The identification and characterization of acute kidney injury (AKI) associated with systemic polymyxins in the management of severe gram-negative infections

Sarah Baradaran

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Beth Devine

Ryan Hansen

Doug Black

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University of Washington

ABSTRACT

The identification and characterization of acute kidney injury (AKI) associated with systemic polymyxins in the management of severe gram-negative infections

Sarah Baradaran

Chair of the Supervisory Committee:

Associate Professor, Beth Devine

Pharmacy

Background

The global rise in antibiotic resistance has led to an increased need for effective antimicrobial treatments. Polymyxins have re-emerged in recent years due to their strong antimicrobial activity against resistant gram-negative pathogens. However, there is concern of renal toxicity associated with the use of polymyxins. This study aims to assess the frequency of occurrence of acute kidney injury (AKI) in the context of incident use of intravenous (IV) polymyxin E (sodium colistimethate; CMS) or IV polymyxin B (PMB), and subsequent mortality, healthcare resource utilization and total hospitalization costs associated with AKI, separately for patients receiving CMS or PMB.

Methods

A retrospective cross-sectional database analysis using Premier was conducted from January 1, 2012 and September 30, 2015. Patients were included if they were ≥18 years of age with incident treatment of CMS or PMB for ≥3 consecutive days (defined as the index admission). Patients with polymyxin use in the previous six months were excluded. Patients with cystic fibrosis or who received both CMS and PMB during the same admission were excluded. The last admission included was on August 31, 2015, allowing for a 30-day follow-up period. Outcome variables included frequency of AKI occurrence, mortality,

healthcare utilization and total hospitalization costs during the index admission, and hospital re-admissions occurring within a 30-day period following discharge for the index admission. Descriptive statistics were used to summarize patient characteristics. Bivariate statistics were used to compare healthcare utilization, costs and readmissions in patients who did and did not experience AKI during the index admission. A multivariable logistic regression was conducted to determine the association between AKI during the index admission and mortality. All analyses were stratified by type of polymyxin (CMS or PMB).

Results

A total of 4,886 patients with incident use of a polymyxin were included; 4,103 patients received CMS and 783 received PMB. The frequency of occurrence of AKI was 31% in the CMS cohort and 27% in the PMB cohort. In the multivariable analysis, the presence of AKI during the index admission was associated with significantly higher mortality in both the CMS cohort (OR 2.26; 95% Confidence Interval (CI) 1.92 to 2.66; p<0.001) and the PMB cohort (OR 2.73; 95% CI 1.81 to 4.12; p<0.001). In both cohorts, patients who experienced AKI had longer hospital stays, more transfers to the ICU, and more days spent in the ICU compared to those who did not experience AKI (p<0.001 for each outcome). The presence of AKI during the index admission was significantly associated with 30-day readmission in the CMS cohort (p<0.001), but not in the PMB cohort (p=0.86). Mean total hospitalization costs for patients in the CMS cohort who experienced AKI were $42,653 higher than for patients who did not experience AKI (95% CI $34,566 to $50,749; p<0.001). Mean total hospitalization costs for patients in the PMB cohort who experienced AKI were $32,978 higher than for patients that did not experience AKI (95% CI $13,926 to $52,030; p<0.001).

Conclusions

In both CMS and PMB cohorts, frequency of AKI occurrence, mortality, healthcare utilization, and mean total hospitalization costs were significantly higher in patients who experienced AKI during incident use of polymyxin.

BACKGROUND

The global rise in antibiotic resistance is a growing public health concern. In the United States, approximately two million people develop hospital-acquired infections with antibiotic resistant pathogens every year, resulting in over 90,000 deaths.[1] A 2014 report published by the World Health Organization indicates that there is an increased need for treatments for antibiotic resistant infections.[2] Drug resistance can be caused by bacterial organisms that carry chromosomal mutations or transfer genetic components, such as a plasmids or transposons, which mediate resistance.[3] These mutations can lead to inactivation of one or multiple antibacterial drugs, known as multidrug-resistance (MDR). MDR can be defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Another type of resistance, extensively drug-resistant (XDR), is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories.[4] The most prevalent drug-resistant gram-negative bacteria include *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species.[5]

Treatment for infections due to MDR gram-negative bacteria is limited. Sodium colistimethate (CMS), also known as polymyxin E, a polypeptide antibiotic used in the 1960s has reemerged in recent years due to its strong antimicrobial activity against MDR and XDR gram-negative bacteria.[6,7] CMS is available in an intravenous (IV) formulation and is converted to colistin (its active form) in the plasma.[8] Polymyxin B (PMB) is structurally similar to CMS, differing in only one amino acid in the peptide ring. As a result, both polymyxins exhibit similar *in vitro* antibacterial properties. However, a key difference between the two antibiotics is that PMB is immediately active upon administration, whereas CMS is administered as an inactive prodrug that is activated in the plasma.[9] Thus, CMS requires a complex dosing regimen with careful monitoring to ensure attainment of adequate drug levels.[10] Although these agents are effective against MDR and XDR gram-negative bacteria, they are not without toxicities.

Nephrotoxicity is a safety concern associated with polymyxin use. With varying interpretations, it is important to define nephrotoxicity (also known as acute kidney injury [AKI]). Clinically, AKI is defined as an abrupt (within 48 hours) increase in serum creatinine of 0.5 mg/dL or a 50% increase above baseline for at least two repeated measurements.[11] However, even with a clear definition there is variability in the clinical assessment of AKI and there is no gold standard for classifying the severity of nephrotoxicity. Several clinical guidelines currently exist: Acute Kidney Injury Network (AKIN); Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE); and urine output (these guidelines are further defined in Appendix A, Table 1). These guideline measures for AKI require access to laboratory data (for serum creatinine) contained in electronic health records. In absence of serum creatinine data, such as

occurs in studies that use solely claims data, the definition of AKI requires use of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. This claims definition has been previously validated to identify AKI in the inpatient setting with positive predictive values of 80.2% and 87.6%. [12,13]

Previous studies have estimated the incidence of polymyxin-associated AKI to be 12 to 48%.[14-16] The results of these studies suggest variability in estimation of AKI due to the differences in patient inclusion/exclusion criteria, risk factors, and definitions of nephrotoxicity among the studies. Separately, there is a gap in literature describing the healthcare utilization of patients receiving polymyxins. Examples of healthcare utilization include length of hospital stay, transfers to the intensive care unit (ICU), and 30-day readmission rates. Similarly, there are no studies published to date that estimate the economic burden, in terms of total hospitalization cost, of AKI in the context of inpatient polymyxin use. The widely different incidence rates of polymyxin-associated nephrotoxicity and the gap in the availability of economic estimates support the need for this analysis.

OBJECTIVE

The primary objective of this study is to determine the frequency of occurrence of AKI in the context of use of each polymyxin (CMS and PMB); to investigate the association between AKI and in-hospital mortality; and to characterize healthcare utilization (i.e. length of stay (LOS), ICU transfers, and total hospitalization costs) between patients who have and who do not have AKI.

