

ABSTRACT

Background:

Since 2006, *Klebsiella pneumoniae* increasingly harbors extended spectrum β -lactamases (ESBL) or carbapenem resistance in our institution. We describe characteristics and outcomes in patients with hematological malignancies and blood stream infections (BSI) due to multi-drug resistant (MDR) *Klebsiella pneumoniae*.

Methods:

Retrospective observational study comparing all cause 30-day mortality in patients with MDR vs. non-MDR *Klebsiella pneumoniae* BSI

Results:

Univariate analysis showed presence of MDR isolates and neutropenia at the time of diagnosis to be statistically associated with 30-day mortality. The association of MDR isolates and mortality was confirmed by Kaplan-Meier analysis (Log-Rank 15.20, $p < 0.0001$). Multivariate analysis showed the resistance pattern to remain highly significant. HR 6.02 (95% CI 1.82 – 21.20)

Conclusions:

MDR *Klebsiella pneumoniae* BSI appear to be associated with significantly higher mortality than non-MDR *Klebsiella pneumoniae* BSI.

INTRODUCTION

- The use of β -lactam antibiotics for more than 60 years has resulted in a dramatic increase in antibiotic resistant bacteria.
- Of increasing concern is the appearance of Enterobacteriaceae harboring ESBLs and carbapenem resistance particularly in *Klebsiella pneumoniae*.¹
- The impact of MDR bacterial infections on outcomes has been demonstrated in some settings, however little is known about outcomes for BSI with these bacteria in patients with hematological malignancies.^{2,3}

PATIENTS AND METHODS

- Retrospective cohort study performed at the Cleveland Clinic, a 1,400 bed academic tertiary care hospital in Cleveland, OH between January 1st 2005 and December 31st 2011.
- Inclusion Criteria: *Klebsiella pneumoniae* BSI in any patient age ≥ 17 , with a hematological malignancy (lymphoma, leukemia) or hematopoietic stem cell transplant (HSCT).
- Susceptibility Testing: VITEK 2 system bioMérieux with the GN58 card for antibiotic susceptibility testing) with susceptibility breakpoints according to the Clinical and Laboratory Standards Institute guidelines.⁴
- Detection of ESBLs: VITEK 2 ESBL test
- Definitions:
 - Carbapenem resistance: isolates with resistant minimal inhibitory concentration (MIC) to meropenem or imipenem by VITEK or with intermediate MIC to carbapenems but positive Modified Hodge Test⁵
 - MDR: presence of ESBLs or carbapenem resistance
 - Nosocomial infections were determined according to CDC definitions.⁶
 - Severity of illness during the onset of BSI was calculated by means of the Pitt bacteremia score.⁷
 - Poly-microbial bacteremia: >1 pathogen isolated from one or more blood cultures within 7 days after the index blood culture. Single isolates for coagulase-negative *Staphylococcus* were considered contaminants.
- Primary outcome: all cause mortality within 30 days from the index blood culture.
- Categorical values were compared using the Chi² test and continuous values using the Mann-Whitney U test.

RESULTS

- Patients with MDR *Klebsiella pneumoniae* had longer duration of BSI, were more likely to receive inappropriate empiric treatment, had longer times to appropriate therapy, and were more likely to have *Klebsiella pneumoniae* isolated from other sites than patients with non-MDR *Klebsiella pneumoniae* BSI.
- Variables significantly associated with all cause 30-day mortality on univariate analysis:
 - Leukemia/lymphoma patients not receiving HSCT
 - Neutropenia at the time of diagnosis
 - BSI with MDR *Klebsiella pneumoniae* (41.7% vs 8.8%; $p = 0.0005$)
- Multivariate proportional hazards analysis incorporating those variables found to be significant in univariate analysis showed BSI with MDR *Klebsiella pneumoniae* isolates to remain highly associated with all cause 30-day mortality (HR 6.02 95% CI 1.8 – 21.2).

Table 1. Baseline characteristics according to resistance pattern.

