The Impact of Serum Glucose on Clinical Outcomes in Patients Hospitalized with Community-Acquired Pneumonia

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ABSTRACT

Purpose: Community-acquired pneumonia (CAP) is a common medical condition resulting in excess morbidity, mortality, and high rates of hospitalization. Despite high hospitalization rates for CAP, the relationship between abnormal glucose levels (hyperglycemia and hypoglycemia) and the seriousness of the illness as measured by length of stay (LOS) is not well established. We examined relationships of CAP to multiple factors that impact predictability and severity of the disease process. They include glycemic control; hospital utilization, including LOS; 30-day hospital readmission; intensive care unit (ICU) admissions, adjusting for comorbidities; illness severity; and timing of antibiotic treatment.

Methods: We conducted a retrospective observational cohort study of adult patients hospitalized for CAP between January 1, 1992 and June 23, 2007. Case screening was conducted electronically using *International Classification of Diseases, 9th Revision (ICD-9)* codes 480.0-487.9. Subsequent medical record abstraction yielded 969 qualifying cases with comprehensive data on past and current medical problems.

Results: Serum glucose levels at admission were independently associated with LOS for CAP patients. Patients with levels between 90 mg/dL and 140 mg/dL on admission had shorter LOS compared to those with levels of < 90 mg/dL and > 140 mg/dL (median 3.9 vs 4.2 days, $P = .04$). Multivariate analyses confirmed the univariate results. Serum glucose levels at initial hospitalization were not associated with 30-day hospital readmission ($P = .34$) or ICU admission ($P = .48$).

Conclusions: Abnormal glucose levels are an independent predictor of increased LOS for CAP. Control of blood glucose may lead to improved outcomes, including shortened LOS, and should be a priority in CAP management.

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INTRODUCTION

Community-acquired pneumonia (CAP) and hyperglycemia are common medical conditions resulting in increased morbidity, mortality, and high rates of hospitalization. Both have been associated with prolonged hospitalization and higher mortality rates in patients undergoing cardiovascular surgery; with acute coronary syndrome, stroke, and trauma; and in surgical and medical intensive care unit (ICU) settings compared to nondiabetics and normoglycemic patients.[1-12] Higher rates of infections and infectious complications in the perioperative period have been described in diabetic patients, and it has been suggested that the cellular components of the immune system are contributing factors.[13-17]

In addition to host immune response, CAP severity is influenced by a number of factors, including immune comorbidities and the virulence of the causative organism.[18-20] The relative impact of glycemic control on length of stay (LOS), readmission rate, and mortality among CAP patients has not been well established. A retrospective study of 2030 community teaching hospital patients diagnosed with CAP reported that 38% were hyperglycemic (blood glucose ≥ 126 mg/dL or 2 measurements ≥ 200 mg/dL).[1] New onset of hyperglycemia in the absence of a history of diabetes was also predictive of increased LOS, higher ICU admission rates, higher in-hospital mortality rates, and long-term care with frequent follow-up visits.[1] A recent study of hospitalized CAP patients showed that secondary medical complications were more prevalent among those whose admission blood glucose exceeded 198 mg/dL.[12]

Evidence that hyperglycemia affects the outcomes of other

conditions suggests a need for its evaluation in the context of CAP-hospitalized patients.[1-12] Indirect evidence from these studies suggests that hyperglycemic patients may have more severe episodes of pneumonia, as evidenced by longer hospitalization periods, more intense resource use during hospitalization, and potentially higher mortality rates compared to normoglycemic patients. To further investigate these relationships, we systematically evaluated the association of serum glucose levels with LOS, 30-day hospital readmission, and mortality in patients with CAP, while controlling factors previously determined to impact CAP severity, including antibiotic use.

