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Healthcare Outcomes and Resource Utilization Associated with Colistin or Tigecycline Use in Patients with Multidrug-Resistant *Acinetobacter baumannii*

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Abstract

Background: Multidrug-resistant *Acinetobacter baumannii* (MDR AB) infections continue to spread worldwide and are considered a serious antimicrobial resistance threat. Several studies examine the burden of MDR AB; few explore treatment-specific outcomes. We examined a large database to assess outcomes and resource utilization associated with tigecycline (TIG) or colistin (COL) use in MDR AB patients.

Methods: Data was derived from the Premier Hospital Database, a US hospital administrative database containing hospital discharge data files, including diagnoses and procedures categorized by ICD-9 codes, medications, and cost data. Analysis was limited to 152 hospitals reporting microbiology data. Patients were included if admitted as inpatients January 1, 2009 – June 30, 2014, had documented MDR AB with primary diagnosis of pneumonia or sepsis, received TIG or COL (but not both) treatment post-specimen date, and were treated for ≥3 days.

Results: 547 patients were eligible for analysis; 126 pneumonia (72 TIG, 54 COL) and 421 sepsis (292 TIG, 129 COL). Unadjusted, all-cause in-hospital mortality among pneumonia patients was 23.6% (TIG) and 18.5% (COL). Mean length of stay (LOS) was 18.26 and 21.98 days; mean hospital costs were $51,277 and $54,694; percent of patients requiring intensive care unit (ICU) was 76.4% vs. 59.3% for TIG and COL cohorts, respectively. Acute renal failure occurred in 12.5% of TIG and 25.9% of COL patients. 30-day readmission rates were 27.8% and 42.6% for patients treated with TIG and COL, respectively. Mortality among sepsis patients was 17.8% (TIG) and 21.7% (COL). Mean LOS was 21.70 and 22.41 days; mean hospital costs were $59,340 and $64,119; percentage of patients requiring ICU was 71.2% and 76.0%. Acute renal failure occurred in 7.5% of TIG and 14.0% of COL patients. 30-day readmission rates were 38.0% and 37.2% for patients treated with TIG and COL, respectively.

Conclusion: MDR AB patients treated with TIG or COL have high mortality and substantial resource utilization, including high costs, long LOS, and high readmission rates. Further research is needed to understand how treatment selection may impact healthcare outcomes and resource utilization in these high acuity patients.

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Introduction

In its publication "Antibiotic Resistance Threats in the United States, 2013," the CDC listed *Acinetobacter baumannii* (AB) as a serious public health threat, with an estimated incidence in 2013 of 12,000 cases per year. Others have estimated there may be as many as ~46,000 cases of AB-related infections annually in the U.S. and approximately 1 million cases per year globally.

A further concern is that the incidence of multidrug resistant (MDR) AB infections is increasing. Between 2000 and 2009, the percentage of imipenem-resistant AB increased from ~5% to approaching 40%, an increase that has been observed across most U.S. states. More recent publications have reported MDR AB rates of approximately 80%.

The increasing prevalence of MDR Acinetobacter has led to a resurgent role for older agents such as polymyxins and tetracyclines. Both of these classes of antibacterial have shown resilient high activity against both AB and MDR AB; however, clinical evidence regarding the effectiveness and outcomes associated with these and other treatment regimens against MDR AB is limited.

Colistin is also known to exhibit nephrotoxic effects while tigecycline has been associated with an increase in all-cause mortality compared to other antibacterial treatments. Here, we examined a large database to assess outcomes and resource utilization associated with tigecycline (TIG) or colistin (COL) use in an MDR AB cohort.

Methods

It was a multi-center retrospective cohort study. Data was derived from the Premier Hospital Database, a US hospital clinical and economic database containing hospital discharge data files, diagnoses and procedures categorized by ICD-9 codes, electronic microbiological laboratory, pharmacy, healthcare resource utilization, and cost data. Actual costs for goods and services are available for approximately 75% of patients, and 25% of bills were constructed using Medicare cost-to-charge ratio. Cost was adjusted to 2014 United States dollar value using the consumer price index. Analysis was limited to 152 hospitals reporting microbiology data.

Study population:

For this study, the target patients were included if
- Adult patients (age ≥ 18 years old)
- Admitted as inpatients between January 1, 2009 and June 30, 2014,
- Documented as MDR AB
- Patients with a diagnosis of pneumonia or sepsis,
- Received TIG or COL (but not both) treatment post-specimen collect date, and
- Duration of treatment (DOT) of TIG or COL ≥3 days.