Characteristic	MDR <i>Klebsiella pneumoniae</i> (n=24)	non-MDR <i>Klebsiella pneumoniae</i> (n=80)	TOTAL (n=104)	p value
Male Gender	12/24 (50%)	40/80 (50%)	52/104 (50%)	NS
Age in years [median (range)]	52 (21 - 75)	56 (17 - 79)	56 (17 - 79)	NS
HSCT	7/24 (29.2%)	41/80 (51.3%)	48/104 (46.2%)	NS
GVHD	7/7 (100%)	9/41 (22.0%)	16/48 (33.3%)	$p=0.0002$
Nosocomial Infection	17/24 (70.8%)	48/80 (60%)	65/104 (62.5%)	NS
Polymicrobial	5/24 (20.8%)	21/80 (26.3%)	26/104 (25%)	NS
<i>Klebsiella</i> at Other Sites	10/24 (41.7%)	13/80 (16.3%)	23/104 (22.1%)	$p=0.0127$
PITT Score [median (range)]	3 (0 - 10)	3 (2 - 12)	3 (0 - 12)	NS
Duration of BSI [median (range)]	2.5 (0 - 21)	1 (0 - 8)	1 (0 - 21)	$p=0.0006$
ID Consult	18/23 (78.3%)	59/73 (80.8%)	77/96 (80.2%)	NS
30-DAY-RECURRENCE	2/24 (8.3%)	5/80 (6.3%)	7/104 (6.7%)	NS
NEUTROPENIA				
Neutropenia	18/24 (75%)	54/80 (67.5%)	72/104 (69.2%)	NS
Neutropenia days prior to BSI [median (range)]	3 (-1 - 76)	3 (-3 - 58)	3 (-3 - 76)	NS
Total Neutropenia Days [median (range)]	8.5 (0 - 67)	9 (0 - 80)	9 (0 - 80)	NS
CENTRAL LINE				
CVC	20/23 (87%)	73/79 (92.4%)	93/102 (91.2%)	NS
CVC Removal	15/23 (65.2%)	51/79 (64.6%)	66/102 (64.7%)	NS
Days to CVC Removal [median (range)]	3 (1 - 8)	3 (0 - 20)	3 (0 - 20)	NS
SOURCE				
GI	4/24 (16.7%)	10/80 (12.5%)	14/104 (13.5%)	NS
Line	5/24 (20.8%)	20/80 (25%)	25/104 (24%)	NS
Primary	12/24 (50%)	48/80 (60%)	60/104 (57.7%)	NS
SSTI	2/24 (8.3%)	0/80 (0%)	2/104 (1.9%)	NS
GU	1/24 (4.2%)	1/80 (1.3%)	2/104 (1.9%)	NS
CNS	0/24 (0%)	1/80 (1.3%)	1/104 (1.0%)	NS
TREATMENT				
Appropriate Empiric Rx	11/23 (47.8%)	76/78 (97.4%)	87/101 (86.1%)	$p<0.0001$
Days to Appropriate Rx [mean (range)]	2 (-4 - 10)	0 (0 - 3)	0 (-4 - 10)	$p<0.0001$

