Evaluation of hyperglycemia as a diagnostic and prognostic tool in systemic inflammatory response syndrome

Columbia University Institutional Review Board proposal, Irving CRC
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September 29, 2013

A. Study purpose and rationale

Sepsis is a leading cause of mortality in critically ill patients. Prompt diagnosis, initiation of antibiotics, and early-goal-directed therapy have been shown to reduce mortality. The diagnosis and appropriate treatment of sepsis is challenging, however, for multiple reasons.

Sepsis is generally thought of as existing along a spectrum of illness, the mildest of which is a combination of nonspecific vital sign abnormalities ("SIRS"), and the most severe being a state of arterial hypotension unresponsive to volume resuscitation with resulting end-organ hypoperfusion ("septic shock"). The systemic inflammatory response syndrome, SIRS, was defined in 1992 by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP-SCCM) with aim to encompass systemic activation of the innate immune response regardless of the presence or absence of infectious source. It is considered to be present when patients have more than one of the following clinical findings: (a) hyperthermia or hypothermia (temp>38°C or <36°C), (b) tachycardia (HR >90/min), (c) tachypnea or hyperventilation (RR>20/min or PaCO2 <32 mmHg), or (d) leukocytosis or leukopenia (WBC of >12,000 or <4,000 cells/mcL)[1]. Sepsis is considered to be present when SIRS is accompanied by infection; severe sepsis when there is also evidence of organ dysfunction or hypoperfusion; and septic shock when sepsis exists with arterial hypotension despite adequate fluid resuscitation. One unfortunate limitation of these definitions is that they suggest that shock can only develop in the presence of infection, though there are other profound inflammatory conditions—burns, trauma, pancreatitis, and acute respiratory distress syndrome, for example—that can result in shock.

Given that expeditious antibiotic therapy has been shown to reduce mortality in patients with sepsis (combined with pressure to reduce inappropriate antibiotic treatment due to concerns of cost and antibiotic resistance), significant focus in critical care medicine has been placed on identifying a biomarker or algorithm that can identify the presence of infection. The gold standard for such determination is the presence of positive microbial cultures, though such data is prone to both false positives and negatives and invariably arrives too late to make expeditious medical decisions about whether to institute antimicrobial therapy. Such focus on identifying infection was entirely justified when the only effective therapy for sepsis syndromes was antibiotics. However, it has since been demonstrated that early goal-directed therapy significantly also improves in-hospital mortality in patients who meet SIRS criteria and have arterial hypotension[2]. The patients in this study

were not limited to those with proven sepsis, and nearly 25% were culture negative. While it is clear neither whether culture-negative patients were truly uninfected, nor whether culture-negative patients benefitted to the same degree as culture-positive patients, early goal-directed therapy may be beneficial in these patients, as well. This is a question certainly deserving of future study, as some reports show that as many of half of patients with presumed sepsis remain culture negative[3].

The primary objective of early goal-directed therapy is to institute aggressive hemodynamic support early after presentation (rather than delaying until after ICU admission)[2]. It follows that optimal outcomes are likely to be obtained when all patients who will develop hypotension secondary to inflammation are identified as early as possible, and treated aggressively. The challenge, however, is that SIRS criteria are nonspecific, and the symptoms and signs of impending sepsis are myriad and variable[4]. It has been estimated that 1/3 of patients in the hospital meet SIRS criteria[5]. Nearly any combination of organs may be affected, and in some patients, the signs and symptoms most associated with infection (fever, leukocytosis, bandemia) may not be present, either because of the patient is not able to mount such a response, or because different stages of illness may present atypically. As such, it would be useful to have additional markers or physiologic readouts that would help clinicians distinguish which patients are likely to become critically ill, in order that aggressive resuscitation be instituted promptly. Although in theory all 4 SIRS criteria as proposed by the ACCP-SCCM can be considered equally predictive of sepsis, in practice many clinicians will presume infection when the patient has leukocytosis or a fever (and often initiate antibiotic therapy), but will not do the same for a patient who is only tachypneic and tachycardic. Thus an additional marker would be most useful if it could distinguish which tachypneic and tachycardic patients (highly non-specific and common signs in the hospital) are likely to have an evolving acute inflammatory illness.

