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Prognosis of emergency department patients with suspected infection and intermediate lactate levels: A systematic review

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ABSTRACT

Purpose: Previous studies have shown a correlation between blood lactate greater than 4.0 mmol/L and mortality in patients with suspected infection in the emergency department (ED), but data are more limited regarding the prognosis of intermediate blood lactate (2.0-3.9 mmol/L), particularly in the absence of hemodynamic instability. We sought to quantify the prognostic significance of intermediate blood lactate levels in ED patients with suspected infection, emphasizing patients without hypotension.

Methods: A systematic review of 4 databases was conducted to identify studies using a comprehensive search strategy. All studies performed on adult ED patients with suspected infection and available data on hemodynamics, intermediate lactate levels, and mortality rates were included.

Results: We identified 20 potential publications, 8 of which were included. Intermediate lactate elevation was found in 11062 patients with suspected or confirmed infection, 1672 (15.1%) of whom died. Subgroup analysis of normotensive patients demonstrated a mortality of 1561 (14.9%) of 10 442, with rates from individual studies between 3.2% and 16.4%.

Conclusion: This systematic review found that among ED patients with suspected infection, intermediate lactate elevation is associated with a moderate to high risk of mortality, even among patients without hypotension. Physicians should consider close monitoring and aggressive treatment for such patients.

1. Purpose

In the United States, emergency departments (EDs) treat approximately 570 000 patients with sepsis yearly [1]. In addition, there are 200 000 US deaths attributed to sepsis annually [2], with estimated mortality rates ranging from 15% to 30% based on administrative databases [3]. Despite active research in the field, early administration of bundled care and quantitative resuscitation protocols remains the most consistently beneficial therapy for the treatment of severe sepsis available in the ED. Despite success in the literature, adoption of such protocols has been slow for numerous reasons, including lack of nursing expertise, inability to measure a central venous pressure [4], and inclusion in early goal-directed therapy based on lactate criteria (rather than hypotension) [5]. Furthermore, the placement of central venous lines is accompanied by certain risks including pneumothorax, arterial injury [6], and exposure to the risk of catheter-related blood stream infections [7], a major target of quality improvement initiatives. Furthermore, such protocols increase medical cost per patient, and although such protocols appear to be cost-effective in terms of life years gained when considering all patients with septic shock [8,9], it is expected that as the risk of death decreases, cost-effectiveness will decrease as well. Thus, it is evident that specific identification of at-risk patients for whom bundled care is appropriate should be balanced against the unnecessary risks and expense that accompanies the overtreatment for low-risk individuals.

The prognostic value of lactate in ED patients with suspected infection and septic shock is well known [10,11], and increasing levels have been demonstrated to have a curvilinear relationship with mortality [12,13] with no clear stepwise “break” to separate low, moderate, or high risk of death, making proscriptive assessment and treatment guidelines based on these criteria difficult. Based on the original study of early goal-directed therapy [14], the current threshold for initiating early goal directed therapy in the absence of hypotension is a serum lactate greater than 4.0 mmol/L [15]. This number appears to have been selected arbitrarily to define “high” serum lactate, though these patients are clearly at a high risk of death. Observations suggest that patients with a lactate in this range (>4.0 mmol/L) without hypotension that undergo quantitative resuscitation have a mortality rate not significantly different from those patients requiring vasopressor requirement [16]. What remains unclear, however, is whether patients with an intermediate range lactate, particularly in the absence of hypotension, might similarly benefit from initiation of some type of quantitative resuscitation protocol. As a first step to address this question, we conducted a systematic review to determine the risk associated with a lactate of 2.0 to 3.9 mmol/L (intermediate range), with an emphasis on the subgroup of patients without hypotension, in order to determine the risk of death in this patient population.

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2. Materials and methods

2.1. Search strategy for identification of studies

We followed a written protocol that was designed in accordance with recommended guidelines and finalized prior to beginning the study [17]. A preliminary search strategy was developed using exploded Medical Subject Heading terms and keywords involving sepsis, systemic inflammatory response syndrome (SIRS), lactate, and outcome. This strategy was revised and improved upon by a medical librarian. We searched MEDLINE (1950–July 2013), SCOPUS (1996–July 2013), Cochrane Library (2005–July 2013), and CINAHL Plus (1937–July 2013) using a search strategy outlined in Appendix 1. Briefly, our final search strategy included the search terms *lactates* or *acidosis, lactic*, and *bacterial infections or brain abscess or central nervous system infections or infections,* or *systemic inflammatory response syndrome* and was limited to human studies that reported either *prognosis* or an *outcome assessment (health care)*. All results were supplemented with a review of their related articles [18].

