates, risk factors for hvKP infections, antibiotic sensitivity pattern and clinical outcome including morbidity and mortality. **Patients and Setting:** Patients who have got admitted under medical intensive care unit (MICU) and had positive culture of *Klebsiella* infections. **Materials and Methods:** This study was conducted at department of MICU at a tertiary care hospital between January 2018 and December 2018. A standardized proforma was prepared and data was collected, which includes basic demographics of the patients, co-morbidities, clinical details and mortality. This study was approved by the Institutional Review Board and Ethics Committee. **Results:** A total of 165 patients (males, 123; 74.5%) had *Klebsiella pneumoniae* infection during the study period, out of whom 32 was hvKP (19.4%). The mean age was 53.1 ± 16.8 years. Among the 32 hvKP patients, 22 (68.8%) were hospital acquired infection (HAI) and 10 were (31.2%) community acquired infection. The overall mortality rate of hvKP infection was 56.2% (18/32). The incidence of mortality rate was similar in patients having pan-drug sensitive and in patients with extreme drug-resistance (61.9% vs. 66.7%; $P = 0.831$). HAI is significantly associated with multi drug resistance of hvKP (odds ratio [OR], 7.917; $P < 0.05$) and diabetes is associated with increased risk of hvKP related mortality (OR, 5.250; $P = 0.054$). **Conclusions:** Our study results showed, increased incidence of HAI with hvKP predominantly associated with pneumonia and increase in trend of drug resistance with *two* cases being pan resistant. More number of studies are required to evaluate the existing antibiotics strategy and steps to curb the spread of this dreaded infection.

Keywords: Community acquired infection, hospital acquired infection, hvKP, hypermucoviscoid *Klebsiella*, *Klebsiella*

Introduction

Klebsiella species cause wide range of infections which includes pneumonia, urinary tract infections, blood stream infections and sepsis. The first *Klebsiella pneumoniae* (*K. pneumoniae*) bacterium was isolated by Carl Friedlander from the lungs of patients who had died from pneumonia in 1882.[1] *Klebsiella* infections are important cause for hospital acquired infections (HAIs), constituting 3%–42% of nosocomial infections with an attributable mortality risk of 20%–67% to *Klebsiella*.[2] In mid 1980s a new strain of *Klebsiella* called Hypermucoviscoid *Klebsiella* (hvKP) strain was detected in patients with pyogenic liver abscess.[3] This hvKP strain is supposed to be more virulent and unique in causing metastatic infections in younger healthy population,[4] however, the hvKP strain can be detected with simple string test.[5,6] The literature is limited and sparse regarding to the incidence, risk factors and attributable mortality to the hvKP strain. In a single observational study from India, the incidence of hvKP strains among *Klebsiella* isolates was more than 80% which were predominantly multidrug resistant (MDR).[7] The hvKP infections are most commonly community acquired infections (CAIs). In Asia, hvKP is the most common cause of pyogenic liver abscesses.[8,9] However, antibiotic-resistant hvKP isolates are increasingly being reported across the world.[10-12]

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In this study, we have evaluated the incidence of hvKP isolates in community acquired and nosocomial infections, risk factors for hvKP infections, antibiotic sensitivity pattern and clinical outcome of patients including morbidity and mortality.

Materials and Methods

Study design

The present study comprised of retrospective as well as prospective cases.

Study area

This study was conducted at department of medical intensive care unit (MICU) at a tertiary care hospital.

Study population

Patients who have got admitted under MICU and had positive culture of *Klebsiella* infections between January 2018 and December 2018, at Mazumdar Shaw Medical Center, Narayana Health City, Bengaluru.

Procedure

After obtaining the ethical committee approval, prospectively we have collected the data of mentioned study period. A standardized proforma was prepared, which includes basic demographics of the patients, co-morbidities, HAI or CAI details, severity of illness, antibiotic sensitivity and clinical response to antibiotics. We also collected other clinical parameters such as length of hospital/MICU stay, ventilation requirement, organ failures and mortality.