METHODS

Data Source

The Premier Database was used for this study. This inpatient and outpatient (outpatient includes ER, same day surgery, observation, and chemotherapy/dialysis clinics) hospital claims database contains patient-level data from 40% of U.S. hospitals. Patient-level data includes patient demographics, diagnoses, procedures, discharge information, medications, microbiological lab cultures [when available] and cost of care. Cost of care includes, but is not limited to, the cost of medications, diagnostic imaging, laboratory services, nursing labor, room and board, and procedures or surgeries. The total cost includes fixed (e.g. overhead and hospital maintenance) and variable costs (related directly to the activities of the admission, e.g. supplies and patient care). Although the Premier Database is robust in ICD-9-CM diagnosis codes, a limitation is that it lacks information concerning the date and time of the occurrence of diagnoses during an admission. However, the dates and times of medication

administrations are provided. The month, quarter, and year of admission and discharge dates are documented, but the day of the month is not specified in Premier.

Sample Selection

We performed a retrospective cross-sectional database analysis of patients admitted to the hospital between January 1, 2012 and September 30, 2015. Patients ≥18 years of age, treated with one of the two polymyxins for ≥3 consecutive days were included. Patients were identified using billing charge codes for either CMS or PMB (Appendix A, Table 6). Patients with an ICD 9-CM diagnosis code of cystic fibrosis (Appendix A, Table 2) and those who received both CMS and PMB during the same admission were excluded. Only the first (index) hospitalization with incident use of CMS or PMB was evaluated. The index admission was defined as the hospitalization with the patient's first use of a polymyxin for ≥3 consecutive days (incident use). Patients with prior use of polymyxins in the prior 6 months [January 1, 2012 through June 30, 2012] of the index admission were excluded. The final index admission date was August 31, 2015, to allow for a 30-day hospital inpatient readmission follow-up period prior to the final date of the dataset, which was September 30, 2015 (Figure 1).

Patient Characteristics

Demographic information included age, gender, race, Deyo version of the Charlson Comorbidity Index (CCI), previous hospitalizations (all-cause), previous AKI, and CKD on index admission. The Deyo version of the CCI assesses the severity of comorbidities that are significantly associated with outcomes such as mortality, hospital admissions, LOS, and complications (Appendix A, Table 4).[17] CKD was identified using the following ICD 9-CM codes: 582.x-583.x and 585.x-587.x. A recent study validated these ICD-9 CM codes for CKD with a positive predictive value of 98.4% for a diagnosis of chronic renal insufficiency compared to the gold standard eGFR <60 ml/min/1.73 m^2.[18]

Clinical Characteristics

Clinical characteristics included average duration of polymyxin use, primary diagnosis, use of other concurrent nephrotoxic drugs, dialysis or kidney transplant, type of infection, and microbiological culture information (causative organism and resistance) was assessed at index admission. The primary diagnosis was ascertained by evaluating the primary ICD-9 CM diagnosis code associated with the index admission. Use of other concurrent nephrotoxic drugs for ≥2 consecutive days overlapping with polymyxin use was evaluated during the patient's index admission (a list of nephrotoxic drugs included is

described in Appendix A, Table 5). Patients who underwent dialysis during the index admission were identified by ICD-9 CM diagnoses and procedure codes (Appendix A, Table 3). The type of infection was classified first by the presence of a Medicare Severity Diagnosis Related Group (MS-DRG) major diagnostic category of infection (00018) and then the corresponding primary ICD-9 CM diagnosis code.

In patients with available microbiological lab data, these data were used to identify the most common causative organisms and the organism's resistance information. A positive culture for a gram-negative infection of *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli, or Proteus mirabilis* was defined as either resistant, or highly resistant. Resistance patterns were stratified by the number of antibiotics to which the organism was resistant (0, 1, 2, or 3+ antibiotics).

Outcomes

We assessed the frequency of AKI occurrence, inpatient mortality, healthcare resource utilization and total hospitalization costs for the index admission. AKI was defined as the presence of an ICD-9 CM diagnosis code for AKI documented during the index admission (Appendix A, Table 3). A period of 6-months pre-index admission (January 1, 2012 through June 30, 2015) was used to identify patients with hospitalizations that included AKI in order to be able to exclude them in our frequency of AKI occurrence. Our definition in capturing the frequency of AKI occurrence only includes those patients who did not have a pre-index admission with an AKI event, and did not have CKD during the index admission. Mortality was assessed from the patient's discharge status of the index hospital admission. Healthcare resource utilization was characterized by length of hospital stay, transfers to the ICU, days in the ICU, and 30-day hospital re-admissions (all-cause). The total hospitalization cost includes the total cost to treat the patient during the index admission.

Statistical Analysis

The analysis was stratified by those who received CMS and those who received PMB. Patient and clinical characteristics measured as continuous variables were reported as means ($\pm$ standard deviation [SD]) and medians (interquartile range [IQR]); counts and proportions were used to summarize categorical variables. Bivariate statistics (t-tests and two-sample tests of proportions) were used to compare patient- and clinical characteristics in patients with and without AKI. Bivariate statistics were also used to compare outcomes (mortality, healthcare utilization and total admission costs) in patients with and without AKI. Multivariable logistic regression analyses were conducted to investigate the

association between AKI and mortality. The model was adjusted for age, gender, Deyo version of the CCI, dialysis at index admission, and a binary indicator for previous AKI or CKD at index admission. Adjustment for concurrent nephrotoxic drug use was considered; however, it was not included in the final model as the association between nephrotoxic drug use and mortality has not been substantiated. Further, the proportion of patients that received nephrotoxic drugs concurrently was not significantly different between those who did and did not experience AKI. We did not adjust for ICU transfers, either. ICU transfers are associated with mortality but not necessarily associated with whether or not the patient was exposed to AKI. All analyses were performed using the statistical software package STATA® Version 14.1. A significance level of alpha=0.05 was used throughout. The University of Washington Human Subjects Division determined that this study did not meet the federal definition of "human subjects research".

RESULTS

We identified 6,970 patients who were admitted between July 1, 2012 and August 31, 2015 and received at least three consecutive days of polymyxin. After applying the inclusion and exclusion criteria, 4,886 patients were included in our final analysis. 4,103 patients received CMS at index admission (CMS cohort) and 783 received PMB at index admission (PMB cohort) [Figure 2]. Microbiological data was available for 853/4886 (17%) of all patients: 744/4103 (18%) patients in the CMS cohort and 109/783 (14%) patients in the PMB cohort.

Study Population

Patient Characteristics

The average age of the patients in the CMS cohort was 62 years (SD 16). Age was significantly different between patients who experienced AKI during the index admission and those who did not (64 years vs. 59 years; $p<0.001$). Patients who experienced AKI were more likely to have a CCI of ≥ 3 (48% vs. 29%, respectively; $p<0.001$). Patients that experienced at least one prior hospitalization with AKI were significantly different between those who did and did not experience AKI during the index admission (25% vs. 14%; $p<0.001$). Similarly, there was a significant difference in CKD between patients who did and did not experience AKI (17% vs. 7%; $p<0.001$) [Table 1].

