Lactate (plasma/whole blood/CSF/fetal scalp/Fluid)

1 Name and description of analyte

1.1 Name of analyte
Lactate

1.2 Alternative names
Lactic acid and lactate can sometimes be used interchangeably.

1.3 Description of analyte
Glycolysis produces an intermediate metabolite, pyruvate. Under aerobic conditions, pyruvate is converted to acetyl CoA which enters the Kreb's (tricarboxylic acid or citrate) cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase (LDH) to lactic acid. At physiological pH, lactic acid almost completely dissociates to lactate and hydrogen ions. Lactate then feeds into the Cori cycle. Lactate exists in two isomers: L-lactate and D-lactate. Current lactate measurements only include L-lactate (the primary isomer produced in humans), which will be the focus of this monograph. Note that D-lactate is responsible for a rare type of lactic acidosis associated in particular with short bowel syndrome, see 3.2.

1.4 Function of the analyte
Lactate is produced by most tissues in the human body. Under anaerobic conditions, lactate is an end product of glycolysis and feeds into the Cori cycle as a substrate for gluconeogenesis.

2 Sample requirements and precautions

2.1 Medium in which measured
- Lactate can be measured in plasma; whole blood measurements are now widely available using blood gas analysers and hand-held instruments.
- Lactate can also be measured in CSF samples.
- Fetal scalp samples are used during labour to assess distressed fetuses.
- Ascitic fluid can be used to measure lactate.

2.2 Precautions re sampling handling
Glycolysis continues *in vitro* after phlebotomy. Because erythrocytes do not contain mitochondria, the pyruvate formed cannot enter the TCA cycle. However, the reduction of pyruvate to lactate continues. The resulting decrease in blood [glucose] is paralleled by an increase in [lactate]. This increase is significant at approximately 0.7mmol/L/h. Sampling

protocols include sodium fluoride and potassium oxalate as preservatives, keeping the blood on ice until centrifugation, and separation within a maximum of 15 mins. It has been suggested that ice is not required for samples collected into sodium fluoride tubes; stability has been shown to be acceptable for up to 8 h. WHO stability guidelines state that lactate is unstable in blood at room temperature but once separated is stable in plasma for 8 h at room temperature or three days at 4–8°C.

Measurement of lactate using a blood gas analyser requires a venous sample taken into a heparinised syringe. Analysis can usually be carried out promptly at point of care; stability is therefore rarely an issue. If a delay is to occur, storage on ice can limit the effect; however, this will have an effect on other analytes such as potassium or pO_2.
CSF samples should also be taken into sodium fluoride potassium oxalate tubes, however most kit inserts state that CSF samples can be used as obtained.

3 Summary of clinical applications and limitations of measurement

3.1 Applications

Lactate measurements are used:

- to determine the presence of lactic acidosis
- to aid in the diagnosis of pyruvate metabolism defects present in the first 48 hours of life.
- in the initial investigation of suspected sepsis
- to help monitor hypoxia and response to treatment
- in the case of fetal scalp blood samples, to help diagnose fetal hypoxia if there is an abnormal fetal heart rate pattern during labour
- in the case of CSF, to help distinguish between viral and bacterial meningitis

3.2 Limitations

Most commercially available lactate assays measure L-lactate. However, there are several conditions in which D-lactate can become increased. D-lactate assays are available. Recent studies have demonstrated increased concentrations of D-lactate in diabetes and in infection, ischemia, and trauma, suggesting that D-lactate might be used as a biomarker in these conditions. However, to further explore the use of D-lactate in this context, there is a need of an improved method for its analysis.

4 Analytical considerations

4.1 Analytical methods

Lactate can be measured by enzymatic, colorimeteric or electrochemical methods. Lactate can be measured on typical laboratory main analyzers but point of care instruments are now becoming widely available.

1. Enzymatic methods

One of the first lactate methods for rapid lactate measurement was the duPont aca, which used self-contained reaction packets to measure lactate in plasma by an enzymatic colorimetric method. Lactate dehydrogenase (LDH) oxidized lactate to pyruvate with simultaneous reduction of NAD^+ to NADH, which was monitored bichromatically at 340 nm (NADH absorbance) and 383 nm (background absorbance).

