The Relation Between Hyperglycemia and Outcomes in 2,471 Patients Admitted to the Hospital With Community-Acquired Pneumonia

FINLAY A. MCALISTER, MD, MSC, FRCPC[1]
SUMIT R. MAJUMDAR, MD, MPH, FRCPC[1]
SANDRA BLITZ, MSC[2]
BRIAN H. ROWE, MD, MSC, CCFP(EM)[2]
JACQUES ROMNEY, MD, MSC, FRCPC[3]
THOMAS J. MARRIE, MD, FRCPC[4]

OBJECTIVE — To examine whether hyperglycemia at the time of presentation was associated with outcomes in patients admitted to non–intensive care settings with community-acquired pneumonia (CAP).

RESEARCH DESIGN AND METHODS — Prospective cohort study of consecutive patients admitted to six hospitals between 15 November 2000 and 14 November 2002.

RESULTS — Of the 2,471 patients in this study (median age 75 years), 279 (11%) had serum glucose at presentation >11 mmol/l: 178 of the 401 patients (44%) with a prior diagnosis of diabetes and 101 of the 2,070 patients (5%) without a history of diabetes. Of patients hospitalized with CAP, 9% died and 23% suffered an in-hospital complication. Compared with those with values ≤11 mmol/l, patients with an admission glucose >11 mmol/l had an increased risk of death (13 vs. 9%, $P = 0.03$) and in-hospital complications (29 vs. 22%, $P = 0.01$). Compared with those patients with admission glucose ≤6.1 mmol/l, the mortality risk was 73% higher (95% CI 12–168%) and the in-hospital complication risk was 52% higher (12–108%) in patients with admission glucose >11 mmol/l. Even after adjustment for factors in the Pneumonia Severity Index, hyperglycemia on admission remained significantly associated with subsequent adverse outcomes: for each 1-mmol/l increase, risk of in-hospital complications increased 3% (0.2–6%).

CONCLUSIONS — Hyperglycemia on admission is independently associated with adverse outcomes in patients with CAP, with the increased risks evident at lower glucose levels than previously reported.

Diabetes Care **28:810–815, 2005**

Each year in the U.S. >5 million people develop community-acquired pneumonia (CAP) and ~600,000 are hospitalized. Direct health care costs associated with the treatment of CAP are approaching $9 billion per annum (1). CAP is the sixth leading cause of death in the U.S. and the most common cause of death related to infection; case fatality rates for inpatients range between 8 and 14% (1). Because the majority of CAP-related morbidity and mortality occurs among people hospitalized at some point during their illness, hospitalized patients are a key focus for studies of pneumonia (1). In particular, finding ways to improve outcomes and decrease health resource utilization in this population that move beyond early recognition and judicious and timely use of antibiotics should be a priority.

Hyperglycemia is an independent predictor of morbidity and/or mortality in patients admitted for acute coronary syndromes, ischemic stroke, heart failure, trauma, and a variety of surgical procedures (2–12). While admission glucose levels ≥14 mmol/l have been identified as one of the 20 factors associated with poor outcomes in CAP (comprising the Pneumonia Severity of Illness scale) (13), it remains unclear whether lesser degrees of hyperglycemia are associated with adverse prognoses.

Thus, we examined the relationship between hyperglycemia and short-term outcomes, with a focus on glucose levels below the 14-mmol/l threshold cited in the Pneumonia Severity Index. This question is important to answer since diabetes is a common comorbidity (present in up to 25% of all hospitalized patients) (14) and the current standard of care on most general medical wards tolerates moderate levels of hyperglycemia. Indeed, it is not uncommon for active treatment of glucose levels to be deferred until they are >14 mmol/l (the threshold for glycosuria) (15–17).

RESEARCH DESIGN AND METHODS

— Capital Health (Edmonton, Alberta, Canada) is one of the largest integrated health systems in Canada and serves ~1 million people. From 15 November 2000 to 14 November 2002, 2,785 adults were admitted with a clinical diagnosis of CAP by 318 different physicians in all six hospitals affiliated with Capital Health. Patients were excluded from this study if they did not have glucose measured at presentation; if they had physician-diagnosed or -suspected aspi-

From the [1]Division of General Internal Medicine, University of Alberta Hospital, Edmonton, Canada; the [2]Department of Emergency Medicine, University of Alberta Hospital, Edmonton, Canada; the [3]Division of Endocrinology, University of Alberta Hospital, Edmonton, Canada; and the [4]Division of Infectious Disease, University of Alberta Hospital, Edmonton, Canada.