In addition to the 4 SIRS criteria noted above, many other physiologic and laboratory abnormalities have been noted in patients with sepsis, including acutely impaired renal function, altered mental status, coagulation abnormalities, hyperlactatemia, hypoxemia, and hyperglycemia[4]. Blood glucose and creatinine are two laboratory measurements routinely documented in patients who present to the emergency department and are admitted to the inpatient medical service. Hyperglycemia in the absence of diabetes is a physiologic abnormality that is often noted in patients with sepsis, with baseline blood glucose level >110 mg/dL in >75% of septic patients and 12% with glucose >200mg/dL[6]. Stress hyperglycemia is thought to result predominantly from inflammation-induced insulin resistance[7]. Although it is not well documented, hyperglycemia is also likely to be common among patients with SIRS. To our knowledge, however, no previous study has examined the value of hyperglycemia in predicting progression to organ dysfunction and/or shock.

We hypothesize that stress hyperglycemia will be a useful marker to predict the progression to sepsis, severe sepsis, septic shock, and consequently requirement for ICU admission in patients who meet SIRS criteria.

B. Study design and statistical analysis

Design:

This study will be a retrospective, single-site study examining the correlation between hyperglycemia at the time of hospital presentation and later requirement for ICU admission in patients with systemic inflammatory response syndrome. To perform this study, we will examine the medical records of 10,000 adults admitted to the inpatient general medicine, non-ICU services at New York Presbyterian-Columbia University Medical Center over the course of the 2007-2013 calendar years whose exam at any point during the first 24 hours after presentation includes the following 2 SIRS criteria simultaneously: (1) HR>90bpm, (2) RR>20 or $pCO2<32$. The above two SIRS criteria were selected on the basis of the assumption that patients with documented abnormalities of body temperature or leukocyte count are more likely to receive empiric antibiotics. Medical records of these patients will be examined in order to extract demographic data including age, race, sex, and pre-existing medical conditions. Subsequently, this patient population will be divided into two groups consisting of patients with maximal documented blood glucose <140mg/dL within the first 24 hours after presentation ("normoglycemic group"), and those with blood glucose $\geq$140 mg/dL ("hyperglycemic group") documented at any time within the first 24 hours after presentation. This blood glucose level was selected because it marks the threshold for diagnosis of impaired glucose tolerance when measured post-prandially.

Outcomes:

The primary outcome measured will be admission to the ICU at any time within the first 28 days of the index hospital admission. This duration was chosen on the basis of previous studies showing that the median interval to sepsis among patients meeting at least 2 SIRS criteria is 21 days[3]; moreover, a marker that predicts progression of disease beyond 28 weeks of hospitalization is less likely to be clinically useful.

Secondary outcomes will include the following:

(1) documented clinical diagnosis of "sepsis," as defined by SIRS criteria *plus* requirement for empiric antibiotic treatment but not requiring culture-proven infection.

(2) diagnosis of "severe sepsis" as defined by the above, in addition to at least one of the following:
   a. a reduction in systolic blood pressure to <90mm Hg in the absence of acute blood loss
   b. a 50% reduction of blood pressure in hypertensive patients
   c. evidence of end-organ hypoperfusion, as assessed by any of the following: lactic acidosis (>1mM); oliguria (<0.5mL/kg/hr for 2 hours) or acute elevation of serum creatinine by $\geq$0.5mg/dL; acutely

altered mental status; *or* hypoxemia (PaO2/FiO2 <200 in presence of pneumonia or <250 in absence of pneumonia)[8]

(3) diagnosis of "septic shock" as defined by "severe sepsis" unresponsive to a 500mL intravenous fluid bolus *or* sepsis plus use of a vasopressor.

(4) death from any cause.

For the purposes of this study, the diagnoses of "sepsis," "severe sepsis" and "septic shock" will not require culture-documented infection.

In addition to these specific diagnoses, we will record culture-documented infections, administration of antibiotics, and development of additional SIRS criteria within the first 28 days of the index hospital admission to be used as additional secondary outcomes.