Statistical analysis

Data was analyzed by using SPPS statistical software for windows (version 11, SPSS Inc., Chicago, IL, USA). Continuous data are presented in terms of mean and standard deviation. Categorical data are presented in terms of number and percentages. Univariate logistic regression model was used to predict the risk factor for hvKP drug resistance and mortality.

Ethical approval

This study was approved by the Narayana Health Medical Ethics Committee, Bengaluru.

Definitions

- MDR: MDR was defined as acquired nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories[13]
- Extreme drug resistance (XDR): XDR was defined as nonsusceptibility to at least 1 agent in all, but two or fewer antimicrobial categories[13]
- Pan drug resistance (PDR): PDR was defined as nonsusceptibility to all agents in all microbial categories[13]
- Extended-spectrum beta-lactamase (ESBL) producing bacteria: ESBL bacteria are defined as nonsusceptibility to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam.

Results

A total of 3115 patients have admitted in MICU over the period of 1 year. Out of whom 5.5% (165 out of 3115) had *K. pneumoniae* infection and 1% (32 out of 3115) of patients had hvKP infections. Figure 1 is showing the depiction of classical *K. pneumoniae* and hvKP on the agar plate. The rate of hvKP incidence among *Klebsiella* culture positivity was 19.4% (32 out of 165). Seventy-five percent (123 out of 165) were males, the overall mean age was 53.1 ± 16.8 years. The mean age (53.1 ± 16.8 vs. 54.2 ± 15.6 years; $P = 0.734$), and gender ($P = 1.000$) were similar between *Klebsiella* infections and hvKP infections.

Among the 32 hvKP patients, 22 (68.8%) were HAIs and 10 were (31.2%) CAIs. The overall mortality rate in hvKP infection was 56.2% (18 out of 32). Ten patients (31.3%) were discharged in stable condition and 4 patients (12.5%) were discharged against medical advice for religious and financial reasons. The basic and clinical characteristics are presented in Table 1.

The predominant site of hvKP samples were obtained from the respiratory tract [Table 1]. The antibiotic sensitivity pattern of hvKP showed, 18 patients had pan-drug sensitive, 2 patients had pan-drug resistant, 11 patients were sensitive to only one drug (Colistin), 5 patients were sensitive to 2 drugs and 6 patients were sensitive to >2 drugs. Most of the (90.6%; $n = 29$) hvKP patient's samples were sensitive to colistin compared to other drugs used [Table 2].

Seventeen (53.1%) of hvKP isolates were XDR, 8 (25%) were pan sensitive, 3 (9.4%) were ESBL producing type, 2 (6.3%) was pan resistance, 1 (3.1%) was MDR and 1 was colonizer.

The incidence of mortality rate in patients with pan-drug sensitive and in patients with extreme drug-resistance were 61.9% and 66.7% respectively ($P = 0.831$). The mortality rate did not differ between pan sensitive group and drug resistance group.

Univariate logistic regression analysis showed, Tracheostomy (odds ratio [OR], 5.385; $P = 0.143$) and HAI (OR, 7.317; $P<0.05$) are the risk factors for the resistance of hvKP to the antibiotics [Table 3]. Whereas, diabetes (OR, 5.250; $P = 0.054$) is the risk factor for mortality of the patients [Table 4]. The mortality rate between HAI and CAI were similar (OR, 0.813; $P = 0.831$).

Discussion

hvKP, is a dreaded variant of *K. pneumoniae*, newly emerged and clinically significant. This pathogen causes life-threatening

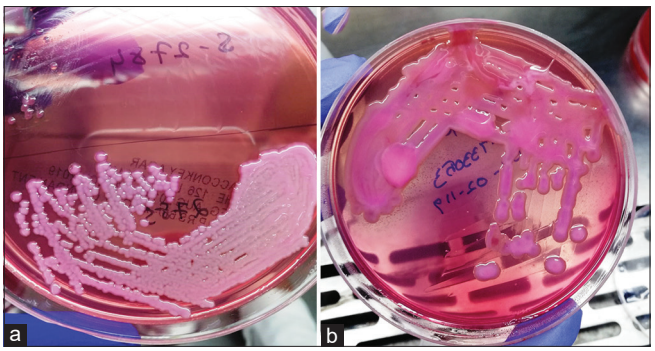

Figure 1: Depiction of (a) classical *Klebsiella pneumoniae* and (b) hypermucoviscoid *Klebsiella* on the agar plate