The average age of the patients in the PMB cohort was 63 years (SD 16). Age was significantly different between patients who experienced AKI during the index admission and those who did not (66 years vs. 62 years; $p<0.001$). Patients who experienced AKI were more likely to have a CCI of ≥ 3 (52% vs.

26%, respectively; p<0.001). Patients that experienced at least one prior hospitalization with AKI were significantly between patients that did and did not experience AKI at index admission (26% vs. 15%; p<0.001). Similarly, there was a significant difference in CKD between patients that did and did not experience AKI (16% vs. 6%; p<0.001) [Table 2].

Clinical Characteristics

Patients who experienced AKI had a significantly higher duration of CMS use compared to patients who did not experience AKI (8.1 days vs. 7.6 days; p=0.002). There were no significant differences in the use of concurrent nephrotoxic drugs or kidney transplants during index admission between patients who did and did not experience AKI (p=0.71, p=1.0, respectively). The majority of patients with an infection had septicemia (95%). The type of infection did not differ significantly between AKI and non-AKI patients (p=0.55). Patients with AKI were more likely to have an infection caused by *Klebsiella pneumoniae* (6% vs. 5%; p=0.02). There were no significant differences in the classification of organisms, in terms of resistance, between patients who did and did not experience AKI (p=0.22) [Table 1].

Patients who experienced AKI had a significantly higher duration of PMB use compared with patients who did not experience AKI (7.5 days vs. 6.4 days; p<0.001). There were no significant differences in the use of concurrent nephrotoxic drugs during index admission between patients who did and did not experience AKI (p=0.44). The majority of patients with an infection had septicemia (91%). The type of infection did not differ significantly between AKI and non-AKI patients (p=0.52). Patients with AKI were more likely to have an infection caused by *Pseudomonas aeruginosa* or *Klebsiella pneumoniae* (p=0.02, p=0.04, respectively). There were no significant differences in the classification of organisms, in terms of resistance, between patients that did and did not experience AKI (p=0.06) [Table 2].

Outcomes

AKI

Of the 4,103 patients who received CMS during the index admission, 1,291 patients without previous AKI or CKD experienced AKI during the index admission—a frequency of occurrence of 31%. Of the 783 patients who received PMB during the index admission, 213 patients without previous AKI or CKD experienced AKI during the index admission—a frequency of occurrence of 27%.

Mortality

In the CMS cohort, the presence of AKI during the index admission was associated with a 15% higher risk of mortality compared to those who did not experience AKI (95% CI 10 to 21, p<0.001). In the multivariable regression, the odds of mortality in patients with AKI is 126% higher than the odds of mortality in patients without AKI (odds ratio (OR) 2.26; 95% CI 1.92 to 2.66) [Table 3].

In the PMB cohort, the presence of AKI during the index admission was associated with a 17% higher risk of mortality compared to those who did not experience AKI (95% CI 5 to 30; p<0.05).
In the multivariable regression, the odds of mortality in patients with AKI is 173% higher than the odds of mortality in patients without AKI (OR 2.73; 95% CI 1.81 to 4.12) [Table 4].

Healthcare Utilization

In the CMS cohort, the presence of AKI was associated with a LOS 11.1 days longer (95% CI 9.1 to 13.2) than in the absence of AKI. AKI patients were 15% (95% CI 12% to 18%) more likely to be admitted to the ICU and stayed in the ICU 6.0 days longer (95% CI 4.6 to 7.4) than non-AKI patients. Patients who experienced AKI were 5% less likely to be re-admitted to the hospital within 30 days than patients that did not experience AKI (95% CI -8 to -3%) [Table 3].

In the PMB cohort, the presence of AKI was associated with a LOS 12.2 days longer (95% CI 7.3 to 17.1) than in the absence of AKI. AKI patients were 24% (95% CI 17 to 31) more likely to be admitted to the ICU and stayed in the ICU 5.1 days longer (95% CI 2.9 to 7.3) than non-AKI patients. Patients who experienced AKI were not associated with 30-day re-admissions (p=0.86) [Table 4].

Total Admission Costs

In the CMS cohort, patients who experienced AKI had a mean total admission cost $42,653 (95% CI $34,566 to $50,750) higher than the mean total admission cost of patients who did not experience AKI. Patients who experienced AKI had an average admission cost of $107,982 (SD $146,800) and a median total admission cost of $63,464 (IQR $31,992 to $129,849). Patients who did not experience AKI had an average total admission cost of $65,329 (SD $115,376) and a median total admission cost of $33,378 (IQR $17,113 to $71,342) [Table 3].

In the PMB cohort, patients who experienced AKI had a mean total admission cost $32,978 (95% CI $13,926 to $52,030) higher than the mean total admission cost of patients who did not experience AKI. Patients who experienced AKI had an average admission cost of $104,174 (SD $123,059) and a median total admission cost of $62,710 (IQR $31,285 to $126,586). Patients who did not experience AKI had an

average total admission cost of $71,197 (SD $148,183) and a median total admission cost of $27,631 (IQR $12,570 to $68,321) [Table 4].

DISCUSSION

In our retrospective cross-sectional database analysis, we examined patients with hospitalizations of first use of polymyxin. This study supports the established risk of AKI in the context of polymyxin use. In both polymyxin cohorts, the burden of this risk impacted patient mortality, healthcare utilization, and cost. The presence of AKI in these hospitalized patients was associated with a higher risk of mortality. We found that patients with AKI experienced longer hospital stays, more transfers to the ICU, and more days spent in the ICU compared to those who did not experience AKI. Although these results were consistent with AKI patients utilizing more healthcare resources, this pattern did not hold for 30-day hospital re-admissions. In the CMS cohort, patients with AKI experienced fewer 30-day hospital re-admissions than those without AKI. In the PMB cohort, there was no significant difference in 30-day hospital readmissions. The 30-day hospital readmission results are unexpected and there are other possible explanations for these unadjusted results. Possible explanations include lack of adjustment for potential confounding variables, which could alter the results. Separately, patients may have utilized a healthcare setting not captured in the Premier Database, such as an urgent care clinic or a doctor's office. Our results suggest that the mean total cost of admission in patients who experienced AKI is approximately $30,000 higher than for patients who did not experience AKI.

The frequency of occurrence of AKI we found in our study (31% in the CMS cohort; 27% in the PMB cohort) is similar to the findings of other investigators. A recently published study conducted by Rigatto et al., found that AKI occurs in 38% of patients who received CMS and 13% of patients who received PMB.[16] Similarly, Tuon et al., found AKI occurred in 39% of patients treated with CMS and 21% of patients treated with PMB.[19] Although the occurrence of AKI in our study is higher in the PMB group and lower in the CMS group, we used different definitions of AKI; Rigatto et al., used the RIFLE criteria and Tuon et al., used the AKIN criteria to define nephrotoxicity.[16,19] The variations in definitions of AKI may account for the different results.