Patients were excluded if he/she received both TIG and COL either as combination therapy or separately.

Microbiology and definition:

AB isolates were classified as susceptible (S), intermediate (I), or resistant (R) based on the susceptibility test results. For the purpose of this analysis, I and R were grouped together as non-susceptible. All microbiology testing was performed at the institutions and conformed to the CLSI standards.

Definition of multidrug resistance:

MDR AB was defined, per Magiorakos et al.[8] as an AB resistant to at least one agent in at least three of the following classes:
- Aminoglycosides – gentamicin, tobramycin, amikacin
- Antipseudomonal penicillins – imipenem, meropenem, doripenem
- Antipseudomonal fluoroquinolones – ciprofloxacin, levofloxacin
- Antipseudomonal penicillins with beta-lactamase inhibitors – piperacillin-tazobactam, ticarcillin-clavulanate
- Extended spectrum cephalosporins – cefotaxime, ceftriaxone, ceftazidime, cefepime
- Folate pathway inhibitors – trimethoprim, sulfamethoxazole
- Penicillins with beta-lactamase inhibitors – ampicillin/sulbactam
- Polymyxins – colistin (also called polymyxin E), polymyxin B
- Tetracyclines – tetracycline, doxycycline, minocycline

Identification of disease conditions:

- Pneumonia: principle diagnosis of ICD-9 codes 481-486, or respiratory failure [518.81 or 518.84] with pneumonia as a secondary diagnosis
- Sepsis: principle diagnosis of ICD-9 codes 038, 020.2, 790.7, 785.52, or 995.92, or respiratory failure [518.81 or 518.84] with sepsis as a secondary diagnosis.

If a patient had both diagnoses of pneumonia and sepsis, the patient was categorized as pneumonia.

Outcomes:

- In hospital mortality: discharge status
- Acute kidney injury (AKI): post-admission diagnosis of ICD-9 code 584
- *C. difficile*: post-admission diagnosis of ICD-9 code 008.45

Healthcare resource utilization:

- Hospital length of stay (LOS) and total costs
- Intensive care unit (ICU) use (%), ICU LOS, and costs during ICU stay
- Costs of antibiotics
- 30-day all-cause readmission rate

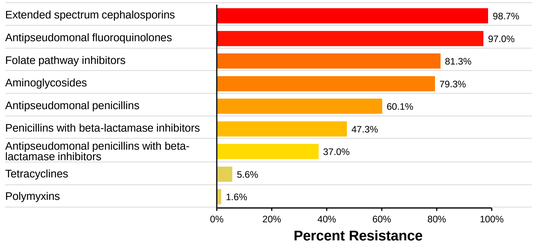
Statistical analyses:

A descriptive analysis was conducted to describe the characteristics of patients with MDR AB infection and diagnosed as either pneumonia or sepsis who were treated with either COL or TIG. Continuous variables were reported as means with standard deviations (SD) when distributed normally, or means with SD plus median when skewed. Categorical variables were summarized as proportions. We utilized the generalized linear modeling technique to explore the incremental costs of acute kidney injury (AKI) and *C. difficile* when COL or TIG was administered. Covariates in the model(s) included patient demographics, Charlson comorbidities, hospital characteristics, measures of illness severity, infection type, length of ICU stay, and days on mechanical ventilation. The inference from adjusted models was estimated using recycled predictions. Data processing, summarization and analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Among 10,029 hospitalized patients with confirmed AB between Jan. 2009 and Jun. 2014, 6,110 (60.9%) demonstrated an AB resistant to at least one agent in at least three classes:
- >97% resistant to extended spectrum cephalosporins and antipseudomonal fluoroquinolones
- ~80% resistant to aminoglycosides and folate pathway inhibitors
- 60% resistant to antipseudomonal penicillins

Figure 1: Antimicrobial resistance of MDR AB



547 patients were eligible for analysis; 126 pneumonia (54 COL and 72 TIG) and 421 sepsis (129 COL and 292 TIG).