Data are n(%), unless otherwise stated. NS: not statistically significant

Table 2. Univariate Analysis for 30-day all cause mortality

Characteristic	30-Day-Mortality		p value
	YES (n=17)	NO (n=87)	
Gender (male)	6/17 (35.3%)	46/87 (52.9%)	NS
Age [median, (range)]	51 (21 - 75)	56 (17 - 79)	NS
HSCT	2/17 (11.8%)	46/87 (52.9%)	$P=0.0026$
GVHD	1/2 (50.0%)	15/46 (32.6%)	NS
MDR <i>Klebsiella pneumoniae</i>	10/17 (58.8%)	14/87 (16.1%)	$P=0.0005$
Nosocomial Infection	12/17 (70.6%)	53/87 (60.9%)	NS
Polymicrobial	5/17 (29.4%)	21/87 (24.1%)	NS
<i>Klebsiella pneumoniae</i> at Other Sites	3/17 (17.6%)	20/87 (23.0%)	NS
PITT Score [median, (range)]	3 (2 - 10)	3 (0 - 12)	NS
Duration of BSI [median, (range)]	1 (0 - 21)	1 (0 - 10)	NS
ID Consult	11/14 (78.6%)	66/82 (80.5%)	NS
30-DAY-RECURRENCE	0/17 (0%)	7/87 (8.0%)	NS
NEUTROPENIA			
Neutropenia @ Dx	16/17 (94.1%)	56/87 (64.4%)	$p=0.0192$
Neutropenia days prior to BSI [median, (range)]	3 (-1 - 77)	3 (-3 - 43)	NS
Total neutropenia days [median, (range)]	7 (0 - 79)	9 (0 - 80)	NS
CENTRAL LINE			
CVC @ Dx	13/16 (81.3%)	80/86 (93.0%)	NS
CVC Removal	8/16 (50.0%)	58/86 (67.4%)	NS
Days to CVC Removal [median, (range)]	2 (1 - 7)	3 (0 - 20)	NS
SOURCE			
GI	4/17 (23.5%)	10/87 (11.5%)	NS
Line	2/17 (11.8%)	23/87 (26.4%)	NS
Primary	10/17 (58.8%)	50/87 (57.5%)	NS
SSTI	1/17 (5.9%)	1/87 (1.1%)	NS
GU	0/17 (0%)	2/87 (2.3%)	NS
CNS	0/17 (0%)	1/87 (1.1%)	NS
TREATMENT			
Appropriate Empiric Rx	12/16 (75%)	75/85 (88.2%)	NS
Days to Appropriate Rx [median, (range)]	1 (-4 - 5)	0 (0 - 10)	NS