We found no other studies that evaluated in-hospital mortality, per se, although previous studies have documented higher ICU mortality in AKI patients.[20-21] However, other studies have estimated mortality 30 days after hospital discharge and found no significant differences between AKI and non-AKI patients (p=0.38).[22-23]

In terms of healthcare utilization, Sekhri et al., assessed efficacy and safety of polymyxins and found no significant difference in the length of hospital stay between AKI and non-AKI patients ($p=0.41$).[21] However, with a sample size of fewer than 50 patients, this study may not have been adequately powered to detect a difference. Our results describing a significant difference in ICU transfers compare well with those of Rigatto et al. who found a significant difference in ICU transfers between patients who did and did not experience AKI ($p<0.001$).[16] A study conducted by Mendonca et al., found similar results, in that patients with AKI spent more days in the ICU compared to non-AKI patients ($p<0.001$).[20] No other studies have investigated the economic impact of AKI in the context of polymyxin use. Future research is needed to adequately ascertain all possible healthcare utilizations before and after polymyxin use.

Strengths and Limitations

The strengths of this study include a robust sample size and patient-level data that enable detailed characterization of in-hospital mortality, healthcare utilization, and total admission costs. There are several limitations to this analysis. First, we attribute an ICD-9 CM diagnosis code of AKI to the use of polymyxin during the index admission. However, we were unable to establish a true temporal association between first administration of a polymyxin and onset of AKI because Premier lacks a date/time stamp associated with ICD-9 CM codes. This differential misclassification of exposure can potentially lead to an overestimation of AKI in this study. Second, we used a claims based definition of AKI (i.e. ICD-9 CM code) instead of a clinical definition based on renal laboratory values, which can introduce misclassification bias if the adverse event of AKI were misclassified or unclassified. Third, laboratory results, with pathogen and resistance information, were not available for all patients in the study; microbiological data were included for only 17% of patients in the dataset, so that we were unable to characterize this information. This is because laboratory and microbiological results were available only for patients who received care at a hospital that contracted with an external laboratory, because it is only these outsourced laboratory data that are included in the Premier dataset. This weakens the generalizability of our study, a form of sample bias. On a similar note, we are unable to determine previous hospital admissions at any hospitals other than the hospital of the index admission due to the lack of a common identifier across hospitals in the Premier Database, which can also potentially lead to a bias sample of patients included in the calculation of frequency of AKI occurrence. This limitation can also lead to an underestimate of 30-day re-admissions if the patient received care within thirty days post-index admission at a different hospital than the index hospital. Fourth, CCI was

calculated in this analysis using ICD-9 diagnoses codes. However, the timing within each hospitalization wherein these diagnoses codes were assigned was unestablished. Since most of these diagnoses codes in the CCI are chronic diseases, an assumption was made that these chronic diseases were diagnosed before the use of polymyxins. The same rationale was applied to the presence of CKD, as it too is a chronic condition. Fifth, the study did not assess the potential long-term complications of AKI. A study with longer duration of follow-up would be needed to fully assess the long-term impact of experiencing drug-induced AKI. Similarly, there is a lack of information describing renal recovery (renal function returning to baseline) and eradication of the infection, both of which limit our understanding of the efficacy of polymyxins and the long-term effects of renal damage. Finally, this study was not intended to establish an association between the use of polymyxin and AKI. Since there was no comparator group (an antibiotic other than polymyxin), we are able to provide information solely about the frequency of occurrence of AKI in patients who receive polymyxin.

CONCLUSION

In this retrospective cross-sectional database analysis, the mortality, healthcare utilization, and mean total cost of admission were significantly higher in patients who experienced AKI, compared to those who did not, during an index admission with first use of polymyxin. Our findings suggest that the clinical and economic burden of AKI in the context of polymyxin use is substantial. Polymyxin use is driven by the limited availability of other equally efficacious and safer antibiotics to which these gram-negative organisms are susceptible. Therefore, these agents should be used judiciously, as the potential may exist for the risks of use to exceed the benefits. To further assess the benefits (in terms of efficacy) and to establish an association between polymyxin use and AKI, a robust prospective study with integrated claims and electronic health record data is needed.