Address correspondence and reprint requests to Dr. F. McAlister, 2E3.24 WMC, University of Alberta Hospital, 8440 112 St., Edmonton, Alberta, Canada T6G 2R7. E-mail: finlay.mcalister@ualberta.ca.

Received for publication 6 October 2004 and accepted in revised form 17 December 2004.

Abbreviations: CAP, community-acquired pneumonia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical factors in patients with CAP*

	Admission glucose (mmol/l)			
	≤6.1	6.11–11.0	11.01–13.99	≥14.0
n	824	1,368	132	147
Demographics				
Age (median)	71	76	77	73
Male (%)	52	53	48	50
Nursing home resident (%)	12	17	23	16
Comorbidities				
Prior history of diabetes (%)	7	12	52	74
Altered mental status (%)	15	14	17	19
Neoplasm (%)	10	9	6	3
Liver disease (%)	5	3	2	1
Congestive heart failure (%)	15	19	27	19
Cerebrovascular disease (%)	7	10	11	8
Renal disease (%)	14	13	17	16
Number of medications reported [median (IQR)]	4 (2–6)	5 (3–7)	6 (3–8)	5 (3–7)
At presentation				
Temperature <35 or ≥40°C	1	2	2	3
Heart rate ≥125 bpm	11	14	18	19
Respiratory rate ≥30/min	20	30	38	31
Oxygen saturation ≤89%	29	32	37	39
Systolic blood pressure <90 mmHg	3	1	2	3
Sodium <130 mmol/l	6	6	5	9
Hematocrit <0.30	11	10	6	10
Blood urea nitrogen ≥11 mmol/l	21	23	25	27

The above factors are components of the Pneumonia Severity Index (13) (except number of medications prior to admission and prior history of diabetes). IQR, interquartile range (25th–75th percentile).

ration pneumonia, tuberculosis, or cystic fibrosis; if they were immunosuppressed (e.g., had HIV infection and CD4 count <250/mm^3, were using >10 mg/day of prednisone or other immunosuppressive agents, were undergoing active treatment for cancer, or had a history of organ transplantation); if they were pregnant or nursing; or if they required direct admission to the intensive care unit. (Note that patients with CAP and diabetic ketoacidosis or hyperosmolar coma would have been directly admitted to intensive care units and thus would not be included in our study cohort.) After initial triage and assessment in the emergency department, an inpatient physician was consulted for hospital admission in all patients with Pneumonia Severity of Illness scores >90 points or those with lower scores in whom the emergency physician felt inpatient care was required (13). All admitted patients were treated in a standardized manner according to a regional critical pathway for CAP inpatients, which has been previously described (18). While choice of antibiotics, conversion from intravenous to oral therapies, and physiotherapy resources were standardized for all patients, management of comorbidities, such as diabetes, was left to the discretion of each patient's attending physician. Six trained research nurses assisted with pathway implementation and prospectively collected standardized data on all study patients.

We decided a priori to examine different degrees of glycemia at admission (>11 mmol/l and ≥14 mmol/l), with the referent group for the bivariate and multivariate analyses being those patients with admission glucose <6.1 mmol/l (the level found to be optimal in a trial of aggressive versus conservative glucose control in intensive care unit patients) (19).

Adverse outcomes before hospital discharge were defined as death, any nonmetabolic complications (i.e., all in-hospital complications except for abnormalities of blood glucose), cardiac complications (acute coronary syndromes and/or heart failure), and nosocomial infections (i.e., in sites other than the lungs). Details were extracted directly from the medical charts. All outcomes were ascertained in an independent and blinded manner by the pneumonia pathway nurses and without knowledge of the hyperglycemia hypotheses outlined herein. The research nurses also assessed which patients had or had not met a priori–defined recovery milestones every 24 h (up to 5 days) after admission, which included becoming afebrile, respiratory rate <24/min, ability to take fluids by mouth, and oxygen saturation improving to ≥89%.

