How to interpret lactate

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ABSTRACT

The association between hyperlactataemia and poorer outcomes in acutely unwell adults and children is well recognised. Blood lactate testing has become readily available in acute settings and is considered a first-line investigation in international guidelines for the management of sepsis. However, while healthcare professionals do appreciate the value of measuring blood lactate in acute severe illness, its clinical significance and interpretation remain less well understood. In this paper, we present the evidence for the use of lactate as a diagnostic test and prognostic marker in acutely unwell children.

BACKGROUND

A widely held misconception is that lactate is a toxic waste product of metabolism, driven by hypoxia and/or hypoperfusion.1 It is now well established that increases in blood lactate due to hypoxia are likely the exception rather than the rule.1 At physiological pH, lactic acid (C₃H₅O₃) is almost completely dissociated into lactate anions (La⁻) and protons (H⁺). In mitochondria, the process of glycolysis generates pyruvate from glucose. Pyruvate is converted to acetyl coenzyme A (Acetyl-CoA) by pyruvate dehydrogenase and enters the Krebs cycle to produce adenosine triphosphate (energy) (figure 1). The enzyme lactate dehydrogenase converts pyruvate to lactate, and, while the reaction goes both ways, the equilibrium is markedly in favour of lactate. Accelerated glycolysis (eg, in physiological stress) will always lead to an increase in lactate production, and lactate serves as a ‘reservoir’ supplying pyruvate to mitochondria. Lactate is shuttled within and between cells and organs where it is either oxidised to produce energy or converted back into glucose. Glucose can be stored as glycogen or released back into the circulation. Lactate itself is not toxic or harmful; indeed, there is some evidence that hyperlactataemia may be beneficial in some conditions, for example, traumatic brain injury and severe hypoglycaemia, and has a central role as a metabolic fuel.1,2

As for any metabolite, blood lactate concentration depends on the ratio between production and consumption.2 When elevated beyond baseline (0.3–1.8 mmol/L), it is most often a sign of altered energy homeostasis, but this may be a physiologically appropriate adaptive response (figure 2).

The term ‘lactate clearance’ is often employed to refer to a fall in blood lactate level; however, this is misleading since changes in lactate levels depend both on lactate production and metabolism.2 That hyperlactataemia is associated with hypoxia, ischaemia and acidosis confounds its clinical interpretation, and a normal level should not offer reassurance in the face of other clinical concerns.1,2

The assessment of hyperlactataemia in the context of inborn errors of metabolism is beyond the scope of this article; suggested resources are provided in box 1.

TECHNOLOGICAL BACKGROUND

Sampling

A venous blood lactate concentration of <2 mmol/L is predictive of a (gold standard) arterial blood lactate of <2 mmol/L, but above this level an arterial sample is most reliable.3 Capillary blood lactate measured on heel-prick samples has been shown to correlate with arterial blood lactate in both preterm and term neonates.4 Though capillary blood gases are used extensively in paediatrics, there is insufficient evidence showing a correlation between capillary and either venous or arterial blood samples in children, and in adults, capillary lactate in acute illness has been shown to correlate poorly with venous lactate.5

Analysing

Blood lactate can be measured by point-of-care-testing (POCT) devices (using...
Interpretations

POCT requires smaller samples, can be performed on user-friendly instruments by staff without laboratory training, provides a rapid turnaround time for results and facilitates increased frequency of testing. Although there is generally a strong correlation between methods across the range of lactate values, at higher lactate concentrations POCT may be less reliable.

CLINICAL CASES
In children with suspected sepsis does a raised blood lactate at presentation predict mortality?
Hyperlactataemia is correlated with increased mortality in studies of children and adults with sepsis; however, its definition (from 2 to 5 mmol/L) and sampling timeframe (eg, initial lactate, peak lactate and/or duration of hyperlactataemia) varies.

Evidence for the accuracy of initial blood lactate in predicting mortality in children with sepsis is provided by several cohort studies; however, there is significant variation in patient populations and lactate thresholds (table 1). These studies demonstrate a large variation in mortality rates (from 1.9% in presentations to a USA emergency department (ED) to 63.5% for undifferentiated paediatric intensive care unit (PICU) admissions in

Figure 1 Lactate metabolism. LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase.

Figure 2 Elevated blood lactate concentration may be due to increased production, decreased consumption or changes in the balance of transport in and out of cells.