Table 1: Basic and clinical characteristics of the study patents

Characteristics	*n* (%) or mean±SD
Gender	
Male	24 (75)
Female	8 (25)
Age (years), range	54.2±15.6 (20-77)
Diabetes	19 (59.4)
Hypertension	14 (43.8)
COPD	3 (9.4)
Intubated	23 (71.9)
Tracheostomy	11 (34.4)
Central venous catheterization	27 (84.4)
Foleys Cather use	26 (81.3)
Infection type	
Hospital acquired	22 (68.8)
Community acquired	10 (31.2)
hvKP positive culture samples	
Blood	9 (28.1)
Urine	2 (6.1)
Tissue	4 (12.5)
Tracheal secretion	16 (50)
Bile	1 (3.1)
PUS	2 (6.3)
Patient outcome	
Discharged	10 (31.3)
Dead	18 (56.2)
Discharge against medical advice	4 (12.5)

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, hvKP: Hypermucoviscoid klebsiella

Table 2: Antibiotic sensitivity pattern of hypermucoviscoid *Klebsiella* isolates in our study

Antibiotic name	Sensitivity (*n*=32), *n* (%)
Colistin	29 (90.6)
Tigecycline	11 (24.4)
Aminoglycosides	15 (46.9)
Carbapenems	12 (37.5)
β-lactam-β-lactamase inhibitor	9 (28.1)
Cephalosporin	10 (31.3)
Chloramphenicol	15 (46.9)
Co-trimoxazole	11 (34.4)

infections in both healthy and immunocompromised patients.[14-17] So far, fewer cases were reported from the community. This study was designed to look at the type and characteristics of the infections.

Half of the patients with hvKP infections are young or do not have co-morbidities, most hvKP infections are CAI which is unusual in *K. pneumoniae*, which are generally nosocomial infections in patients with immunosuppression.[18] In our study, we observed that CAI was 32% and HAI was 68%, which is an alarming message that the rate of HAI is increasing with this variant.

hvKP infections are associated with a higher mortality rate, in our study, we found that the attributable mortality to hvKP infection was

Table 3: Univariate logistic regression analysis to predict factors influencing hypermucoviscoid *Klebsiella* resistance to antibiotics

Predictors	Logit (B)	SE	Wald	*P*	OR	95.0% CI
Age (years) ≥55	−2.208	1.149	3.695	0.055	0.110	0.012-1.044
Female	0.770	0.888	0.752	0.386	2.160	0.379-12.316
Diabetes	−1.012	0.917	1.217	0.270	0.364	0.060-2.194
Hypertension	0.424	0.841	0.254	0.614	1.528	0.294-7.945
Intubation	−0.272	0.934	0.085	0.771	0.762	0.122-4.751
Tracheostomy	1.684	1.149	2.148	0.143	5.385	0.567-51.172
CVC	−0.388	1.202	0.104	0.747	0.679	0.064-7.161
Foleys catheter	0.460	0.985	0.218	0.641	1.583	0.230-10.904
Dialysis	−1.012	0.917	1.217	0.270	0.364	0.060-2.194
HAI	2.069	0.914	5.121	0.024*	7.917	1.319-47.512

**P* value is significant at 0.05 level. CVC: Central venous catheter, HAI: Hospital acquired infection, SE: Standard error, OR: Odds ratio, CI: Confidence interval

Table 4: Univariate logistic regression analysis to predict factors influencing mortality of hypermucoviscoid *Klebsiella* infection