FIGURE

Figure 1. Study Design

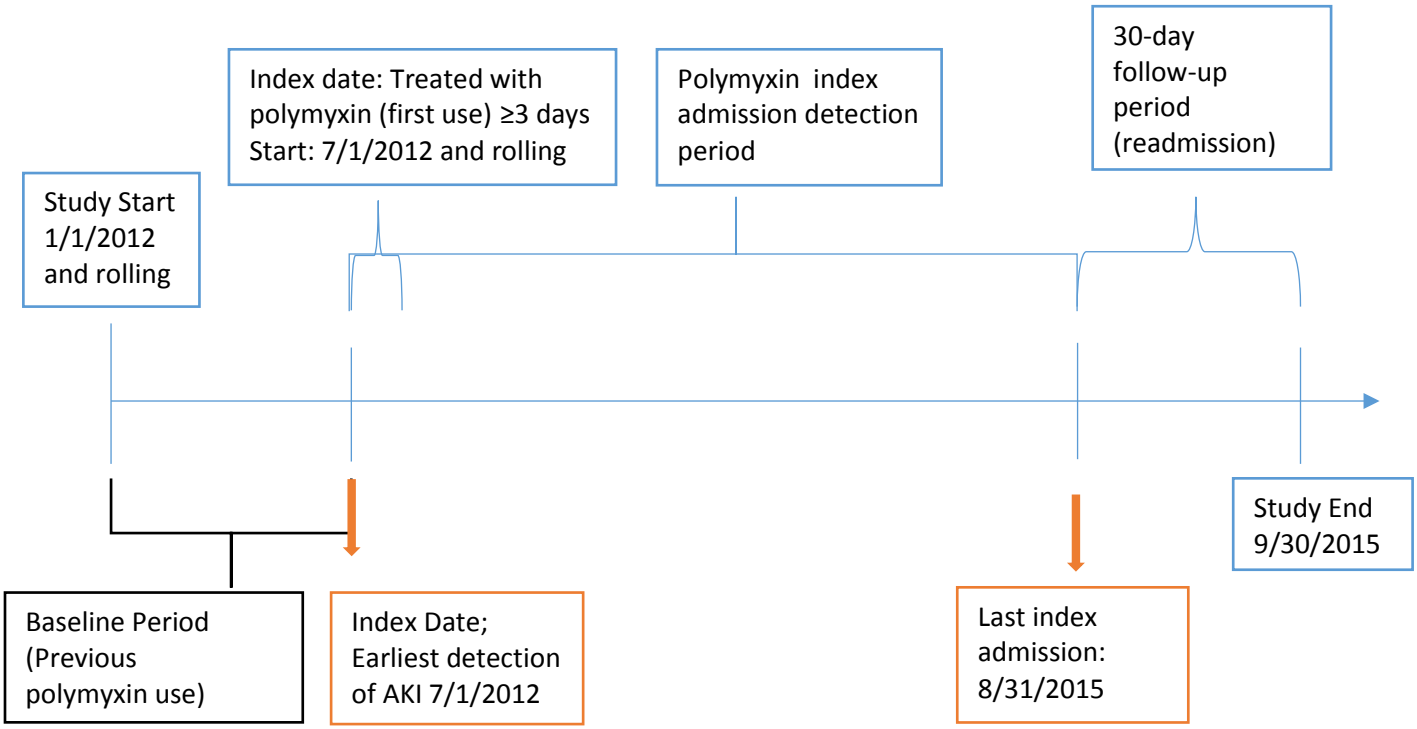

Figure 2: Patient Selection Flowchart

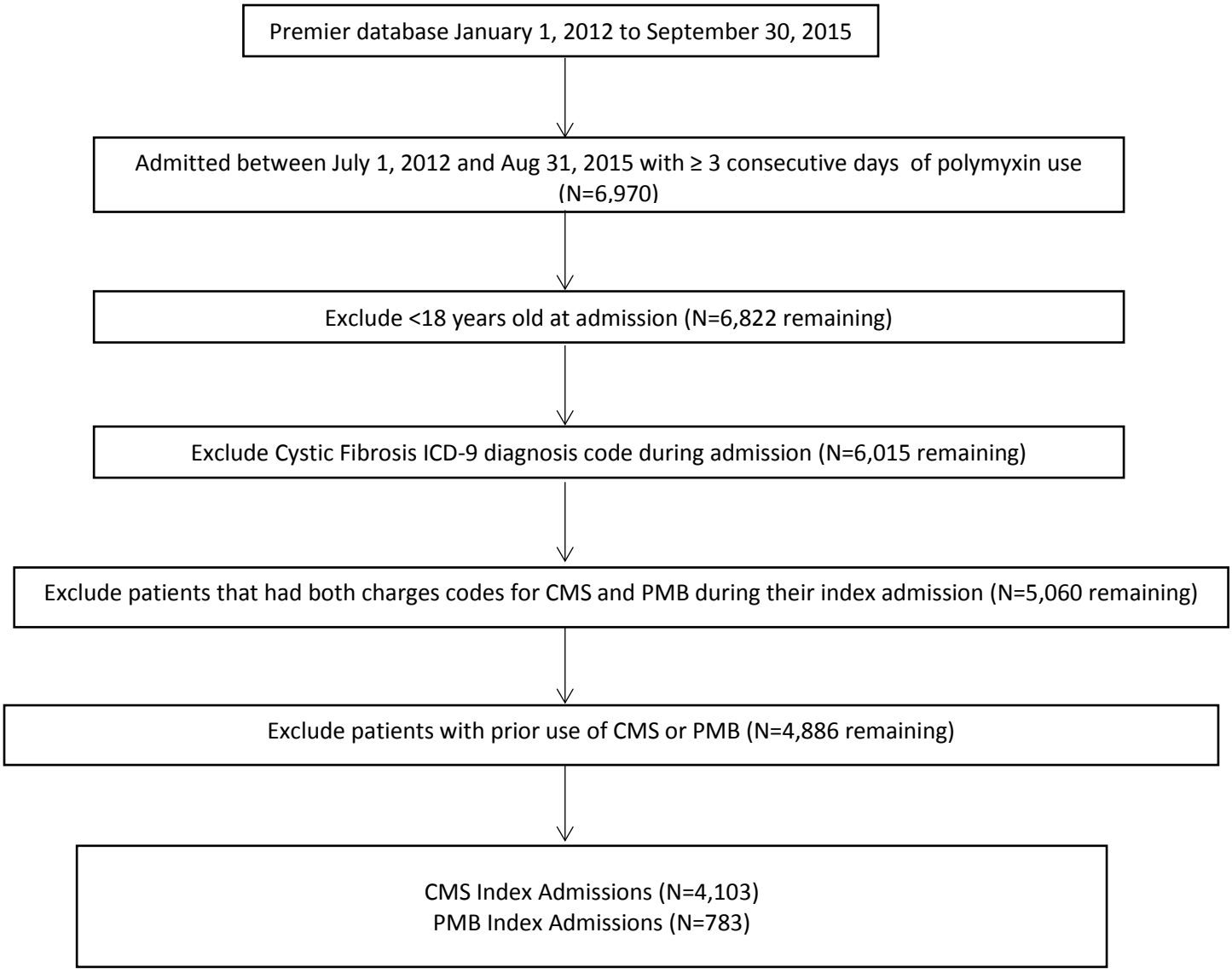

Table 1. CMS Characteristics

Patient Characteristics	**All patients (n=4103); n (%)**	**Patients with AKI- (n=2022); n (%)**	**Patients without AKI (n=2081); n (%)**	**p-values**
Age (years) [mean ± SD]	61.7 ± 16.4	64.0 ± 15.0	59.4 ± 17.3	<0.001
Gender (male)	2341 (57%)	1194 (59%)	1147 (55%)	0.01
Race*				
White	2446 (60%)	1178 (58%)	1268 (61%)	0.08
Black	781 (19%)	412 (20%)	369 (18%)	0.03
Hispanic	408 (10%)	175 (9%)	233 (11%)	0.006
Other	859 (21%)	427 (21%)	432 (21%)	0.78
Unknown	17 (0.4%)	5 (0.3%)	12 (0.6%)	0.1
Comorbidities during index admission (Charlson Comorbidity Index [CCI])				
0	879 (21%)	304 (15%)	575 (28%)	<0.001
1	825 (20%)	322 (16%)	503 (24%)	<0.001
2	842 (21%)	435 (22%)	407 (20%)	0.12
3+	1557 (38%)	961 (48%)	596 (29%)	<0.001
Previous 6-month hospitalizations (all-cause)	2449 (60%)	1155 (57%)	1294 (62%)	0.001
Previous 6-month hospitalizations with AKI	800 (20%)	514 (25%)	286 (14%)	<0.001
CKD during index admission	488 (12%)	341 (17%)	147 (7%)	<0.001
Clinical Characteristics	**All patients (n=4103); n (%)**	**Patients with AKI (n=2022); n (%)**	**Patients without AKI (n=2081) ; n (%)**	**p-values**
Average total duration of CMS (days)[mean ± SD]	7.8 ± 5.5	8.1 ± 5.9	7.6 ± 5.1	0.002
Primary diagnosis for index admission				
SEPTICEMIA	1056 (26%)	560 (28%)	496 (24%)	0.005
SEPTICEMIA, GRAM-NEGATIVE ORGANISM	195 (5%)	118 (6%)	77 (4%)	0.001
RESPIRATORY FAILURE, ACUTE & CHRONIC	146 (4%)	59 (3%)	87 (4%)	0.03
SEPTICEMIA—PSEUDOMONAS	108 (3%)	65 (3%)	43 (2%)	0.02
PNEUMONIA—PSEUDOMONAS	97 (2%)	33 (2%)	64 (3%)	0.002
Use of other concurrent nephrotoxic drugs	1196 (29%)	584 (28.88%)	612 (30%)	0.71
Dialysis during index admission	771 (19%)	478 (24%)	293 (14%)	<0.001
Kidney transplant during index admission	4 (0.1%)	2 (0.1%)	2 (0.1%)	1
Infection Type**	**All patients (n=1726); n (%)**	**Patients with AKI (n=972); n (%)**	**Patients without AKI (n=754); n (%)**	**p-values**
SEPTICEMIA	1642 (95%)	922 (95%)	720 (95%)	0.55
POSTOPERATIVE INFECTION	48 (3%)	30 (3%)	18 (2%)	0.38
BACTEREMIA	7 (0.4%)	2 (0.2%)	5 (0.7%)	0.15
Causative Organism***	**All patients (n=1094); n (%)**	**Patients with AKI (n=572); n (%)**	**Patients without AKI (n=522) ; n (%)**	**p-values**
Pseudomonas aeruginosa	349 (32%)	166 (29%)	183 (35%)	0.51
Acinetobacter baumannii	271 (25%)	149 (26%)	122 (23%)	0.052
Klebsiella pneumoniae	230 (21%)	130 (23%)	100 (19%)	0.02
Escherichia coli	125 (11%)	64 (11%)	61 (12%)	0.65
Proteus mirabilis	119 (11%)	63 (11%)	56 (11%)	0.41
Classification of Organism	**All patients (n=744); n (%)**	**Patients with AKI (n=379); n (%)**	**Patients without AKI (n=365) ; n (%)**	**p-values**
Resistant to 0 antibiotics	101(14%)	37 (10%)	46 (13%)	0.22
Resistant to 1 antibiotics	15 (2%)	6 (2%)	9 (2%)	0.39
Resistant to 2 antibiotics	17 (2%)	8 (2%)	9 (2%)	0.74
Resistant to 3+ antibiotics	629 (85%)	328 (87%)	301 (82%)	0.13