Box 1 Inborn errors of metabolism—online resources
- Vademecum Metabolicum (Assessment and Treatment of Inborn Errors of Metabolism): http://www.vademetab.org/
India), clearly representing significantly different populations.\(^9\)–\(^13\)

In a large observational cohort study of 1299 children with suspected sepsis presenting to a US ED,\(^9\) those with initial lactate >4 mmol/L had higher 30-day mortality (4.8% vs 1.7%). However, it is important to note that, in this patient group with a low mortality overall (1.9%), 80% (20/25) of all deaths were in children with initial lactate <4 mmol/L and >95% patients with lactate >4 mmol/L survived, yielding a sensitivity of only 20%. In a large study of children admitted to PICUs in Australia and New Zealand with sepsis and/or septic shock (n=1697), mortality was independently correlated with lactate on presentation to ICU, with the highest mortality in children with hypotension requiring vasopressors and lactate >2 mmol/L (32% vs 7.7%) in the hypotensive non-vasopressor group with lactate <2 mmol/L.\(^14\)

The recently published Surviving Sepsis Campaign (SSC) International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children states: “we were unable to issue a recommendation about using blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction” and that levels should “be interpreted as part of a more comprehensive assessment of clinical status and perfusion” \(^8\) (see online supplementary infographic: decision-tree).

**In children with suspected sepsis, does lowering lactate levels improve outcomes**?

In adults with septic shock, there is some evidence that lactate-guided resuscitation reduces mortality though these findings remain under debate.\(^1\)

In children, evidence for lactate as a therapeutic target is limited to observational studies.\(^10\)–\(^12\) \(^15\)

**Table 2**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Population</th>
<th>Overall mortality (%)</th>
<th>Thresholds for lactate reduction</th>
<th>Relative risk of death</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Mortality timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions (East Africa)(^1)&lt;br&gt;60 days to 12 years with severe non-malarial febrile illness (n=1906)</td>
<td>5.98&lt;br&gt;Failure to fall by &gt;40% and/or lactate &gt;2.5 mmol/L&lt;br&gt;at 8 h</td>
<td>2.0&lt;br&gt;64%&lt;br&gt;54.3%&lt;br&gt;8.2%&lt;br&gt;96%</td>
<td>72 h</td>
<td><strong>Hospital admissions (Uganda)</strong>(^1)&lt;br&gt;5 years with a diagnosis of pneumonia (n=75)</td>
<td>17.33&lt;br&gt;Failure to fall by &gt;40% by 8 h</td>
<td>2.8&lt;br&gt;53.8%&lt;br&gt;75.8%&lt;br&gt;31.8%&lt;br&gt;88.7%</td>
<td>In-hospital death or survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICU admissions (India)(^2)&lt;br&gt;1 month to 12 years with septic shock (n=148)</td>
<td>63.5&lt;br&gt;Failure to fall &gt;10% from baseline at 24 h</td>
<td>2.5&lt;br&gt;78.7%&lt;br&gt;(68.8% to 86.2%)&lt;br&gt;72.2%&lt;br&gt;(58.1% to 83.1%)&lt;br&gt;83.1%&lt;br&gt;(73.4% to 93.9%)&lt;br&gt;66.1%&lt;br&gt;(52.5% to 77.5%)</td>
<td>In-hospital death or survival</td>
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<tr>
<td>PICU admissions (India)(^3)&lt;br&gt;1 month to 17 years with septic shock (n=112)</td>
<td>31.3&lt;br&gt;Failure to fall &gt;20% from baseline at 24 h</td>
<td>12.1&lt;br&gt;92%&lt;br&gt;63%&lt;br&gt;84.5%&lt;br&gt;78.6%</td>
<td>60 days</td>
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*95% CIs provided (in brackets) where available in text or via author correspondence. NPV, negative predictive value; PPV, positive predictive value.
Lactate is an important molecule with complex biological functions—it is not a simple marker of hypoxia or a waste product of metabolism.

Elevated lactate levels indicate a metabolic imbalance between production, consumption, and cellular transport.

A normal lactate at presentation does not rule out severe sepsis or septic shock and should not be considered reassuring in the presence of adverse clinical signs.

In sepsis, a high blood lactate at presentation should prompt careful monitoring, as persistent hyperlactataemia is associated with organ dysfunction and mortality.

Elevated lactate does not assist in the diagnosis of necrotising enterocolitis (NEC), but in neonates with confirmed NEC, hyperlactataemia is associated with poorer outcomes.
insufficient evidence to support the use of lactate as a diagnostic marker for the disease.

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