Table 1. Case Definition of Community-acquired Pneumonia

New radiographic evidence dictated on an x-ray report containing any of the following terms:	Symptoms of acute respiratory infection including 1 or more of the following:
Infiltrate	Documented evidence of fever (≥38°C/104°F) or hypothermia (≤36°C/96.8°F)
Air bronchogram	Rigors or chills
Interstitial	Sweats or diaphoresis
Air space disease	New cough with or without sputum production
Consolidation	Change in color of respiratory secretions in a patient with a chronic cough
Opacity	Chest discomfort or chest pain
Pneumonitis	Onset of dyspnea or shortness of breath
Density	

Table 2. Study Inclusion and Exclusion Criteria

Inclusion Criteria
Age >17 years at diagnosis
Radiologic evidence of CAP within 6 hours of presentation, including pulmonary infiltration, air space disease, consolidation, interstitial, density, infiltrate, opacity, or overt pneumonitis
One or more symptom(s) of acute lower respiratory tract infection, including fever (≥38°C or 100.4°F) or hypothermia (≤36°C or 96.8°F), rigors or chills, sweats or diaphoresis, new cough with or without sputum production, or the worsening of a chronic cough (frequent/more intense), increase in the quantity of respiratory secretions, appearance of new secretions, or change in color of respiratory secretions associated with a chronic cough, chest discomfort or chest pain (included "chest pressure"), and onset of new or worsening dyspnea or shortness of breath
At least 1 fasting glucose measure within 6 hours of presentation
Hospital admission to a short-term general-stay hospital
Exclusion Criteria
Antibiotics initiated for respiratory symptoms within 3 weeks prior to reference hospitalization
Intensive care unit admission or transfer within 12 hours following reference hospital admission
Patients transferred from another hospital
Patients who left the hospital against medical advice during reference hospitalization
Hospital discharge <30 days preceding reference hospital admission date (to rule out nosocomial pneumonia)
Pneumonia diagnosed ≥48 hours after reference hospital admission date
History of or suspected:
Aspiration, fungal, or viral pneumonia at reference hospitalization (ie, influenza pneumonia, RSV, adenoviruses, aspergillosis, histoplasmosis, coccidoidomycosis, blastomycosis, sporotrichosis)
Pulmonary tuberculosis or pneumocystis carinii pneumonia within 1 year prior to admission
Acquired immune deficiency syndrome or human immunodeficiency virus infection
Tracheostomy

METHODS

This study was approved by the Institutional Review Board of Marshfield Clinic/St. Joseph's Hospital with waiver of informed consent.

We conducted a retrospective observational cohort study of all adult patients admitted to St. Joseph's Hospital (Marshfield, Wisconsin) for CAP between January 1, 1992 and June 23, 2007. Initial screening was performed electronically using *International Classification of Diseases, 9th Revision (ICD-9)* codes 480.0-487[9] followed by manual chart review. The manual review was intended to restrict CAP cases with bacterial pneumonia accompanied by new radiographic evidence and 1 or more symptoms that were highly consistent with acute lower respiratory infection. These criteria are summarized in Table 1. Study inclusion and exclusion criteria are summarized in Table 2.

We validated electronically obtained diagnoses, hospital admission and discharge dates, and 30-day readmission dates. Patient demographic and clinical data relevant for CAP were abstracted, including timing and quality of antibiotic treatment, alcohol abuse, diabetes, current treatment for malignancy, antihyperglycemic control, and corticosteroid use 3 weeks prior to hospitalization. Serum glucose levels were obtained at admission and periodically during the remaining hospital stay. Hyperglycemia was defined as a serum glucose measurement ≥140 mg/dL. Comorbidities applied to any medical conditions recorded at presentation and up to 1 year prior to admission.

Timing and appropriateness of antibiotic treatment during the first 24 hours of care were developed to assess initial CAP management. The former was based on the difference in time (in minutes) between the first documentation of medical