Patient Profile (Table 1)

- Compared to TIG-treated patients, COL-treated patients were more likely to be younger and female, regardless of infection type.
- Regardless of treatment, MDR AB patients were very ill; ≥85% of patients were at extreme severity level per APR-DRG severity of illness category (except TIG-treated pneumonia patients [69.4%]), average CCI score ranged between 3.14 and 3.93, immunocompromised patients and those with chronic lung disease, diabetes, chronic renal disease, or congestive heart failure were more likely to have MDR AB infections.
- Large, teaching hospitals were more likely to treat MDR AB infection with COL than with TIG

Unadjusted, all-cause in-hospital mortality and other adverse events (Table 2)

- In-hospital mortality rate of MDR AB patients was high regardless of infection type and antibiotic choice of COL or TIG (17.8% — 23.6%).
- Acute kidney injury rate was doubled for COL-treated patients compared to TIG-treated patients for pneumonia (25.93% vs. 12.50%) and sepsis (13.95% vs. 7.53%).
- Another known adverse consequence after use of antibiotic medications is *C. difficile* infection. This study showed that *C. difficile* rate was higher for COL-treated patients (9.26% and 5.43% for pneumonia and sepsis respectively) than TIG-treated patients (2.78% and 3.08% for pneumonia and sepsis respectively).

Healthcare resource utilization (Table 2)

- MDR AB was associated with length of stay (LOS) ranging from 18.3 – 22.4 days. LOS was similar across treatment and infection types.
- Costs associated with MDR AB ranged from $51,277 - $64,119. Costs were similar between treatment arms, however sepsis was associated with slightly higher overall costs compared to pneumonia.
- Percent of patients requiring intensive care unit was 59.3% vs. 76.4% for COL and TIG cohorts with MDR AB pneumonia, respectively, compared to 76.0% vs. 71.2% for COL and TIG cohorts with MDR AB sepsis.
- The median duration of COL treatment was 7 and 8 days for pneumonia and sepsis patients respectively, while the median duration of TIG treatment was 6 and 8 days for pneumonia and sepsis patients respectively.
- Antibiotic costs accounted for about 6.0% of total hospital costs.
- 30-day readmission rates varied between 27.8% and 42.6%.

Incremental costs of acute kidney injury (AKI) and *C. difficile* in patients with MDR AB (Table 3)

- Unadjusted and adjusted incremental costs of acute kidney injury were $29,138 (95%CI: [$13,033, $45,242]) and $13,596 (95%CI: [$12,764, $14,413]).
- The unadjusted and adjusted incremental costs of *C. difficile* were $18,089 (95%CI: [-$7,777 – $43,955]) and $11,940 (95% CI: [$11,022 – $12,843])

Table 1. Patient Baseline Characteristics and Hospital Characteristics

	MDR AB Pneumonia		MDR AB Sepsis	
	Colistin (N=54)	Tigecycline (N=72)	Colistin (N=129)	Tigecycline (N=292)
Age, mean±SD	64.9±15.3	66.4±13.3	61.6±15.2	62.6±15.1
≥65 years old, %	57.4%	52.8%	46.5%	49.7%
Male, %	51.9%	55.6%	53.5%	57.9%
White, %	77.8%	70.8%	70.5%	63.7%
Payor, %				
Medicare	75.9%	63.9%	64.3%	67.5%
Medicaid	5.6%	13.9%	24.0%	18.8%
Commercial/Managed care	14.9%	16.7%	10.1%	10.6%
Self-pay	3.7%	1.4%	0.8%	2.4%
APR-DRG severity level, %				
Extreme	85.2%	69.4%	93.8%	89.4%
Severe	13.0%	27.8%	6.2%	9.6%
Moderate	1.9%	2.8%	0.0%	1.0%
CCI score, mean±SD	3.93±2.55	3.14±2.28	3.36±2.29	3.65±2.57
Most frequent comorbidities, %				
COPD	75.9%	69.4%	51.9%	37.3%
CHF	59.3%	45.8%	31.8%	38.7%
Diabetes w/o complication	55.6%	45.8%	42.6%	38.7%
Chronic renal disease	40.7%	16.7%	34.9%	36.3%
Teaching Hospitals, %	57.4%	33.3%	52.7%	37.3%
Bed size, %				
<400	48.1%	66.7%	42.6%	58.2%
400-599	22.2%	20.8%	24.0%	20.5%
≥600	29.6%	12.5%	33.3%	21.2%

