



# Risk Factors for Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections: A Case-Control Study

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## ABSTRACT

**Background:** Carbapenem resistant (CR) *Klebsiella pneumoniae* (KP) are an emerging medical concern. Reported risk factors for infection with CR KP include higher severity of illness, increased length of stay, and intensive care unit (ICU) stay. Some evidence indicates that cumulative antibiotic exposure may be more important to the development of CR *Enterobacteriaceae* infection than the use of any specific antibiotic class.

**Methods:** A case-control study was conducted of patients at Temple University Hospital during 6/2006 – 10/2010. Case group inclusion criteria included a positive blood culture for CR KP, first episode of CR KP bacteremia, and age  $\geq$  18 years. Exclusion criteria included lack of clinical evidence of infection and hospitalization  $\leq$  72 hours. Controls were matched to cases by date and hospital unit. The primary objective was to determine independent risk factors for developing CR KP bacteremia. The secondary objective was to determine specific antibiotic classes associated with infection. Univariate and multivariate analyses were used to analyze the data.

**Results:** 44 case patients were identified and matched accordingly. Antibiotics associated with CR KP bacteremia included cephalosporins, penicillins, carbapenems, fluoroquinolones, metronidazole, and vancomycin, but none were significant on multivariate analysis. Independent risk factors for CR KP bacteremia included the number of antibiotics used in the past 90 days (OR 3.92 [CI 1.60-9.67]), increased length of stay (OR 1.07 [1.03-1.12]), and mechanical ventilation (OR 6.64 [CI 1.16-38.12]). 45% of cases died, as compared to 18% of controls [OR 3.8 (CI 1.4-9.9)].

**Conclusion:** Risk factors identified in this study were similar to those reported in the literature. Overall antibiotic exposure was a stronger predictor of CR KP bacteremia than any individual drug class. The findings support the importance of antibiotic stewardship to limit drug resistance.

## INTRODUCTION

Carbapenem resistance is often the result of *Klebsiella* producing carbapenemase (KPC) production. Associated mortality is high ( $\geq$  50%).<sup>1</sup>

KPC producing *Klebsiella pneumoniae* (KP) infection is associated with beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones, and carbapenems.<sup>2</sup>

Some studies indicate that cumulative antibiotic exposure may be more important than any specific antibiotic exposure in regards to the risk of developing infection with a CR pathogen.<sup>3,4</sup>

## OBJECTIVES

Primary - Determine independent risk factors for developing CR *Klebsiella* bacteremia

Secondary - Determine if exposure to specific antibiotic classes predisposes patients to CR *Klebsiella* bacteremia

## METHODS

### Study Design

- IRB approved, single center, retrospective chart review
- Patients admitted to Temple University Hospital (TUH) during the period of July 2006 – October 2010

Case patients were identified as follows:

**Inclusion Criteria**

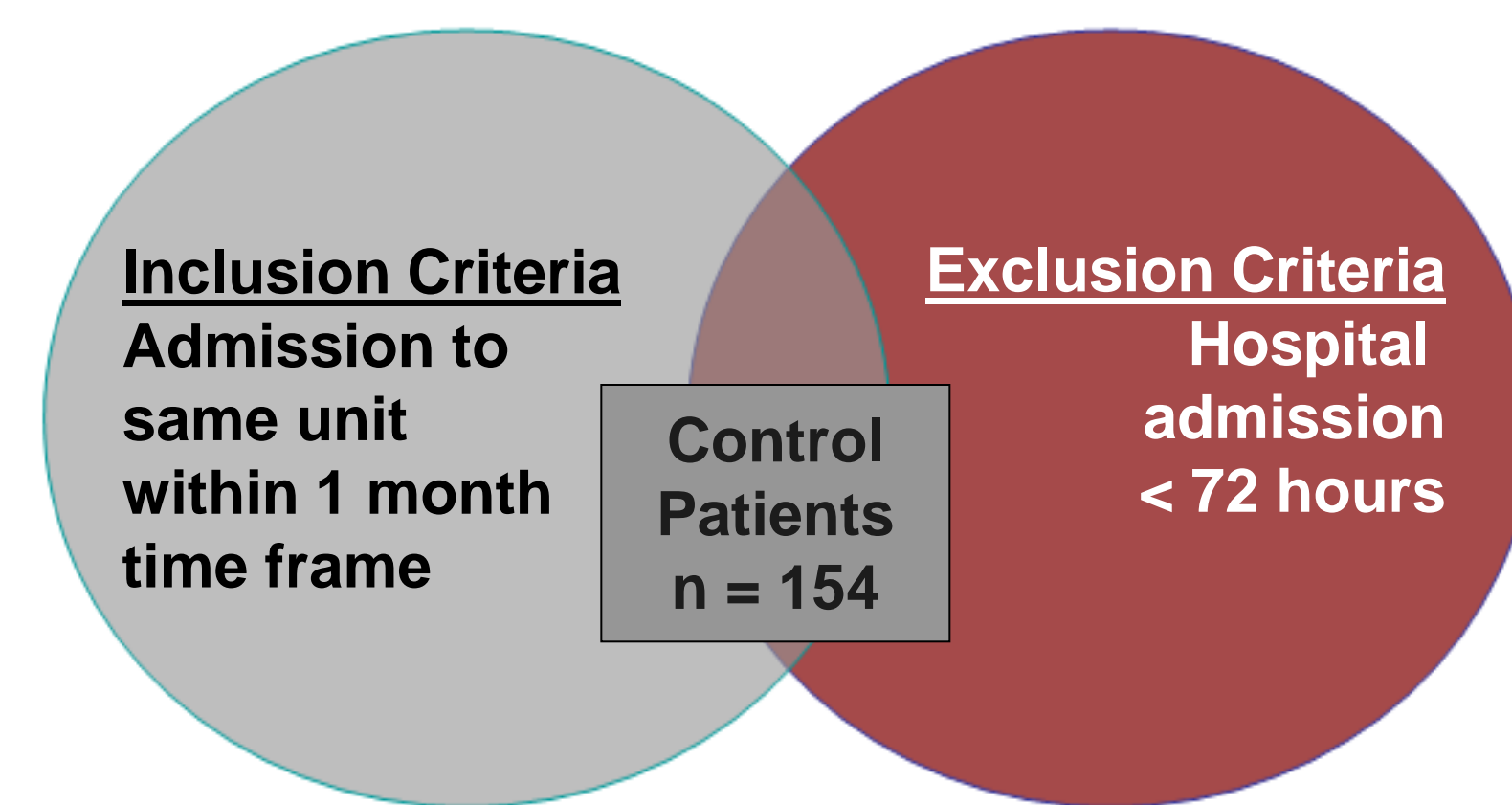
- Adults > 18 years of age
- Positive blood culture for *K. pneumoniae*
- First episode of *K. pneumoniae* bacteremia

**Exclusion Criteria**

- Patients without clinical evidence of infection
- Recurrent *K. pneumoniae* bacteremia

***K. pneumoniae* resistant to carbapenems**  
n = 44

Control patients were matched to case patients on a 1 to 1 basis:



## STATISTICAL ANALYSIS

Using univariate and multivariate analysis, patients with CR KP infections were compared to controls.

## RESULTS

Table 1: Baseline Characteristics

	KPC Group (n=44)	Control Group (n=44)
Male (%)	61	61
Age (yrs)	56 $\pm$ 15	58 $\pm$ 18
Body Mass Index (kg/m <sup>2</sup> )	33 $\pm$ 12	30 $\pm$ 10
Charlson Comorbidity Index	3 $\pm$ 2	3 $\pm$ 3
Pulmonary Disease (%)	50	41
Cardiovascular Disease (%)	55	57
Diabetes (%)	32	34
Immunocompromised (%)	18	16
Recent Hospital Admission (%)	43	25
Recent ICU Admission (%)	32	9
Antibiotic use in past 90 days (%)	41	15