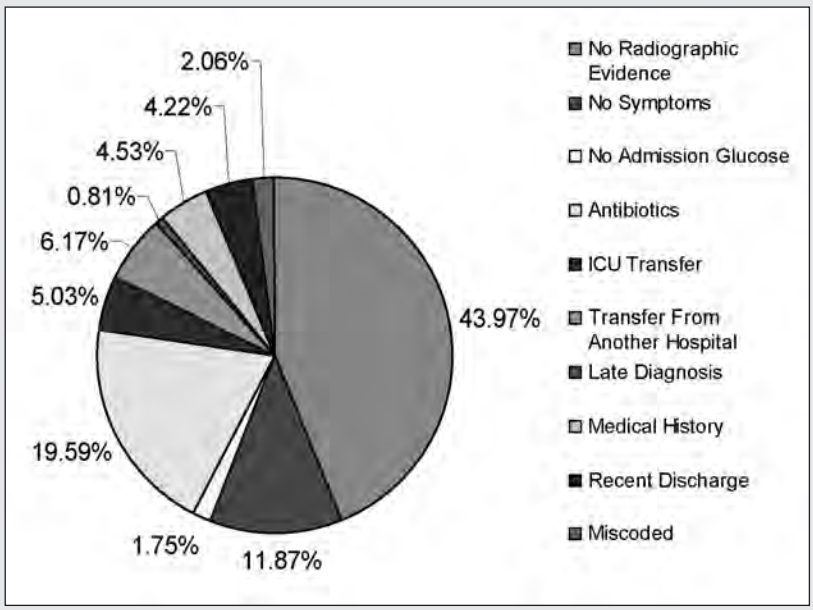

Figure 1. Reasons for exclusion of the 672 cases (41% [672/1641]).

care for CAP and antibiotic administration. Appropriateness of initial antibiotic treatment was determined based on Infectious Disease Society of America (IDSA) guidelines that were first developed in 1998 and subsequently revised in 2000 and 2003.[21-23] The 1998 guidelines were applied to hospitalizations that occurred in 1999 and 2000, the 2000 guidelines were applied to hospitalizations that occurred from 2001 to 2003, and the 2003 guidelines were applied to hospitalizations from 2004 to 2007. Since IDSA guidelines did not exist before 1998, we applied the 1998 IDSA recommendations retrospectively to assign "approximate appropriateness" of antibiotic selection for hospitalizations that occurred between 1992 and 1998.

The Pneumonia Severity Index (PSI)[24] and the Charlson Comorbidity Index (CCI)[25] were used to stratify illness severity and the number and severity of comorbid conditions. High CCI scores have been shown to be predictive of hospital readmission at 1 year or death in elderly patients with CAP.[26]

Statistical Analyses

A Wilcoxon rank-sum test was performed to evaluate the association between LOS and other factors, including demographic characteristics, diabetes and other comorbid conditions, clinical measurements, PSI, and CCI. Univariate logistic regression analysis was applied to determine which factors were associated with ICU admission. In addition, univariate analyses (including Wilcoxon rank-sum test and logistic regression) were used to analyze factors related to 30-day readmission. Finally, multivariate logistic regression analyses were conducted to build the predictive models of mortality at various time periods (1 year, 90 days, 60 days, and 30 days).

RESULTS

Initial electronic screening identified 1641 potential cases. Subsequent chart review validated 969 CAP cases. The most common reasons for exclusion were a normal chest x-ray (44%), antibiotic treatment within 3 weeks prior to presentation (20%), and no symptoms (12%) (Figure 1). Because the vast majority of subjects were Marshfield Clinic patients, there were no systematic data problems, including data needed for PSI and CCI measures, which are believed to have affected results.

Data on demographic factors and selected clinical measures related to CAP are summarized in Table 3. The mean age of subjects was 74 years. There were 544 males (56%) and 425 females (44%). Hyperglycemia (ie, glucose ≥140 ml/dL) at admission was documented in 38.2% (370/969) of subjects, including 19 subjects with serum glucose levels ≥200 mg/dL who did not have a diagnosis of diabetes prior to admission. Median time to antibiotic intervention was 4.9 hours (interquartile range [IQR] = 3.0, 7.1). Median LOS was 4.0 days. The 30-day readmission rate was 8% (77/969).

Length of Stay

Median LOS for admission glucose levels between 90 mg/dL and 140 mg/dL was 3.9 days compared to 4.2 days for glucose levels outside this range ($P = .04$). Univariate results for the other demographic and clinical factors are summarized in Table 4. History of diabetes did not demonstrate a strong univariate statistical relationship to any outcome measure; its strongest relationship was to LOS ($P = .24$).