APR-DRG=All Patients Refined Diagnosis Related Groups; CCI=Charlson Comorbidity Index; CHF=Congestive heart failure; COPD=Chronic obstructive pulmonary disease; MDR AB=Multidrug resistant *Acinetobacter baumannii*; SD=Standard Deviation

Table 2. Patient Outcomes and Resource Utilization

	MDR AB Pneumonia		MDR AB Sepsis	
	Colistin (N=54)	Tigecycline (N=72)	Colistin (N=129)	Tigecycline (N=292)
Mortality and other adverse events				
In-hospital mortality, %	18.5%	23.6%	21.7%	17.8%
Acute Kidney Injury, %	25.93%	12.50%	13.95%	7.53%
C. difficile, %	9.26%	2.78%	5.43%	3.08%
Hospital resource utilization				
Length of hospital stay (days)	22.0±16.4 (17)	18.3±14.7 (14.5)	22.4±19.9 (17)	21.7±23.2 (14)
Total costs ($)	$54,694± 40,083 ($40,980)	$51,277± 47,774 ($39,442)	$64,119± 65,798 ($44,929)	$59,340± 66,304 ($37,013)
Total antibiotic costs ($)	$2,916±2,466 ($2,464)	$3,144±2,357 ($2,342)	$4,132±6,522 ($2,449)	$3,608±4,498 ($2,239)
ICU use, %	59.3%	76.4%	76.0%	71.2%
Days in ICU	15.1±10.2 (12.5)	10.9±11.3 (7)	14.3±11.6 (12)	13.7±15.8 (9)
Costs in ICU ($)	$52,865± 40,729 ($38,304)	$40,639± 45,216 ($20,088)	$54,458± 56,296 ($34,816)	$50,454± 57,105 ($33,214)
MV use, %	77.8%	66.7%	72.1%	57.9%
Days in MV (days)	15.9±9.5 (14.5)	11.8±11.4 (8)	18.2±19.0 (13)	14.0±17.3 (9)
DOT (days) for COL/TIG	7.85±4.03 (7)	8.46±5.66 (6)	8.95±5.74 (8)	9.05±6.16 (8)
30-day all-cause re-admission*, %	42.6%	27.8%	37.2%	38.0%

DOT=Duration of treatment; ICU=intensive care unit; MV=mechanical ventilation.
All continuous variables were summarized as mean±standard deviation (median).
*Re-admission occurred in the same month or next month after the index hospitalization.

Table 3. Incremental costs of acute kidney injury (AKI) and *C. difficile* in patients with MDR AB

	w AKI (N=63)	w/o AKI (N=484)	Difference and 95%CI
Unadjusted	$84,729	$55,591	$29,138 ($13,033 – $45,242)
GLM			$13,596 ($12,764 – $14,413)

	w *C. difficile* (N=23)	w/o *C. difficile* (N=524)	Difference and 95%CI
Unadjusted	$76,276	$58,187	$18,089 (-$7,777 – $43,955)
GLM			$11,940 ($11,022 – $12,843)

Conclusions

MDR AB patients treated with TIG or COL have high mortality and substantial resource utilization, including high costs, long LOS, and high readmission rates.

AKI was common (11.5% in the MDR AB population overall), particularly with use of colistin,(12.95-23.93%) and associated with substantial incremental costs of $13,596. Given approximately 46,000 cases of AB-related infections each year in the US[2] and an MDR rate of 60-80%[4], AKI in this patient population may cost the US healthcare system ~$43-$57 million/year.

Identifying strategies to reduce AKI may substantially reduce healthcare expenditure as well as avoid serious adverse clinical events.

C. difficile was rare but substantially increased hospital costs.

Further research is needed to understand how treatment selection may impact healthcare outcomes and resource utilization in these high acuity patients.

Limitations

- Inherent in most secondary database analyses, we have assumed that hospitals have coded ICD-9 accurately and consistently and there was no source verification across with the original medical charts.
- The available data were derived from administrative records rather than a prospectively defined and standardized data collection.
- Full clinical detail, such as clinical and microbiological cure, and chemistry laboratory results are not available in the Premier database
- MDR AB patients with sepsis are often exposed to several nephrotoxins, including intravenous contrast agents, and additional factors associated with AKI were not adjusted.

Despite those limitations, the data were derived from a broad sample of both hospitals and patients and are representative of most current real world use of COL and TIG.

Disclosures

- This study was funded by The Medicines Company, Parsippany, NJ, USA

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