*For Race, they can be in more than one category; ** Only 1726/4103 (42.1%) of patients overall had a Medicare Severity Diagnosis Related Group (MS-DRG) major diagnostic category of infection (0018);***Not mutually exclusive; Patients can have more than one causative organism; Only 744 patients in the CMS cohort had microbiological data

Table 2. PMB Characteristics

Patient Characteristics	**All patients (n=783); n (%)**	**Patients with AKI (n=336); n (%)**	**Patients without AKI (n=447); n (%)**	**p-values**
Age (years) [mean ± SD]	63.5 ± 16.1	65.6 ± 14.4	61.9 ± 17.0	0.001
Gender (male)	414 (53%)	186 (55%)	228 (51%)	0.23
Race*				
White	449 (57%)	196 (58%)	253 (57%)	0.63
Black	145 (19%)	71 (21%)	74 (17%)	0.1
Hispanic	56 (7%)	22 (7%)	34 (7%)	0.57
Other	189 (24%)	69 (20%)	120 (27%)	0.04
Unknown	0 (0%)	0 (0%)	0 (0%)	------
Comorbidities during index admission (Charlson Comorbidity Index [CCI])				
0	196 (25%)	52 (15%)	144 (32%)	<0.001
1	155 (20%)	46 (14%)	109 (24%)	<0.001
2	140 (18%)	64 (19%)	76 (17%)	0.46
3+	292 (37%)	174 (52%)	118 (26%)	<0.001
Previous 6-month hospitalizations (all-cause)	424 (54%)	183 (54%)	241 (54%)	0.88
Previous 6-month hospitalizations with AKI	152 (19%)	86 (26%)	66 (15%)	<0.001
CKD during index admission	81 (10%)	54 (16%)	27 (6%)	<0.001
Clinical Characteristics	**All patients (n=783); n (%)**	**Patients with AKI (n=336); n(%)**	**Patients without AKI (n=447); n (%)**	**p-values**
Average total duration of PMB (days)[mean ± SD]	6.9 ± 4.8	7.5 ± 5.5	6.4 ± 4.1	0.001
Primary diagnosis for index admission				
SEPTICEMIA	159 (20%)	82 (24%)	77 (17%)	0.01
SEPTICEMIA, GRAM-NEGATIVE ORGANISM	38 (5%)	22 (7%)	16 (4%)	0.06
POSTOPERATIVE INFECTION	23 (3%)	10 (3%)	13 (3%)	0.95
RESPIRATORY FAILURE, ACUTE & CHRONIC	17 (2%)	8 (2%)	9 (2%)	0.73
URINARY TRACT INFECTION (UTI)	16 (2%)	2 (0.6%)	14 (3%)	0.01
Use of other concurrent nephrotoxic drugs	277 (35%)	124 (37%)	153 (34%)	0.44
Dialysis during index admission	106 (14%)	65 (19%)	41 (9%)	<0.001
Kidney transplant during index admission	0 (0%)	0 (0%)	0 (0%)	-------
Infection Type**	**All patients (n=287); n (%)**	**Patients with AKI (n=155); n (%)**	**Patients without AKI (n=132); n (%)**	**p-values**
SEPTICEMIA	260 (91%)	142 (92%)	118 (89%)	0.52
POSTOPERATIVE INFECTION	23 (8%)	10 (6%)	13 (10%)	0.29
Causative Organism***	**All patients (n=114); n (%)**	**Patients with AKI (n=56); n (%)**	**Patients without AKI (n=58); n (%)**	**p-values**
Pseudomonas aeruginosa	50 (44%)	27 (48.21%)	23 (39.66%)	0.02
Klebsiella pneumoniae	23 (20%)	13 (23.21%)	10 (17.24%)	0.04
Escherichia coli	22 (19%)	11 (19.64%)	11 (18.97%)	0.81
Acinetobacter baumannii	13 (11%)	4 (7.14%)	9 (15.52%)	<0.001
Proteus mirabilis	6 (5%)	1 (1.79%)	5 (8.62%)	<0.001
Classification of Organism	**All patients (n=109); n (%)**	**Patients with AKI (n=48); n (%)**	**Patients without AKI (n=61); n (%)**	**p-values**
Resistant to 0 antibiotics	33 (30%)	10 (21%)	23 (38%)	0.06
Resistant to 1 antibiotics	6 (6%)	3 (6%)	3 (5%)	0.76
Resistant to 2 antibiotics	0 (0%)	0 (0%)	0 (0%)	-------
Resistant to 3+ antibiotics	70 (64%)	35 (73%)	35 (57%)	0.09

*For Race, they can be in more than one category; **Only 287/783 (36.7%) of patients overall had a Medicare Severity Diagnosis Related Group (MS-DRG) major diagnostic category of infection (0018); ***Not mutually exclusive; Patients can have more than one causative organism; Only 109 patients in the PMB cohort had microbiological data