Statistical analyses

In addition to reporting summary statistics for the overall sample, we compared the frequency (for categorical data) and means (for continuous variables) between four patient subgroups defined by admission glucose levels. We examined for differences between the groups in covariates or outcomes using χ^2 tests for trend for categorical variables and Kruskal-Wallis test for continuous variables. Multiple logistic regression models were used to examine the relationship between a variety of covariates, admission glucose, and outcomes. The final multivariate model was fit using the forward stepwise technique with P to include set at 0.05 and P to exclude at 0.10. For all other comparisons, statistical significance was set at $P < 0.05$. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS — Of the 2,785 patients admitted to non–intensive care unit settings with CAP during this study, 314 did not meet our eligibility criteria. The clinical features of the 2,471 patients forming our study sample are outlined in Table 1. Median age was 75 years, 52% were male, 15% were nursing home residents before admission, and 49% were taking at least four prescribed medications before admission. At the time of presentation, 178 of the 401 patients (44%) with a known diagnosis of diabetes and 101 of the 2,070 patients (5%) without a prior diagnosis had glucose exceeding 11 mmol/l. Overall, 9% of patients hospitalized with CAP died, 23% suffered an in-hospital complication, and the median length of stay was 6 days (Table 2).

As can be seen from the bivariate analyses in Table 3, a prior history of diabetes was not associated with mortality (odds ratio [OR] 1.00 [95% CI 0.69–1.45]) or in-hospital complication rates (1.14 [0.89–1.47]).

Table 2—*In-hospital outcomes, grouped by admission glucose level*

	Admission glucose (mmol/l)			
	≤6.1	6.11–11.0	11.01–13.99	≥14.0
n	824	1,368	132	147
Died	8	9	13	12
Length of stay [median days (IQR)]	6 (3–12)	6 (3–11)	8 (4–15)	8 (3–15)
Complications				
At least one in-hospital complication*	21	23	29	29
Cardiac complication (acute coronary syndrome and/or heart failure)	4	6	11	10
Nosocomial infection (nonpulmonary)	2	2	6	3
Milestones				
Failed to meet all milestones	15	14	18	23
Specific milestones not met				
Temperature <37.5°C	8	6	8	12
Respiratory rate <24/min	8	7	9	13
Able to take oral fluids	10	8	10	15
Oxygen saturation returned to baseline	11	10	14	19

Data are expressed as percentages, unless otherwise indicated. *In-hospital complications do not include abnormalities of blood glucose.

However, admission glucose was a significant predictor of adverse outcomes and prolonged length of stay (Table 2). Compared with those with values ≤11 mmol/l, patients with an admission glucose >11 mmol/l had an increased risk of death (13 vs. 9%, $P = 0.03$) and in-hospital complications (29 vs. 22%, $P = 0.01$). These differences were particularly pronounced in those without a prior diagnosis of diabetes (15 vs. 9%, $P = 0.03$ for death and 30 vs. 22%, $P = 0.07$ for in-hospital complications). Patients with an admission glucose >11 mmol/l were less likely to attain a priori–defined milestones for pneumonia recovery by the 5th day of admission (21 vs. 14% in those with admission glucose ≤11 mmol/l, $P = 0.03$) (Table 2). For example, by the 5th hospital day, 90% of patients with an admission glucose ≤11 mmol/l had their oxygen saturations return to normal or baseline compared with 83% of those with glucose >11 mmol/l ($P = 0.02$).

Table 3—*Association between prognostic factors and outcomes in community-acquired pneumonia, results of bivariate analysis*