Data are n(%), unless otherwise stated. NS: not statistically significant

Figure 1. Kaplan-Meier 30-day survival curve

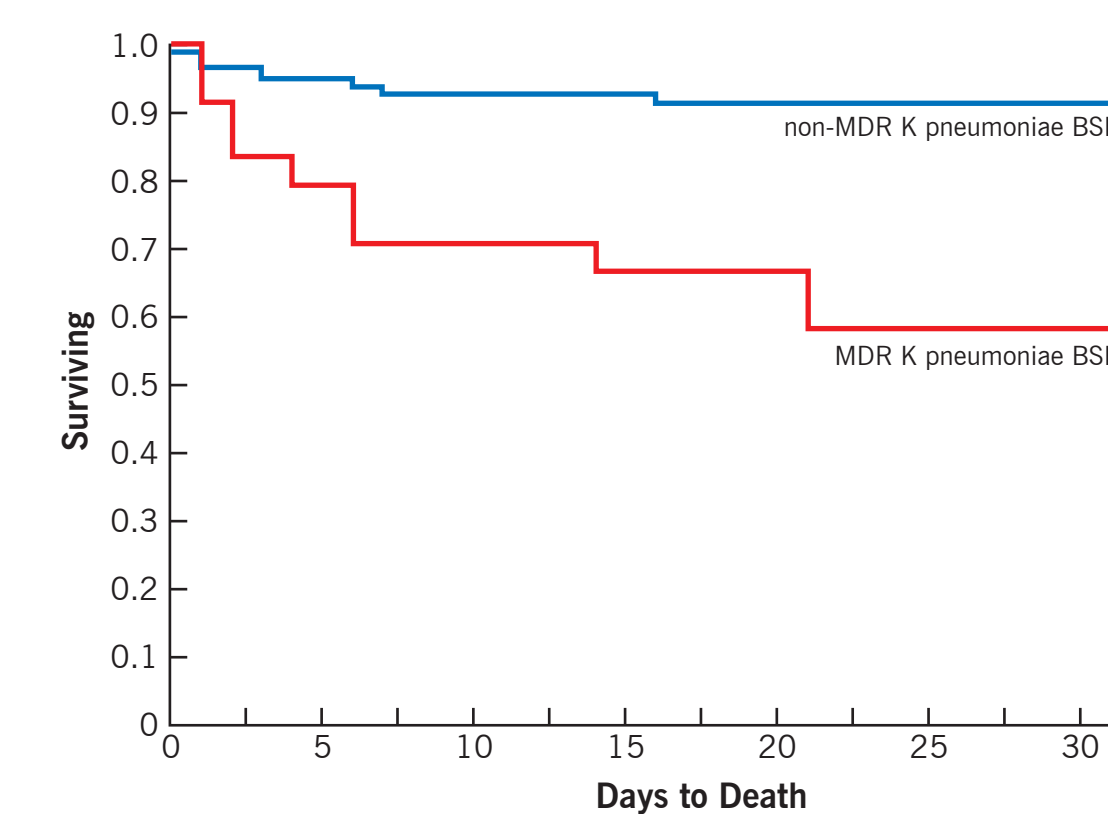
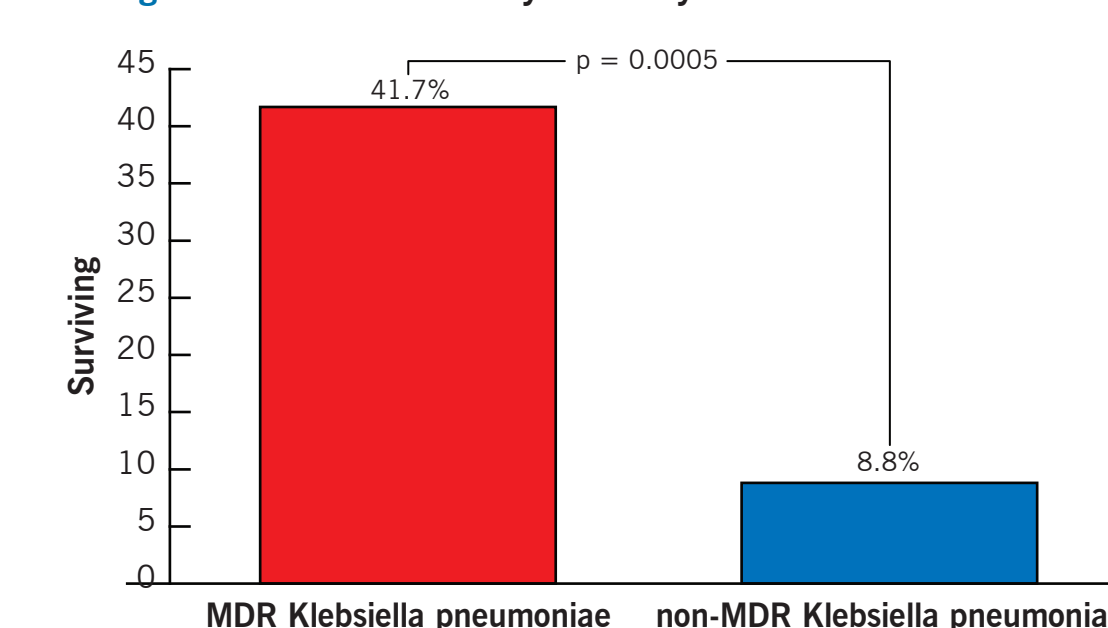


Table 3. Multivariate logistic regression analysis for 30-Day mortality.

Source	Chi ²	p value	OR	Lower 95%	Upper 95%
Non-HSCT Dx	3.853	0.0496	4.46	1.002	31.551
Neutropenia	2.937	0.0866	5.13	0.814	100.863
MDR <i>Klebsiella</i>	8.627	0.0033	6.02	1.818	21.192

Figure 2. All Cause 30-day Mortality



CONCLUSIONS

- MDR *Klebsiella pneumoniae* BSI appear to be associated with significantly higher mortality than non-MDR *Klebsiella pneumoniae* BSI.
- Patients with MDR *Klebsiella pneumoniae* BSI were more likely to have received inappropriate initial antibiotic therapy, longer duration of BSI, and longer time to appropriate treatment than patients with on-MDR *Klebsiella pneumoniae* BSI; however these variables did not have a statistically significant association with 30-day mortality.

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