A frequently used enzymatic assay for lactate uses lactate oxidase. Lactate is oxidized to pyruvate and hydrogen peroxide by lactate oxidase (LOD). A coloured product is produced by the reaction of peroxidase (POD), hydrogen peroxide, 4 -aminoantipyrine (4-AA) and a hydrogen donor, N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline (TOOS). The coloured product is measured photometrically. The colour intensity is proportional to the concentration of lactate in the sample under examination.

$$\text{Lactate} + O_2 \xrightarrow{\text{LOD}} \text{Pyruvate} + H_2O_2$$

$$H_2O_2 + \text{4-AA} + \text{TOOS} \xrightarrow{\text{POD}} \text{Chromogen} + 2H_2O$$

2. Dry-slide methods

Multi-layered slides coated on a polyester support are used. After centrifugation, plasma is deposited on the slide. As the sample penetrates into the chemical layers, lactate in the sample is oxidized by *LOD* to pyruvate and hydrogen peroxide (H_2O_2). The H_2O_2 then oxidizes dye precursors which are measured by reflectance spectrophotometry. These methods cannot analyze whole blood, but require plasma from blood collected in a tube containing sodium fluoride/potassium oxalate.

3. Electrochemical sensors

The principle of measurement is based on diffusion of lactate from the whole-blood sample through a membrane that both screens out interfering substances and oxidizes lactate to pyruvate. A platinum electrode then oxidizes the H_2O_2 generated in this reaction. The current generated is proportional to the lactate concentration. The typical reaction sequence is:

$$\text{Lactate} + O_2 \xrightarrow{\text{Lactate oxidase}} \text{Pyruvate} + H_2O_2$$

$$H_2O_2 \xrightarrow{675\ \text{mV}} 2H^+ + O_2 + 2e^-$$

4.2 Reference method

There is currently no reference method for lactate measurement.

4.3 Reference material

Not determined.

4.4 Interfering substances

Interference from indices such as haemolysis, lipaemia and bilirubin may vary depending on the method of choice. The following is the interference associated with the enzymatic LOD method:

- bilirubin: none of significance up to 274 µmol/L bilirubin
- hemolysis: none of significance up to 5.0 g/L haemoglobin
- lipemia: none of significance up to 11.3 mmol/L triglyerides
- ascorbate: none of significance up to 568 µmol/L

4.5 Sources of error

Incorrect sample handling, as detailed in section 2.2, may cause a spuriously elevated [lactate].

The ethylene glycol metabolites glycolate and glyoxylic acid have been shown to falsely elevate L-lactate results due to cross-reactivity with the oxidase enzyme. This is most commonly found in blood gas analysers, but not is the methods on routine chemistry analyzers.

The use of the 'lactate gap' can help differentiate ethylene glycol poisoning from lactic acidosis. The term 'lactate gap' is used to describe a difference between a lactate result from a point of care instrument to one provided by the main laboratory method. This usually occurs as a result of interference in one of the methods from the ethylene glycol metabolites.

Note: A true increase in [lactate] can occur in ethylene glycol poisoning and should not be ignored as it may add prognostic value.

5 Reference intervals and variance

5.1.1	Reference interval (adults):	0.5– .8 mmol/L	
5.1.2	Reference interval (children):	1–12 months	1.1–2.3 mmol/L
		1– y	0.8–1.5 mmol/L
		7–15 y	0.6–0.9 mmol/L
	CSF reference intervals:	neonate	1.1–6.7 mmol/L
		3–10 days	1.1–4.4 mmol/L
		>10 days	1.1 – 2.8 mmol/L
		Adult	1.1 – 2.4 mmol/L

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 27.2 %
5.1.3.2 Intraindividual CV: 16.7%
5.1.3.3 Index of individuality: 1.6
5.1.3.4 CV of method: typically <5%
5.1.3.5 Critical difference: 1.5 mmol/L

5.1.4 Sources of variation

The main source of variation is likely to be due to pre-analytical factors. [Lactate] increases after exercise or physical activity, therefore this should be avoided prior to sampling.

6. Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation

1 Investigation of inborn errors of metabolism and causes of congenital lactic acidosis.
Of the inborn errors of metabolism [lactate] is raised in pyruvate dehydrogenase (PDH) deficiency and Krebs cycle defects as well as in mitochondrial disorders. The [lactate] to [pyruvate] ratio is used to distinguish between PDH and other causes of congenital lactic acidosis. However, it is thought that the usefulness of this is limited for values of [lactate] >5.0 mmol/L.

2 Assessment of critically ill patients and prognosis
Hyperlactataemia is common among the critically ill and has important implications for morbidity and mortality. [Lactate] >5mmol/L in association with acidosis (pH <7.35, $[H^+]$ >45 nmol/L), carries a mortality of 80%. Admission lactate ≥2 mmol/L has been shown to be a significant predictor of mortality in adults in intensive care units (ICU). Lactate concentrations have a role in risk-stratification of patients in the emergency department (ED).

3 Diagnosing sepsis
The use of lactate as a method to detect severe sepsis and septic shock and as a rationale for further therapies was evaluated in the 2012 Surviving Sepsis Campaign Guidelines. The guidelines committee recommended the quantitative resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L).

4 Lactate-directed therapy
Recent studies have advocated the use of lactate-directed therapy in post-cardiac surgery patients. Targeting a 20% decrease in [lactate] over a 2 h period seems to be associated with reduced in-hospital mortality. However the relevance of lactate-directed therapy needs to be investigatee by more studies.

5 CSF Lactate
CSF lactate is used to help distinguish between bacterial meningitis (BM) from acute asceptic meningitis (AM). Values > 6 mmol/L are regarded as being indicative of BM, 4–6 mmol/L found in partially treated meningitis and <2 mmol/L in AM.

6 Fetal scalp lactate

During labour, the aim is to identify fetuses at risk for severe adverse outcome so as to be able to intervene before damage has occurred. Upon identification of an abnormal fetal heart rate, fetal scalp samples are taken to measure pH. However, it has been suggested that the use of lactate measurements may facilitate earlier diagnosis, primarily because a much smaller volume of blood is required for the new handheld lactate meters than for blood gas analyzers. A suggested clinical guideline for scalp blood determination and management is as follows:

Lactate (mmol/L)	Description	Management
<4.2	Normal	Continue labour
4.2–4.8	Preacidaemia	Repeat 20–30mins later
>4.8	Acidaemia	Consider delivery

7. Fluid lactate
Lactate has been used along with pH to help differentiate bacterial peritonitis from uncomplicated ascites. However it is not as accurate as leucocyte counts and elevated [Lltate] has been found in malignant and tuberculous ascites. It has also been suggested that a value for {peritoneal fluid [lactate] - plasma [lactate] ≥1.5mmmol/L} can help separate patients with viscous perforation, gangrenous intestine, peritonitis or intraabdominal abscess from other conditions producing acute abdominal issues. The evidence for clinical utility in this context is, however, limited.