Predictors	Logit (B)	SE	Wald	*P*	OR	95.0% CI
Age (years) ≥55	0.000	0.789	0.000	1.000	1.000	0.213-46.693
Female	0.405	0.893	0.206	0.650	1.500	0.261-8.636
Diabetes	1.658	0.859	3.725	0.054	5.250	0.975-28.278
Hypertension	1.070	0.837	1.634	0.201	2.917	0.565-15.054
Intubation	1.204	0.904	1.775	0.183	3.333	0.567-19.593
Tracheostomy	0.934	0.927	1.016	0.313	2.545	0.414-15.652
CVC	0.693	1.090	0.405	0.525	2.000	0.236-16.928
Foleys catheter	1.674	0.990	2.862	0.091	5.333	0.767-37.093
Dialysis[#]	20.866	-	0.000	0.999	-	0.000
HAI	−0.431	0.950	0.206	0.650	0.650	0.101-4.181
Drug resistance	−0.208	0.976	0.045	0.831	0.813	0.120-5.499

[#]All 4 patients were died in the dialysis group, hence no comparison happened. CVC: Central venous catheter, HAI: Hospital acquired infection, SE: Standard error, OR: Odds ratio, CI: Confidence interval

56.2%, which is higher than the previous reports ranging from 3% to 42%[15,18-22] and this can be one of the indicators for independent predictor of mortality. A simple "string test" can be used to determine the hypermucoviscosity of the phenotype. The string test is positive when a viscous string >5 mm in length [Figure 2] is formed by stretching bacterial colonies on an agar plate.[6]

The non-effectiveness of the therapy for nosocomial infections and sepsis is mainly due to antibiotic resistance. According to the WHO report, the antibiotic resistance of *K. pneumoniae* strains is associated mainly with the production of ESBL and it was included in the most dangerous superbugs.[23] But the antibiotic resistance of hvKP is mainly due to the hypermucoviscous, it is typically produced by the bacteria by overproduction of polysaccharide capsule.[17] Whereas, *K. pneumoniae* strains are hypervirulent, but not hypermucoviscous.[24] Unlike *K. pneumoniae*, hvKP can cause serious CAI even in healthy individuals.[25] However, in our study we found more HAI infections than CAI.

Table 5: Antibiotics resistance pattern of extreme drug resistance, pan drug resistance, extended-spectrum beta-lactamase and multidrug resistance patients, and their corresponding minimal inhibitory concentration values as per CLSI

n=23	AMI (>32)	TOB (>8)	CFZ (>32)	NOR (>8)	CIP (>2)	GEN (>2)	COL (>4)	CHL (>18)	CFP (>16)	IMI (>16)	MER (>16)	CFT (>32)	ERT (>4)	TG (>2)	AMP (>16)	CXT (>32)	TR-SM (>8/152)	PC-TB (>64/4)	AM-CA (>16/8)
X-1	S	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-2	R	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	S	R	R
X-3	R	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R
X-4	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-5	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-6	R	R	R	R	R	R	S	R	R	R	R	R	R	I	R	R	R	R	R
X-7	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-8	R	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R	R
X-9	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	S	R	R
X-10	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-11	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-12	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-13	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
X-14	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R	R	R
X-15	R	R	R	R	R	R	S	R	R	R	R	R	R	S	R	R	R	R	R
X-16	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R	R	R
X-17	R	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R
E-1	R	R	R	R	R	R	S	S	R	S	S	R	S	S	R	S	R	S	R
E-2	S	R	R	R	S	S	S	S	I	S	S	R	S	NT	R	R	R	S	R
E-3	S	S	R	R	S	S	S	S	R	S	S	R	S	S	R	S	S	S	R
P-1	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
P-2	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
M-1	S	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R	R