2.2. Inclusion criteria

We considered studies eligible for review, regardless of language or publication type, if they were observational studies of human adults (age >17 years) admitted through the ED, with a diagnosis of SIRS, sepsis, or infection-related diagnosis with available lactate and hemodynamic data. Reviews, correspondence, editorials, and nonhuman studies were excluded; however, their reference lists were screened if relevant to identify further studies for inclusion. We attempted to contact corresponding authors for clarification of missing or incomplete data.

2.3. Study selection and data abstraction

Two reviewers (B.M.I. and A.E.J.) independently screened the titles and abstracts of identified studies for potential eligibility. Cases of disagreement were resolved by conference between the reviewers. If agreement could not be reached, the full manuscript was obtained for review. The full manuscript of each study that passed the relevance screen was reviewed by one of the investigators (B.M.I.). Study data were abstracted independently by each reviewer using a standardized data collection form. In cases of disagreement in abstracted data, a third reviewer abstracted the data and consensus was reached by conference between the 3 reviewers.

2.4. Outcome measurements

The primary outcome of interest was 28-day mortality. Other mortality data were also accepted, such as in-hospital mortality and 30-day mortality. To assess the prognostic significance of an intermediate lactate in the setting of normotension on morbidity, we report the rates of progression to either shock or Sequential Organ Failure Assessment (SOFA) score increase of more than 1 if available.

2.5. Subgroup analysis

A predefined subgroup of patients with an intermediate lactate and no evidence of hypotension was examined to describe the mortality in this group of patients and compared with those patients with an intermediate lactate and hypotension, when specified. If hemodynamic data were unavailable, we attempted to contact the authors to obtain these data. If the data were unavailable or we failed to receive a response, these patients were excluded from the subgroup analysis. To assess if our choice of outcome measure affected our results, we compare the summary 28- and 30-day mortality rates with the summary in-hospital mortality rate.

2.6. Data analysis

Given significant methodological differences between studies, combining the data using meta-analytic techniques was deemed inappropriate. Therefore, we used simple descriptive statistics to present mortality rates as percentages, with accompanying ranges, when appropriate. Summary mortality rates for various groups are reported as a raw sum of total number of deaths divided by total number of patients.

3. Results

3.1. Study selection

Searching the databases identified 302 potential publications for review (Fig. 1). Reviewing reference lists and related articles found 5 other potential studies. After removing duplicates and screening titles and abstracts, 287 articles were excluded as irrelevant and 20 articles were found to be appropriate for further review. The 20 relevant articles were retrieved in full text. A single reviewer examined all of the references obtained. Twelve of these articles were excluded for failing to meet inclusion criteria. Reasons for exclusion include using a main diagnosis other than sepsis in patient cohorts, lack of

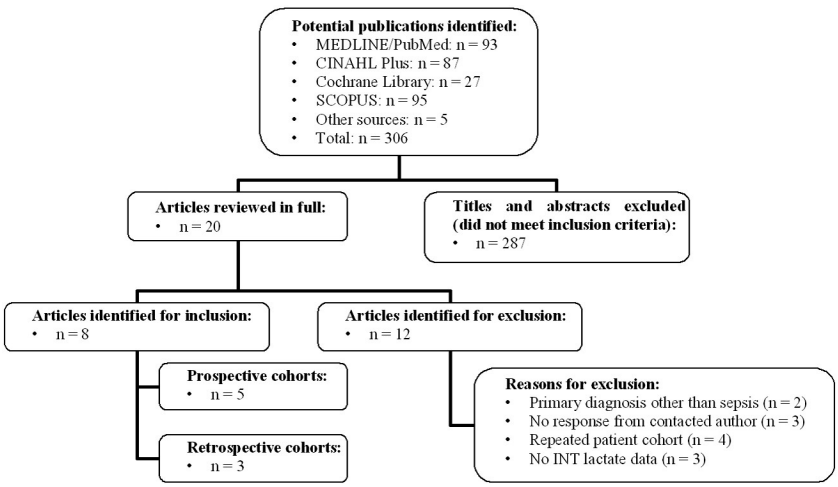

Fig. 1. Search, inclusion, and exclusion flow diagram.