6.2 Confounding factors
As reported in section 4.5

7. Causes of abnormal results

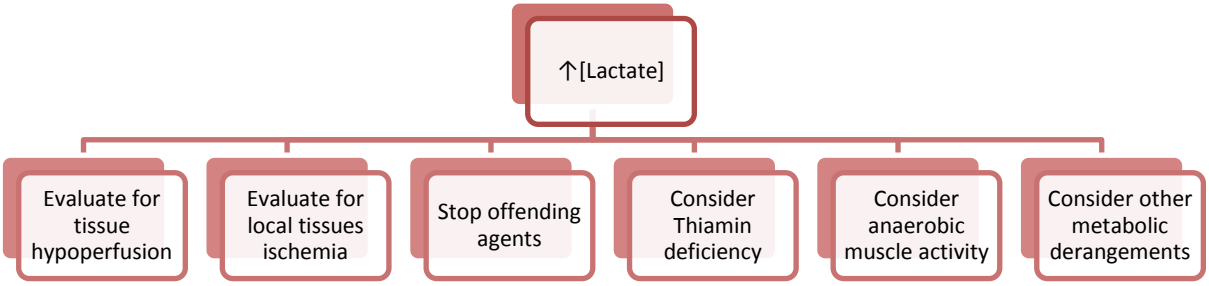
7.1 High Values
High [lactate] can determine indicate to the presence of a lactic acidosis. However, any form of shock or tissue hypoperfusion will result in elevated [lactate]. In general, lactate elevation may be caused by increased production, decreased clearance, or a combination of both.

7.1.1 Causes
Causes of a high lactate can be broadly classified into hypoperfusion driven and non-hypoperfusion driven.

Hypoperfusion driven	Non-hypoperfusion driven
Shock	Seizure
Post-cardiac arrest	Malignancy
Regional ischemia (e.g. mesenteric ischemia)	Thiamin deficiency
Haemorrhagic shock	Drugs e.g. metformin, salicylate
Trauma (particularly related to blood loss)	DKA
	Mitochondrial disease
	Liver/renal dysfunction

7.1.2 Investigations

The following algorithm is a suggested approach to investigate increased [lactate].



This investigation will be mostly clinical but the following laboratory tests will aid the diagnosis:

- blood gas measurement
- full blood count
- blood cultures
- CRP
- urea, creatinine and 'electrolytes'
- blood clotting screen.

7.2 Low values

Low lactate values are not clinically significant

7.2.1 Causes

Not applicable

7.2.2 Investigations

Not applicable

7.3 Notes

It is important is recognise that while a high [lactate] may indicate the presence of lactic acidosis, it is not always associated with it. See 7.1.

8. Performance

8.1 Sensitivities, specificities

Plasma [lactate] of 0–2.4, 2.5–3.9 and ≥4 mmol/L have been associated with mortalities of 4.9% (95% CI: 3.5% – 6.3%), 9.0% (95% CI: 5.6% – 12.4%) and 28.4% (95% CI: 21% –36%) respectively.

Elevated [lactate] values are 96% sensitive and 38% specific for mesenteric ischemia.

CSF lactate is a useful tool in the early diagnosis of bacterial meningitis with high sensitivity (92%) and specificity (99%) as well as in differentiating bacterial from viral meningitis.

Sensitivities and specificities for ascetic fluid lactate are approximately 90% using a cut-off of 4.4mmol/L, with a positive predictive value of 62%.

Fetal scalp blood lactate has been shown to be superior in predicting hypoxic ischaemic encephalopathy (HIE), with a sensitivity of 67% and a specificity of 93% in predicting moderate to severe HIE versus 49% and 93% respectively for pH.

9. Systematic reviews and guidelines

9.1 Systematic reviews

Kruse O, Grunnet N, Barfod C . Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. Scand J Trauma, Resusc Emerg Med 2011;19:74.

Lewis CT, Naumann DN, Crombie N, Midwinter MJ. Prehospital point-of-care lactate following trauma: A systematic review. Journal of trauma and acute care surgery, 2016 81:748-55

Vincent J-L, Quintairos e Silva A, Couto Jr L, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review, Crit Care, 2016; 20:257.

Huy NT, Thao NT Diept DT *et al*. Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: a systematic review and meta-analysis. Critical Care 2010,14:R240.

9.2 Guidelines

Sepsis: recognition, diagnosis and early management, NICE guideline, published: 13 July 2016 www.nice.org.uk/guidance/ng51

Dellinger RP, Levy MM, Carlet TM *et al*. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012, J Crit Care Med 2013; 41:580-637.

Sepsis Management . Irish Health Service National Clinical Guideline No. 6**,** ISSN 2009-6259**,** Published November 2014.

10. Links

10.1 Related analytes
Glucose
Ketones
CRP

10.2 Related tests
Blood gases

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