30-Day Hospital Readmission

Overall, 8% of CAP cases (77/969) were readmitted for various causes. We examined univariate relationships between readmission probability and demographic and clinical factors relevant for CAP including glycemic control, diabetes, and the timeliness and quality of antibiotic therapy. Only age demonstrated an association with 30-day readmission; the median age for readmitted subjects was 80.6 years compared to 76.9 years for those not readmitted ($P < .01$).

Treatment with Hyperglycemic Agents and Corticosteroids

Changes in serum glucose are reported as the difference between the patient's first glucose measurement occurring within 6 hours of admission and median glucose levels obtained dur-

ing their hospitalization. Patients treated with antihyperglycemic medications during hospitalization (n = 212) experienced a large decrease in serum glucose levels (median = 37.7 mg/dL [$P < .01$]). Patients not treated with corticosteroids within 3 weeks prior to hospital admission (n = 839) also experienced a decrease in serum glucose levels (median 5.6 mg/dL [$P = .09$]). Patients with a low PSI score (n = 925) (PSI = high if > 4, and PSI = low if < 3) demonstrated a significant decrease in serum glucose during hospitalization (median difference of 4.5 mg/dL [$P < .02$]).

ICU Transfer

High risk glucose levels were not associated with ICU admission. However, patients who were not treated according to IDSA guidelines were more likely to experience an ICU admission (OR = 3.24, $P < .02$), as were patients who developed at least 1 medical complication (ie, sepsis, neurological, cardiac, renal, pulmonary) (OR = 8.22, $P < .01$). Additionally, those with a high PSI score (≥ 4) and CCI score (≥ 5) were also more likely to develop medical complications (Table 5).

Mortality

Approximately 21% of study subjects (205/969) died within 365 days of the reference hospital admission. Multivariate predictive models were constructed to investigate the relationship between mortality and study demographic and clinical factors. Although serum glucose levels were not predictive of mortality in any time interval, treatment with corticosteroids was positively associated with mortality at 1 year (OR = 1.80, $P < .01$). Risk factors associated with mortality at 30 days, 60 days, 90 days, and 1 year are reported in Table 6.

Table 3. Demographic and Risk/Severity Factors

Factor	N/Measure	%
Study subjects	969	100.0
Age (mean)	73.8 years	--
Gender		
Male	544	56.1 (544/969)
Female	425	43.9 (425/969)
Diabetes Diagnosis	212	21.9 (212/969)
PSI Risk Group		
PSI ≥91	35	3.6 (35/969)
PSI <91	934	96.4 (934/969)
CCI Class		
0	185	19.1 (185/969)
1-2	437	45.1 (437/969)
3-9	334	34.5 (334/969)
≥10	13	1.3 (13/969)
Glucose at Admission (mg/dL)		
<90	22	2.3 (22/969)
90-139	577	59.5 (577/969)
≥140	370	38.2 (370/969)
1-year mortality	205	21.16 (205/969)
Admission Symptoms		
Fever	473	49.22 (473/961)
Chills	494	51.30 (494/963)
Sweats	161	16.91 (161/952)
New cough	819	84.78 (819/966)
Change in secretions	63	6.57 (63/959)
Chest pain	327	34.06 (327/960)
Shortness of breath	699	72.29 (699/967)

PSI=Pneumonia Severity Index; CCI=Charlson Comorbidity Index.

DISCUSSION

Recent studies have shown that patients with elevated blood glucose at hospital admission experience a more complicated medical course, higher infection rates, higher mortality rates, and longer length of hospitalization than those with normal blood glucose levels.[1,2,4,5,11,12] Despite these findings and the high frequency of CAP hospitalizations, there is a paucity of literature regarding the effect of hyperglycemia and/or diabetes mellitus on clinical outcomes for these patients.[1] Results of previous studies suggest that elevated glucose levels are a contributing factor to increased morbidity and mortality in patients with CAP.