	In-hospital mortality		In-hospital complications*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographics				
Age (per decade)	1.88 (1.65–2.14)	<0.001	1.19 (1.12–1.26)	<0.001
Male	1.01 (0.77–1.34)	0.93	1.02 (0.84–1.23)	0.85
Nursing home resident	3.84 (2.84–5.18)	<0.001	1.72 (1.35–2.19)	<0.001
Comorbidities				
Prior history of diabetes	1.00 (0.69–1.45)	0.99	1.14 (0.89–1.47)	0.29
Altered mental status	2.97 (2.18–4.06)	<0.001	2.20 (1.73–2.80)	<0.001
Neoplasm	2.48 (1.69–3.64)	<0.001	1.82 (1.35–2.46)	<0.001
Liver disease	0.57 (0.21–1.57)	0.28	0.93 (0.53–1.63)	0.80
Congestive heart failure	1.65 (1.20–2.29)	0.002	1.38 (1.09–1.74)	0.008
Cerebrovascular disease	1.72 (1.15–2.59)	0.009	1.61 (1.19–2.17)	0.002
Renal disease	2.96 (2.16–4.07)	<0.001	1.93 (1.51–2.48)	<0.001
Pleural effusion on CXR	1.93 (1.43–2.60)	<0.001	1.62 (1.30–2.01)	<0.001
Taking four or more medications	1.62 (1.22–2.15)	<0.001	1.50 (1.24–1.82)	<0.001
At presentation				
Temperature <35 or ≥40°C	0.59 (0.14–2.47)	0.47	1.96 (0.99–3.89)	0.06
Heart rate ≥125 bpm	1.53 (1.06–2.19)	0.02	1.21 (0.93–1.59)	0.16
Respiratory rate ≥30/min	2.23 (1.68–2.97)	<0.001	1.38 (1.12–1.70)	0.002
Oxygen saturation ≤89%	1.36 (1.01–1.83)	0.04	0.97 (0.79–1.20)	0.79
Systolic blood pressure <90 mmHg	4.21 (2.23–7.96)	<0.001	1.51 (0.82–2.79)	0.19
Laboratory measurements, glucose (mmol/l)				
6.11–11.0 compared with ≤6.1	1.20 (0.88–1.65)	0.25	1.10 (0.89–1.36)	0.37
11.01–13.99 compared with ≤6.1	1.79 (1.01–3.16)	0.05	1.53 (1.01–2.32)	0.04
≥14 compared with ≤6.1	1.69 (0.97–2.94)	0.07	1.52 (1.02–2.25)	0.04
Sodium <130 mmol/l	1.43 (0.85–2.38)	0.17	1.44 (0.99–2.07)	0.05
Hematocrit <0.30	2.15 (1.48–3.13)	<0.001	1.70 (1.27–2.27)	<0.001
Blood urea nitrogen ≥11 mmol/l	4.69 (3.50–6.28)	<0.001	1.98 (1.59–2.46)	<0.001

The above factors are components of the Pneumonia Severity Index (except number of medications prior to admission and prior history of diabetes). *In-hospital complications do not include abnormalities of blood glucose.

Compared with those patients with admission glucose ≤6.1 mmol/l, patients with admission glucose >11 mmol/l had a 73% higher (95% CI 12–168%) mortality risk and a 52% higher (12–108%) risk of in-hospital complications. Of note, these increased risks were not driven solely by those patients with admission glucose ≥14 mmol/l (as has been previously reported in the Pneumonia Severity Index). A breakdown of the risks in patients with admission glucose 11.01–13.99 and ≥14 mmol/l, along with covariates from the Pneumonia Severity Index, are presented in Table 3. Even after adjustment for other non–glucose-related covariates in the Pneumonia Severity Index (13), hyperglycemia on admission remained significantly associated with subsequent adverse outcomes. For each 1-mmol/l increase in admission glucose, risk of in-hospital complications increased 3% (0.2–6%) in the entire cohort and 5% (1–9%) in those with a history of diabetes; the risk of in-hospital death increased 8% (1–15%) per mmol/l in those with a history of diabetes.

CONCLUSIONS — Using a large dataset from all six hospitals in a large Canadian urban community linked by a common pathway for the treatment of CAP, this analysis indicates that individuals who are hyperglycemic at the time of admission to the hospital are at increased risk for adverse outcomes, including increased mortality, morbidity, and prolonged length of stay. The risk is graded and related to the degree of hyperglycemia; however, contrary to earlier reports (including the Pneumonia Severity Index) (13) and current clinical doctrine, the risk of adverse outcomes is increased at lower glucose levels than are currently felt to warrant intervention in non–intensive care unit patients. Over one-third of our patients with elevated admission glucose levels did not have a prior history of diabetes.

Our results confirm earlier studies suggesting a relationship between hyperglycemia at the time of admission and adverse outcomes (particularly nosocomial infections, cardiac complications, and death) in individuals admitted to the hospital with a wide range of clinical disorders (2–12). Akin with other investigators, we have shown that glucose levels are a more important prognostic factor in hospitalized patients than a prior diagnosis of diabetes (6). Furthermore, our data suggest that the occurrence of these complications is correlated with blood glucose on initial presentation even after adjusting for other confounding factors known to carry prognostic significance in CAP. Patients with hyperglycemia are prone to dehydration secondary to osmotic diuresis and exhibit a variety of perturbations of platelet function and endothelial function, as well as delayed chemotaxis, diminished granulocyte adherence, impaired phagocytosis, and reduced microbiocidal capacity (20–26). These abnormalities tend to develop when glucose exceeds 11 mmol/l and do improve in vitro with better glycemic control (20–26). An observational study, however, cannot be considered definitive, and alternative explanations could account for our findings. For example, hyperglycemia may not be a causal risk factor but merely a marker for an unmeasured confounder.