Table 3. Outcomes for CMS

Outcomes	All patients (n=4103) n (%)	Patients with AKI (n=2022) n (%)	Patients without AKI (n=2081) n (%)	Point Estimate** (95% Confidence Intervals)[1-3]
Clinical Outcome				
Mortality				
• Unadjusted	875 (21%)	590 (29%)	285 (14%)	15% (10 to 21)[3]
• Adjusted[†] OR (95% CI)				OR 2.26 (1.92 to 2.66)[3]
Healthcare Utilization				
Length of hospital stay (days)				
• Unadjusted				
Mean ± SD	29.1 ± 34.5	34.8 ± 38.1	23.7 ± 29.7	11.1 days (9.1 to 13.2)[3]
Median (IQR)	19 (11 to 34)	23 (14 to 41)	15 (9 to 27)	
Admissions to the ICU				
• Unadjusted	2461 (60%)	1370 (68%)	1091 (52%)	15% (12 to 18)[3]
Days in the ICU				
• Unadjusted				
Mean ± SD	11.9 ± 22.8	14.9 ± 23.2	8.9 ± 22.1	6.0 days (4.6 to 7.4)[3]
Median (IQR)	3 (0 to 16)	8 (0 to 21)	1 (0 to 10)	
30-day hospital readmission				
• Unadjusted	677 (17%)	278 (14%)	399 (19%)	-5% (-8 to -3%)[3]
Cost				
Total admission cost (dollars)				
• Unadjusted				
Mean ± SD	$86,349 ± $133,500	$107,982 ±$146,800	$65,330 ± $115,376	$42,653± ($34,566 to $50,749)[3]
Median (IQR)	$45,841 ($22,447 to $99,976)	$63,464 ($31,992 to $129,849)	$33,378 ($17,113 to $71,342)	

**Unless otherwise indicated; Point Estimate=Difference in means or proportions of patients with AKI compared to patients without AKI

[1]p-value <0.05; [2]p-value <0.01; [3]p-value <0.001

[†]Covariates: age, gender, CCI, dialysis, previous AKI or current CKD [grouped into one variable]

Table 4. Outcomes for PMB

Outcomes	All patients (n=783) n (%)	Patients with AKI (n=336) n (%)	Patients without AKI (n=447) n (%)	Point Estimate** (95% Confidence Intervals)[1-3]
Clinical Outcome				
Mortality • Unadjusted	137 (18%)	92 (27%)	45 (10%)	17% (5 to 30)[1]
• Adjusted[†] OR (95% CI)				OR 2.73 (1.81 to 4.12)[3]
Healthcare Utilization				
Length of hospital stay (days) • Unadjusted Mean ± SD	30.0 ± 34.8	36.9 ± 35.3	24.8 ± 33.6	12.2 days (7.3 to 17.1)[3]
Median (IQR)	19 (10 to 36)	26 (14 to 48)	14 (8 to 27)	
Admissions to the ICU • Unadjusted	377 (48%)	208 (62%)	169 (38%)	24% (17-31)[3]
Days in the ICU • Unadjusted Mean ± SD	7.8 ± 15.5	10.8 ± 16.5	5.6 ± 14.4	5.1 days (2.9 to 7.3)[3]
Median (IQR)	19 (11 to 34)	23 (14 to 41)	15 (9 to 27)	
30-day hospital readmission • Unadjusted	140 (18%)	61 (18%)	79 (18%)	0.6% (-5 to 6) p-value=0.86
Cost				
Total admission cost (dollars) • Unadjusted Mean ± SD	$85,348 ± $138,844	$104,174 ± $123,059	$71,197 ± $148,183	$32,978 ($13,926 to $52,030)[3]
Median (IQR)	$41,783 ($17,505 to $94,849)	$62,710 ($31,285 to $126,586)	$27,631 ($12,570 to $68,321)	

**Unless otherwise indicated; Point Estimate=Difference in means or proportions of patients with AKI compared to patients without AKI

[1]p-value <0.05; [2]p-value <0.01; [3]p-value <0.001

[†]Covariates: age, gender, CCI, dialysis, previous AKI or current CKD [grouped into one variable]

Appendix A

Table 1. Classification and Staging of Acute Kidney Injury[24-26]

AKIN (Acute Kidney Injury Network)
Stage 1: Increase in serum creatinine of ≥0.3 mg/dL or >50% above baseline
Stage 2: Increase in serum creatinine of >100% above baseline
Stage 3: Increase in serum creatinine of >200% above baseline
RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease)
Risk: Increase in serum creatinine of >50% above baseline
Injury: Increase in serum creatinine of >100% above baseline
Failure: Increase in serum creatinine of >200% above baseline
Loss: Need for renal replacement therapy for >4 weeks
End-Stage: Need for renal replacement therapy for >3 months
Other (Urine output)
Equivalent to Stage 1 or Risk: Urine output of <0.5 ml/kg/hour for >6 hours
Equivalent to Stage 2 or Injury: Urine output of <0.5 ml/kg/hour for >12 hours
Equivalent to Stage 3 or Failure: Urine output of <0.3 ml/kg/hour for □24 hours or anuria for □12 hours

Table 2. ICD-9 Diagnosis Codes: Cystic Fibrosis

ICD-9 Codes:	Description
277	Cystic fibrosis without meconium ileus
277.01	Cystic fibrosis with meconium ileus
277.02	Cystic fibrosis with pulmonary manifestations
277.03	Cystic fibrosis with gastrointestinal manifestations
277.09	Cystic fibrosis with other manifestations

Table 3. ICD-9 Diagnosis and Procedure Codes: Adverse Events with Acute Kidney Injury[12,13]

ICD-9 Codes:	Description
584	Acute renal failure, unspecified
584.5	Acute tubular necrosis
584.6	Cortical acute renal failure
584.7	Medullary acute renal failure
584.8	Acute renal failure with other specified pathologic lesion
584.9	Acute renal failure, not otherwise specified
V39.95	Hemodialysis
V45.1	Renal dialysis status
V56.0	Extracorporeal dialysis
V56.8	Other dialysis [peritoneal dialysis]
V56.1	Fitting and adjustment of dialysis catheter
582, 583, 585, 586, 587	Chronic Renal Insufficiency
39.95	Hemodialysis
54.98	Peritoneal dialysis
55.69	Transplant of the kidney

Table 4. ICD-9 for Charlson Comorbidities[17]

ICD-9 Codes:	Comorbidities	Score
410.x, 412.x	Myocardial Infarction	1
428.x	Congestive heart failure	1
443.9, 441.x, 785.4, V43.4 Procedure 38.48	Peripheral vascular disease	1
430.x-438.x	Cerebrovascular disease	1
290.x	Dementia	1
490.x-505.x, 506.4	Chronic pulmonary disease	1
710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x	Rheumatic disease	1
531.x-534.x	Peptic ulcer disease	1
571.2, 571.4-571.6	Mild liver disease	1
250.0-250.3, 250.7	Diabetes without chronic complication	1
250.4-250.6	Diabetes with chronic complication	2
344.1, 342.x	Hemiplegia or paraplegia	2
582.x, 583-583.7, 585.x, 586.x, 588.x	Renal Disease	2
140.x-172.x, 174.x-195.8, 200.x-208.x	Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	2
456.0-456.21, 572.2-572.8	Moderate or severe liver disease	3
196.x-199.1	Metastatic solid tumor	6
042.x-044.x	AIDS/HIV	6