MIC value for colistin sensitivity is <1 for all sensitive patients except X-7 (<0.5); MIC value for amikacin sensitivity is <4 for all sensitive patients; MIC value for imipenem sensitivity is <0.5, for meropenem is <0.125 and for ertapenem is <0.125 for all sensitive patients; MIC value for tigecycline sensitivity is <1 and for intermediate is 2. MIC value for trimethoprim-sulfamethoxazole is <1/19 for all sensitive patients; MIC value for piperacillin-tazobactam is 16/4 for E-1 and 4/4 for E-2 and E-3; MIC value for cefepime intermediate sensitivity is 8; MIC vale for chloramphenicol sensitivity is <8; MIC values for resistance is mentioned adjacent to antibiotics headers. X: Extreme drug resistance, P: Pan drug resistance, M: Multidrug resistance, I: Intermediate resistance, NT: Not tested, MIC: Minimal inhibitory concentration; AMI: Amikacin; TOB: Tobramycin; CFZ: Cefazolin; NOR: Norfloxacin, CIP: Ciprofloxacin, GEN: Gentamicin, COL: Colistin, CFP: Cefepime, IMI: Imipenem, MER: Meropenem, CFT: Ceftriaxone, ERT: Ertapenem, TG: Tigecycline, CXT: Cefoxitin, AMP: Ampicillin, TR/SM: Trimethoprim/sulfamethoxazole, PC/TB: piperacillin/tazobactam, AM/CA: Amoxicillin/clavulanic acid, CLSI: Clinical & Laboratory Standards Institute

The high prevalence of antibiotic resistance is more common in conventional *K. pneumoniae*, whereas the prevalence of antibiotic resistance in hvKP isolates is rare.[16,17] But in our study, 75% (n = 24) had drug-resistance hvKP, out of whom 53.1% (n = 17) were XDR, 9.4% (n = 3) were ESBL producing type, 6.3% (n = 2) was pan resistance, 3.1% (n = 1) was MDR and 1 was colonizer. The antibiotic resistance pattern of all resistance isolates in our present study is described in Table 5 and the clinical profile of all resistant isolates are presented in Table 6. Lee *et al*.,[18] in their review, reported that the antibiotic-resistance are increasingly being reported for hvKP isolates across the world, most commonly in countries with an epidemic dissemination of hvKP, which correlates with our study.

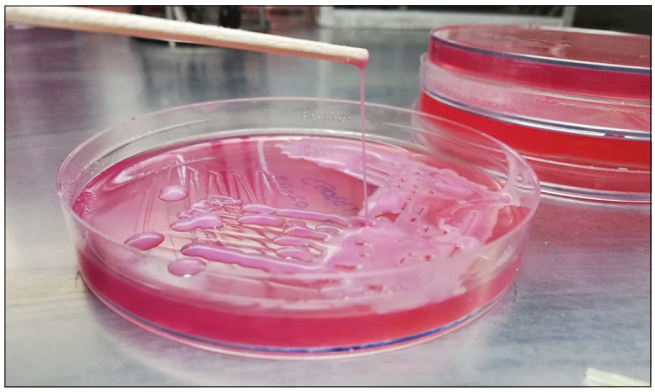

Figure 2: String test showing the length of string >5 mm in hypermucoviscoid klebsiella

Twenty-five percentage of patients had pan sensitive, out of whom 4 patients were dead (50%), which imply that *in vitro* sensitivity did not correlate with the *in vivo* scenario. This might be the indicator, that the existing antibiotic strategy might not be adequate enough to penetrate the thick mucoid layer.

We found, about 90% of hvKP isolates are sensitive to colistin in our study, however 2 (6.3%) isolates were pan resistant, which is a major concern. The antibiotic resistance is a multifactorial complex process.[26]

Studies from different regions reported lower rate of hvKP incidence than in Asia. A study in Spain reported 5.4% of hypermucoviscosity phenotype,[27] a Canadian study reported 8.2% of hvKP from patients with community-acquired bacteremia.[28] Similarly, 6.7% of isolates from Brazil[29] and 9.2% of isolates from Algeria were reported in the literature.[30] All the above results are supporting that the incidence and spread of hvKP are more common in the Asian region. Our study showed 19.4% hvKP among the *Klebsiella* isolates from the patients got admitted under MICU for different medical conditions.