While there have not been any trials examining whether strict glycemic control improves outcomes in patients admitted to general medical wards, two trials provide some evidence that can inform this debate. In the first trial, 1,548 patients were admitted to a Belgian surgical intensive care unit (87% did not have diabetes, 73% had undergone coronary artery bypass graft, and the median APACHE II score was 9 [interquartile range 6–13]). Patients who were randomized to intensive blood glucose control (with a glucose-insulin infusion to keep their plasma glucose between 4.4 and 6.1 mmol/l) had 46% fewer septic complications and 34% lower mortality compared with those patients managed in conventional fashion (in whom mean fasting glucose averaged 8.5 mmol/l) (19). These results, taken in concert with another trial that demonstrated a 29% relative reduction in 1-year mortality after myocardial infarction in diabetic patients randomized to intensive glucose control (27), suggest that close attention should be paid to glycemic control in hospitalized patients irrespective of whether they have a prior diagnosis of diabetes.

Although this is a prospective study with rigorous collection of data in a standardized fashion and all patients had their pneumonia managed in a similar fashion as per a validated critical pathway, there are four limitations to our study. First, since glucose monitoring was not a component of the CAP care map, we were not able to examine changes in glucose levels during hospitalization in a standardized fashion. Nonetheless, because our results are based only on admission glucose, it is likely that we have underestimated the risks associated with hyperglycemia (given that the patients with the highest levels of glucose would have been more likely to be treated in the hospital setting). Second, even though we analyzed one of the largest community-based cohorts of hospitalized patients with CAP studied to date, we had insufficient numbers to examine the role of various antiglycemic treatments (e.g., insulin, metformin) on outcomes. Third, we did not routinely collect measures of long-term glucose control, such as HbA_{1c}. This would have allowed us to distinguish long-term poorly controlled diabetic patients (irrespective of a formal diagnosis) from those with hyperglycemia as a measure of significant physiological stress. However, given that a history of diabetes was not associated with outcomes on univariate or multivariate analyses in our study, we believe that acute hyperglycemia is more important than long-term glycemic control in predicting prognoses for patients admitted with CAP. Finally, although our cohort was population based and drawn from six different hospitals, all of our patients are from one Canadian health region, and whether our findings are generalizable may be questioned by some. However, our results are similar to those reported by Umpierrez et al. (6) from a community teaching hospital in Atlanta (where one-third of all hyperglycemic patients also did not have a prior history of diabetes and hyperglycemia was independently associated with mortality even after covariate adjustment in 2,030 consecutive adult admissions).

In conclusion, we found that a substantial proportion of our hospitalized patients with pneumonia had hyperglycemia and that this was associated with poor outcomes, even after adjusting for known prognostic factors in CAP. While observational studies (28,29) in non–intensive care unit settings echo the randomized trial evidence (19,27) from critical care units suggesting that stringent glucose control benefits ill patients, we believe that a large randomized trial is required to compare stringent glycemic control on regular inpatient wards with usual care in patients with CAP. The past few years have provided clear illustrations that the

injudicious application of observational evidence or the overly zealous application of evidence from randomized trials conducted in highly specialized settings is fraught with potential harm (30,31). Based on our data, we estimate that a trial enrolling ~900 patients with CAP (using the composite outcome of "death or in-hospital complication") would be required to provide definitive answers about both the safety and the efficacy of stringent glycemic control versus usual care on general medical inpatient units.

Acknowledgments— This research was supported by an Independent Research Establishment Grant from the Alberta Heritage Foundation for Medical Research (AHFMR) to T.J.M. and by grants-in-aid from Capital Health, Abbott Canada, Pfizer Canada, and Janssen Ortho Canada. F.A.M. and S.R.M. are supported by the AHFMR and the Canadian Institutes of Health Research (CIHR). F.A.M. is also supported by the Merck Frosst/Aventis Chair in Patient Health Management at the University of Alberta. B.H.R. is supported by the CIHR through the Canada Research Chairs Program.

We thank the staff of EPICORE (The Epidemiology Coordinating and Research Centre, University of Alberta) for data management services and the Community-Acquired Pneumonia Pathway research nurses: JoAnne de-Jager, Linda Gardner, Lynne Korobanik, Tammy Pfeiffer, Cynthia Proskow, Sue Marshal, and Fredrika Herbert.

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