We anticipate that some of the patients with hyperglycemia at admission will have pre-existing diabetes mellitus that is undiagnosed, not known to the patient despite a previous diagnosis, and/or not recorded in the medical record. Therefore, in addition to the above analysis, this study will include a subgroup analysis excluding patients who are undiagnosed diabetics at the time of the index hospitalization. Such patients will be defined by hemoglobin A1C $\geq$ 6.5% or formal diagnosis of diabetes made within 3 months of the index hospitalization and documented in the electronic medical records of the New York Presbyterian Hospital system (Eclipsys, Webcis, or Crown databases).

Sample size & power analysis

In a previous study, ~50% of patients meeting SIRS criteria became septic (suspected or culture-verified infection) within 28 days; ~40% developed severe sepsis; and ~7% developed septic shock[3]. Accounting for the possibility that tachycardia and tachypnea are less likely than other SIRS criteria to predict progression to sepsis, severe sepsis or septic shock, we will anticipate a 50% reduction in such cases. This will yield an approximately 25% chance of developing sepsis, 20% chance of developing severe sepsis, and 3.5% chance of a patient developing septic shock within 28 days of admission. We anticipate that the pool of patients admitted to the intensive care unit will include all patients with septic shock, and at least 25% of patients with severe sepsis, for a total of 8.5% of patients. In order to be clinically useful as a diagnostic and prognostic marker, hyperglycemia would have to confer at least a 50% increase in risk (from 8.5% to 12.75%, or an effect size of 4.25% for ICU admission) We anticipate conservatively that at least 25% of studied patients will meet criteria for hyperglycemia. In order to obtain of α=0.05 and a power of 0.80 with these estimated proportions, we would required 2083 normoglycemic patients and 521 hyperglycemic patients. To measure a 50% increase in risk of developing septic shock (from 3.5% to 5.25%, or 1.75% effect size), we would require 5379 normoglycemic patients, and 1345 hyperglycemic patients, or a total of 6,734 patients. Thus, we will plan to include 10,000 subjects in our analysis in order to detect a clinically significant difference in the primary and all secondary endpoints. Data will be subjected to chi-square analysis.

C. Study procedure

For the purpose of this study, 10,000 patient records meeting the above-specified criteria will be reviewed as described. All patient identifiers will be removed after data extraction from the electronic medical records. As this is a retrospective study, no additional diagnostic or treatment procedures will be performed on study subjects.

D. Study drugs

No study drugs will be used.

E. Medical device

No medical device will be used.

F. Study questionnaires

No study questionnaires will be used.

G. Study subjects

Inclusion criteria:

1. ≥ 18 years of age
2. HR>90bpm *and* either RR>20 or pCO2<32 observed simultaneously at any time within the first 24 hours of presentation
3. Admitted to NYP-CUMC through the emergency department to medicine (non-ICU) service

Exclusion criteria:

1. previous diagnosis of diabetes, as defined by any of the following:
    a. hemoglobin A1C >6.5% prior to the index hospitalization
    b. previous chart-documented diagnosis of diabetes
    c. patient report of previous diagnosis of diabetes
2. temperature >38°C or <36°C concurrent with the inclusion criteria of tachycardia and tachypnea
3. leukocytosis, leukopenia *or* bandemia (WBC of >12,000 or <4,000 cells/mcL, *or* ≥ 10% immature forms) concurrent with the inclusion criteria of tachycardia and tachypnea

H. Recruitment of subjects

This study will not recruit subjects, but rather use a retrospective chart review of previously-treated patients.

I. Confidentiality of study data

All patient data will be stored on encrypted, password-protected computers that will be accessible only to the study investigators. Data will originate from the electronic medical records of New York Presbyterian Hospital.

J. Potential conflict of interest

There are no anticipated potential conflicts of interest.

K. Location of study
This will be a single-site retrospective study conducted from the medical records of New York Presbyterian Hospital-Columbia University Medical Center.

L. Potential risks
There are no potential risks to subjects in this retrospective study, other than the potential risk of loss of confidential data. This risk will be minimized through the use of encrypted, password-protected computers as described above.

M. Potential benefit
There is no anticipated direct benefit to subjects in this study.

N. Alternative therapies

O. Compensation to subjects
There will be no compensation to subjects in this study.

P. Costs to subjects
There will be no cost incurred by the subjects in this study.

Q. Minors as subjects
There will be no minors included in this study.

R. Radiation
No radiation will be used in this study

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