Our study validates previously published findings showing that admission glucose values are useful in predicting clinical outcomes such as LOS in hospitalized patients.[12] In contrast, a past history of diabetes did not demonstrate strong association with any study outcome measure and for that reason was excluded from multivariate analyses. Together these findings reinforce results from a few other studies that found that admission blood glucose level may be a more useful prognostic tool than a past history of diabetes, especially as a predictor of mortality among patients both with and without a pre-admission diagnosis of diabetes.[12,27] Although this finding may reflect the incidence of undiagnosed diabetes, it nonetheless reinforces the importance of obtaining glucose measurements upon admission for suspected CAP.

Our *a priori* expectation, that patients with hyperglycemic glucose levels (>140 mg/dL) would experience longer LOS, was confirmed.[12] However, we also found that patients with glucose values < 90 mg/dL also experienced a longer LOS. The latter finding was unexpected, and the underlying reasons for it are unclear. Intensive control of blood glucose levels has been found to be associated with a higher incidence of significant hypoglycemia as well as increased mortality.[28-30] A recent publication in a population-based sample of patients hospitalized with pneumonia and hypoglycemia (defined as < 4 mmol/L [72 mg/dl]) showed increased in-hospital and 1-year mortality in patients with an admission glucose < 4 mmol/L.[31,32] Thus, our study confirms findings from prior studies showing that suboptimal control of serum glucose—hyperglycemia as well

Table 4. Association between Risk Factors and Length of Stay, Univariate Analysis

Factor	LOS median days (N)	*P*-value
PSI (≥4 vs ≤3)	6.95 (35) vs 4.02 (934)	0.0016
CCI (≥5 vs ≤4)	4.19 (107) vs 4.02 (862)	0.1856
Complication[a] (at least 1 vs none)	7.52 (124) vs 3.84 (845)	<0.0001
Smoking (current/previous smoker vs never smoked)	3.78 (507) vs 4.10 (462)	0.0064
Alcohol (current/previous abuse vs never abuse)	4.89 (71) vs 4.02 (898)	0.0109
Corticosteroids use (yes vs no)	4.69 (121) vs 3.97 (848)	0.0098
Treatment for malignancy (yes vs no)	5.82 (41) vs 4.02 (928)	0.0193
Transfer to ICU (yes vs no)	13.26 (29) vs 4.00 (937)	<0.0001
Admission glucose (90<Glu<140 vs ≤90 and ≥140)	3.99 (572) vs 4.16 (397)	0.0398

PSI=Pneumonia Severity Index; CCI=Charlson Comorbidity Index.
[a] Complication includes diagnosis of sepsis, neurological, cardiac, renal, and pulmonary.

Table 5. Univariate Analysis of Potential Risk Factors Associated with Development of Complications

Risk Factor	Odds Ratio	*P*-value
High Pneumonia Severity Index Score[a]	3.033	0.0067
High Charlson Comorbidity Index Score[b]	1.853	0.0269

PSI=Pneumonia Severity Index; CCI=Charlson Comorbidity Index.
[a] High PSI Score ≥ Category 4
[b] High CCI Score ≥5

as hypoglycemia—may contribute to poorer outcomes among hospitalized patients with CAP.

Time to Administer Antibiotics

Previous guidelines recommended that antibiotics be administered within 4 to 8 hours of presentation because mortality rises when first administration occurs beyond an 8-hour time frame. However, analysis of 13 observational studies comparing outcomes associated with early versus delayed antibiotic treatment did not provide sufficient evidence that antibiotic treatment within 4 hours yields better outcomes.[33] Studies assessing an 8-hour cutoff time also did not produce significant evidence of improved patient outcome.[33] As a result of these conflicting findings, the validity of a 4-hour or 8-hour time frame in which to initiate antibiotics remains controversial.[34]

Adherence to IDSA guidelines has been shown to reduce LOS and mortality rate.[35,36]