Table 5. Other Nephrotoxic Drugs[27-28]

Foscarnet	Vancomycin
Contrast Dye	Amphotericin B
Aminoglycosides: Gentamicin, Tobramycin, Amikacin, Streptomycin	
Platinum Chemotherapy Agents: Cisplatin, Carboplatin, Oxaliplatin	

Table 6. Standard Charge Codes for CMS & PMB

250250015320000	COLISTIMETHATE NA VL 150MG
250999003940000	COLISTIMETHATE NA MISC
250250052830000	POLYMYXIN B, AEROSPORIN VL 500,000U
250999014290000	POLYMYXIN B MISC

Appendix B

Table 1. Patient Selection (Inclusion/Exclusion Criteria): Premier Specific Information

Field Name	Data Type	Description	Response Options	
pat_key	Integer	Premier-generated code that provides an unique identifier for each patient per hospital visit		
medrec_key	Char(12)	Premier-generated code that links patients at the hospital/medical record number level. Using this field, a patient can be tracked across multiple visits to a hospital.		
disc_mon	Integer	Month patient was discharged, formatted: YYYYQMM where Q is the calendar quarter		
adm_mon	Integer	Month patient was admitted, formatted: YYYYQMM where Q is the calendar quarter		
i_o_ind	Char(1)	Inpatient/Outpatient indicator	I	Inpatient
			O	Outpatient
pat_type	Char(2)	A Premier defined field to denote service type of patient, example: 08 - inpatient, 10 - skilled nursing.	8	Inpatient
			10	Skilled Nursing
			22	Long Term Care
			23	Rehabilitation
			24	Psychiatric
			25	Hospice
			26	Chemical Dependency
			27	Same Day Surgery
			28	Emergency
			29	Observation
			30	Diagnostic Testing
			31	Recurring/Series
			32	Pre-Surgical Testing
			33	Home Health
			34	Clinic
			90	Other

Table 2. Healthcare Utilization: Premier Specific Information

Field Name	DataType	Description
los	Smallint	Number of days patient was under direct care of the healthcare organization
std_chg_code	Char(15)	Perspective Standard Charge Master Code Version 10
hosp_qty	Decimal (12, 2)	Hospital submitted quantity for each charge item
std_qty	Decimal (12, 2)	Standard quantity for each charge item
days_from_prior	Integer	Calculated days from prior hospital encounter, admit date of current hospital encounter – discharge date of prior hospital encounter when sorted by discharge date.
pat_cost	Decimal(12,2)	The actual cost to treat the patient. This includes all supplies, labor, depreciation of equipment, etc. Calculation = Variable Costs (direct) + Fixed Costs (Overhead)
pat_fix_cost	Decimal(12,2)	The actual fixed cost (overhead) to treat the patient.
pat_var_cost	Decimal(12,2)	The actual variable cost (direct) to treat the patient.

Table 3. Patient Characteristics: Premier Specific Information

Field Name	Data Type	Description	Valid Values	
drg Assigned to inpatients only	Smallint	Diagnosis-Related Group code, as defined by Medicare. Classifications are based on: Primary diagnosis, Secondary diagnosis, Surgical procedures (if any), Age, Gender, Presence of complications		
ms_drg Assigned to inpatients only	Smallint	Medicare Severity Diagnosis-Related Group code, as defined by Medicare. Classifications are based on: Primary diagnosis, Secondary diagnosis, Surgical procedures (if any), Age, Gender, Presence of complications		
gender	Char(1)	UB-04 Gender code	F -	Female
			M -	Male
			U -	Unknown
			8 -	Invalid
race	Char(1)	UB-04 Race code	W -	White
			B -	Black
			O -	Other
			U -	Unknown
hispanic_ind	Char(1)	Hispanic indicator	Y-	Yes
			N-	No
			U-	Unknown
age	Smallint	Patient age in years, calculated as admit_date - birth_date	0 - 89	age

Table 4. Clinical Variables: Premier Specific Information

Field Name	Data Type	Description	Valid Values	
disc_status	Smallint	UB-04 Discharge status code	1	Home
			2	Short-Term Gen Hosp
			3	SNF
			4	ICF
			5	Other Institution
			6	Home Under HHO
			7	Left AMA
			8	Home On IV Meds
			9	Admitted As I/P To This Hosp
			20	Expired
			30	Still A Patient
			40	Expired At Home (Hospice)
			41	Expired Hosp, SNF,ICF (Hospice)
			42	Expired,Place Unknown(Hospice)
			43	Dischrgd/Trnsfrd To Fed Hosp
			50	Discharge To Hospice-Home
			51	Discharge To Hospice-Facility
			61	Dischg/Transfer To Swing Bed
			62	Dschg/Transfer Other Rehab
			63	Dschg/Transfer To LTC Hosp
			64	Dischrgd/Trnsfrd To A Nursing
			65	Dischrgd/Trnsfrd To Psyc
			66	Dischg/Trnsfrd to a CAH
			70	Dischg/xfered oth hlth inst not in list
			71	Dschg Other Inst For OP Svcs
			72	Dischg This Inst For OP Svcs
			98	Invalid Code Provided
			99	Information Not Available

std_chg_desc	Char(50)	Perspective Standard Charge Master Code Description, Version 10		
admit_number		Facility-assigned; identifies unique visit.		
specimen_id		Identifies unique specimen. Data includes results for all tests run on same specimen.		
Spec_day_number/ time_of_day		Hospital Day number and time stamp of specimen submission.		
test and test_method		test= Type of specimen and test method where applicable (example—blood culture). test_method= laboratory method used (example—MIC).		
result_organism and observation		result_organism= Specific organism for which sensitivity testing was conducted. observation= Test result including organism identification.		
medication		Type of medication sensitivity testing was conducted.		
result		Lab value of test result.		
interpretation		Categorical result of Susceptible, Intermediate, or Resistant.		

Appendix C. Polymyxin Gram-Negative Spectrum of Activity[10,29-30]

Gram-Negative Bacilli	**Spectrum of Activity**
Acinetobacter baumannii	Active
Pseudomonas aeruginosa	Active
Escherichia coli	Active
Klebsiella pneumoniae	Active
Stenotrophomonas maltophilia	Active
Aeromonas species	Active
Citrobacter species	Active
Enterobacter species	Active
Serratia and *Proteus* species	Intrinsically Resistant
Providencia species	Intrinsically Resistant
Morgenella species	Intrinsically Resistant
Burkholderia cepacia	Intrinsically Resistant

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