Table 2: Inpatient Characteristics

	KPC Group (n=44)	Control Group (n=44)
Admitted from (%):		
Home	59	70
Long Term Care	18	5
Outside Hospital	23	25
Mechanical Ventilation (%)	84	34
Dialysis (%)	27	18
Urinary Catheterization (%)	80	52
Central Venous Catheter (%)	75	41
Length of Hospital Stay (days)	54 $\pm$ 39	19 $\pm$ 13
Length of Stay in Intensive Care (days)	22 $\pm$ 21	7 $\pm$ 11
Inpatient No. Antibiotic Classes	5	3
Inpatient Total Antibiotic Days	27 $\pm$ 24	10 $\pm$ 11
Pitt Bacteremia Score	4 $\pm$ 3	-
APACHE II Score	19 $\pm$ 7	-
Mortality (%)	45	18

## RESULTS (Cont.)

Table 3: Significant Risk Factors by Univariate Analysis

	Odds Ratio	Confidence Interval
Recent ICU Admission	4.7	1.4-15.6
Antibiotics in Past 90 Days	2.8	1.1-7.3
No. Antibiotics in Past 90 Days	1.6	1.1-2.5
4 <sup>th</sup> Generation Cephalosporins in Past 90 Days	3.0	1.1-8.3
Length of Hospital Stay	1.1	1.0-1.1
Length of ICU Stay	1.1	1.0-1.1
Antifungal Therapy	5.1	2-13
Inpatient Total Antibiotic Days	1.1	1.0-1.1
Inpatient No. Antibiotic Classes	1.4	1.1-1.6
Penicillin Class Therapy	3.1	1.3-7.3
Duration of Penicillin Class Therapy	1.1	1.1-1.2
Duration of Carbapenem Therapy	1.1	1.0-1.2
Duration of Fluoroquinolone Therapy	1.1	1.0-1.2
Metronidazole Therapy	4.5	1.7-11.8
Duration of Metronidazole Therapy	1.1	1.0-1.2
Vancomycin Therapy	4.1	1.6-10.3
Duration of Vancomycin Therapy	1.1	1.0-1.1
Mechanical Ventilation	10.2	3.7-28.3
Urinary Catheterization	3.6	1.4-9.1
Central Venous Catheter	4.3	1.7-10.8

Table 4: Significant Risk Factors by Multivariate Analysis

	Odds Ratio	Confidence Interval
No. Antibiotic Classes in Past 90 Days	3.9	1.6-9.7
Length of Hospital Stay	1.1	1.0-1.1
Mechanical Ventilation	6.6	1.2-38.1

## DISCUSSION

In this study, antibiotics associated with CR KP bacteremia included cephalosporins, penicillins, carbapenems, fluoroquinolones, metronidazole, and vancomycin.

No specific antibiotic class was found to be an independent risk factor for CR KP bacteremia.

## DISCUSSION (Cont.)

The number of antibiotics administered in the past 90 days was identified as an independent risk factor for the development of CR KP bacteremia. Length of stay and mechanical ventilation were also independent risk factors for CR KP bacteremia.

In the CR group 45% of patients died, as compared to 18% in the control group [OR 3.8 (CI 1.4-9.9)]

Limitations of the study include:

- Retrospective, single center design
- Inability to identify mechanisms of resistance
- Lack of outside hospital records, especially regarding antibiotic exposure

## APPLICATION

► Risk factors associated with CR KP bacteremia were similar to reported risk factors for extended spectrum beta-lactamase (ESBL) producing pathogens. This makes differentiation of patients at risk for CR KP infection difficult, which in turn complicates the initiation of appropriate empiric therapy.

► Local resistance patterns and individual patient history must be evaluated when treating patients empirically.

► The importance of antibiotic exposure to the development of these multi-drug resistant infections reinforces the rationale behind antimicrobial stewardship.

## DISCLOSURES

Jason Gallagher: Has received funding from Merck.  
Safia Kuriakose: No conflicts of interest to disclose.

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