In our study, we developed a continuous measurement of time-to-antibiotic using initial presentation time, whether in the emergency department or urgent care, as the index time. However, despite this approach, we did not identify an association between the time-to-antibiotic treatment and LOS, medical complications, 30-day readmission, or mortality. We did find an association between ICU admission and lack of adherence to IDSA guidelines for the treatment of CAP that is suggestive of a relationship between ISDA guideline adherence and LOS through ICU admission effects on LOS. This finding is consistent with results from an earlier study that found hospitalized CAP patients not treated according to IDSA guidelines were more likely to be transferred to the ICU.[34]

PSI

Over 96% of our study cohort were classified as PSI risk level III and below, and over 90% were level II or below, indicating generally low levels of severity that can often be successfully treated on an outpatient basis.[21] Our results differ from other studies that reported only 31%-43% of patients categorized into PSI risk levels III and below, when PSI values were used as a guide for needed hospitalization.[37] Some of these differences may be attributable to socioeconomic factors and/or medical needs not accounted for by the PSI, including lack of home-care support, medication compliance, social disposition, differences in the structure of CAP treatment guidelines, and failure of outpatient treatment.

In addition, the study periods also may have affected these results. The first published report of the PSI appeared in 1997,[21] and although it appears to have been rapidly accepted into medical practice, its adoption was likely not widespread until over halfway through our study period, resulting in a larger proportion of low-risk PSI patients in our cohort. The mid-study period diffusion of the PSI into hospitalization decision for CAP patients combined with our older study cohort (mean age 73.8 years) also likely contributed to higher levels of hospitalization among otherwise low risk PSI patients. Prior to the widespread use of the PSI, there appears to have been a significant bias in physician decision toward hospitalizing older CAP patients (65 years and older).[38]

Limitations

Our study cohort comprises a disproportionately large number of less severely ill CAP patients. More than 90% of the cohort was classified in PSI categories I and II, which are indicative of an expected 30-day mortality risk of <1%. Only 1 study subject was classified in PSI category V, which is associated with a >10% 30-day mortality risk. This somewhat healthier CAP cohort may have made it more difficult to detect LOS and mortality risks associated with CAP complications stemming from serum glucose levels. It also may have made it more difficult to isolate the effects of appropriate and timely antibiotic

Table 6. Multivariate Logistic Regression Results for Mortality Risks at Various Time Periods

Mortality Risk Factor	30-Day Odds Ratio	P-value	60-Day Odds Ratio	*P*-value	90-Day Odds Ratio	*P*-value	1-Year Odds Ratio	*P*-value
PSI ≥4	6.97	<0.0001	6.63	<0.0001	8.85	<.0001	4.62	< 0.0001
CCI ≥5	—	—	—	—	—	—	1.70	0.0264
Complication	2.48	0.0052	2.09	0.0137	—	—	1.74	0.0138
Comorbidities	4.93	0.0290	6.93	0.0078	5.44	0.0045	3.85	0.0002
Transfer to ICU	3.56	0.0122	4.13	0.0021	4.23	0.0011	—	—
Corticosteroid	—	—	—	—	—	—	1.80	0.0091
Alcohol abuse	—	—	—	—	2.10	0.0351	1.94	0.0191
Malignancy treatment	—	—	—	—	—	0.0218	2.23	—
Concordant (%)	54.1		51.3		45.3		58.3	
AUC	0.724		0.711		0.682		0.691	

PSI=Pneumonia Severity Index; CCI=Charlson Comorbidity Index; ICU=Intensive Care Unit; AUC=Area under curve.

administration on clinical outcomes.

We relied on fasting blood glucose measurements as our indicator of glucose level and differences in glucose levels during hospitalization as our measure of glucose control. It may have been more beneficial to measure glucose control using a broader-based measure, such as the hyperglycemic index.[39]

CONCLUSION

Further investigation and elucidation of the impact of serum glucose on hospital outcomes in patients with CAP should expand our understanding with direct translational benefit on informed care management decisions. Prospective studies are needed to compare clinical and mortality outcomes associated with intensive versus conventional hypoglycemia/hyperglycemia treatment in patients hospitalized with CAP.

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