Table 6: Clinical profile of all resistant isolates

ID	Age/sex	Culture	Clinical details	Outcome
X-1	51/male	Blood	Postcardiac arrest, secondary to STEMI with refractory septic shock	Dead
X-2	62/male	Trachea	Medullary hemangioblastoma, meningitis, VAP	Discharge
X-3	55/male	Trachea	DM, left lower limb diabetic foot with sepsis and septic shock, s/p debridement, respiratory failure	DAMA
X-4	20/male	Trachea	Severe necrotizing pancreatitis with refractory septic shock, multiorgan failure	Dead
X-5	51/male	Trachea	Advanced COPD, respiratory failure secondary to pneumonia	Dead
X-6	24/male	PUS	Necrotizing pancreatitis, right side empyema with pleura parenchymal fistula	Dead
X-7	47/male	Trachea	DM, HTN, CAD, CKD on maintenance HD, s/p cardiac arrest, pulmonary TB with respiratory failure	Discharge
X-8	70/male	Tissue	DM, HTN, malignancy MCA infarct, s/p cardiac arrest with anoxic encephalopathy, Grade IV bed sore, septic shock	DAMA
X-9	56/male	Tissue	CKD on maintenance HD, rhinocerebral mucormycosis	Dead
X-10	52/female	Trachea	Cardioembolic stroke and brain stem infarct with respiratory failure on mechanical ventilation	Dead
X-11	23/male	Trachea	Acute necrotizing pancreatitis status postpancreatic necrosectomy.	Discharge
X-12	77/male	Trachea	DM, HTN, old pulmonary koch's with TB sequelae, hydropneumothorax s/p intercostal drain	Dead
X-13	57/female	Trachea	Alzheimer's disease, recent H1N1 pneumonia, DVT with HCAP and gastroenteritis	Discharge
X-14	73/male	Tissue	Atypical Parkinson's, Grade IV bed sore infected, septic shock	Dead
X-15	43/male	Blood	DM, acute myeloid leukemia-relapse with ischemic stroke and fungal pneumonia	Dead
X-16	22/male	Trachea	Autoimmune encephalitis and seizures. Intubated in view of seizures and extubated after 6 days of ventilator support	Discharge
X-17	52/male	Blood	Morbid obesity, severe ARDS secondary to H1N1 pneumonia and rhabdomyolysis, sudden cardiac arrest secondary to massive pulmonary embolism	Dead
E-1	54/female	Blood	Hepatitis-C, CKD on maintenance HD, catheter related blood stream infection	Discharge
E-2	46/male	Trachea	DCLD, bilateral lower limb cellulitis, septic shock, respiratory failure on ventilator	Dead
E-3	55/male	Tissue	Diabetic foot with sepsis, s/p debridement	Discharge
P-1	77/male	Blood	Parkinson's, CKD on maintenance HD, recurrent UTI, catheter related blood stream infection	Dead
P-2	58/male	Blood	Old SAH, bed ridden status, pneumonia with Respiratory failure	Dead
M-1	62/female	Trachea	Massive intracerebral bleed, s/p decompression, Grade III bed sore	Discharge

STEMI: ST-segment-elevation MI, CKD: Chronic kidney disease, HD: Hemodialysis, s/p: Status post, SAHL: Subarachnoid hemorrhage, DAMA: Discharge against medical advice, UTI: Urinary tract infection, ARDS: Acute respiratory distress syndrome, HCAP: Healthcare-associated pneumonia, DVT: Deep vein thrombosis, DM: Diabetes mellitus, HTN: Hypertension

Limitations of the study

This study did not compare the clinical characteristics and outcome of hvKp with conventional *Klebsiella*.

Conclusions

Our study results showed, increased incidence of HAI with hvKP predominantly associated with pneumonia and increase in trend of drug resistance with two cases being pan resistant. The mortality rate in hvKP was higher than *Klebsiella* and it was similar in pan sensitive and drug resistant hvKP. It requires a simple technique (string test) to detect hvKP, and advisable to include this technique in the routine clinical practice since hvKP has higher attributable mortality. More number of studies are required to evaluate the existing antibiotics strategy and steps to curb the spread of this dreaded infection.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require the Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is NHH/MEC-CL-2018-501. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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Conflicts of interest

There are no conflicts of interest.

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