

GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF NRTI-ASSOCIATED SYMPTOMATIC HYPERLACTATAEMIA AND LACTIC ACIDOSIS

Southern African HIV Clinicians Society

Expanding access to antiretrovirals (ARVs) in southern Africa has dramatically impacted on the lives of those HIV-infected people who are able to obtain these drugs. Highly active antiretroviral therapy (HAART) has been shown to significantly reduce HIV-related morbidity and mortality in developed and developing world settings.^{1,2} However, ARVs, like most pharmaceutical agents, can result in side-effects and toxicities that in some instances may be life-threatening, especially if there is delay in their recognition.

One of the most challenging and dangerous side-effects is symptomatic hyperlactataemia that may evolve to lactic acidosis, a toxicity that may result from treatment with the nucleoside reverse transcriptase inhibitors (NRTIs). The first cases were described in the late 1980s, with fatalities being described in 1993.

PATHOPHYSIOLOGY

Lactate is normally produced by all the body's cells, as part of anaerobic metabolism. Certain cells (such as erythrocytes) lack mitochondria for aerobic respiration and are obligate lactate producers, while other cells will switch to predominant lactate production if the aerobic cycle is compromised, because of either a lack of available cellular oxygen or compromised mitochondrial oxidative phosphorylation. The liver is a key organ for the removal of lactate from the circulation, along with the kidneys. The steady state of lactate production and removal is usually only compromised when there is significant over-production *and* compromised liver function. Impairment of renal function seems to increase the risk.

NRTIs suppress HIV replication by inhibiting the viral enzyme reverse transcriptase. However, this class of drugs also has the potential to directly inhibit the human enzyme mitochondrial DNA polymerase gamma (γ), which is responsible for mitochondrial DNA synthesis. Reduced DNA synthesis results in less synthesis of essential mitochondrial proteins. The consequence is the formation of mitochondria which are structurally and functionally impaired, resulting in decreased oxidative capacity of each mitochondrion. Lactate over-production and cellular dysfunction result.

Important: The management of this condition is complex and these guidelines are based on expert experience rather than prospective clinical trials. Clinical common sense is advised in all cases. Guidelines may change as better evidence becomes available.

Different NRTIs have different risk profiles for causing hyperlactataemia. Their risk is directly proportional to their inhibitory effect on polymerase γ , in the following order (highest to lowest risk):

1. Combination of didanosine (ddl) and stavudine (d4T)
2. ddl
3. d4T
4. Zidovudine (AZT)
5. Lamivudine (3TC), abacavir (ABC) and the nucleotide reverse transcriptase inhibitor, tenofovir (TDF). These drugs are usually only implicated if used in combination with higher-risk drugs.

Other manifestations of NRTI mitochondrial toxicity are hepatic steatosis, peripheral neuropathy, lipoatrophy, pancreatitis, myopathy, cardiomyopathy, HIV-associated neuromuscular weakness syndrome (a Guillain-Barré-like syndrome that occurs secondary to NRTIs³) and cytopenias.

DEFINITIONS

A normal venous lactate level is less than 2.5 mmol/l and arterial lactate less than 2.0 mmol/l.

Hyperlactataemia is present when lactate is raised but blood pH is > 7.35 and standard bicarbonate > 20 mmol/l, and may be asymptomatic or symptomatic. Asymptomatic hyperlactataemia is common in patients on NRTIs (occurs in up to 25% of patients), but does not predict for the symptomatic form of the disease. It represents a state of physiological compensation. Symptomatic hyperlactataemia carries a good prognosis if recognised early and if there is no liver dysfunction.

Lactic acidosis is diagnosed when pH < 7.35 and/or standard bicarbonate < 20 together with raised lactate. The lactate level in this setting is typically > 5. Reaching this stage means that significant failure of the physiological compensating mechanisms is present, and this carries a much worse prognosis. In lactic acidosis the pH may be in the normal range (due to respiratory compensation) but the standard bicarbonate is always < 20. There is invariably multiple organ dysfunction, especially hepatic.

Symptomatic hyperlactataemia occurs in 0.4 - 9% of patients on NRTI therapy, whereas lactic acidosis occurs in 0.1 - 0.4%.⁴

RISK FACTORS

The following have been identified as risk factors:

- High body mass index (BMI) – evidence from one of the South African cohorts suggests that rapid weight gain is also a risk factor.
- Gender – women are at greater risk.
- Pregnancy – a high risk of lactic acidosis has been noted in pregnancy when the ddI and d4T combination has been used.
- Underlying liver disease – this may impair lactate clearance.
- Age – symptomatic hyperlactataemia/lactic acidosis appears to be unusual in younger children, as are the other manifestations of mitochondrial toxicity, although cases have been reported in South Africa.

It is unclear whether co-administration with metformin is a risk factor. Metformin can also cause lactic acidosis in patients with organ dysfunction. However, it is a key drug in the treatment of diabetes, and its co-administration with NRTIs that have a high potential for hyperlactataemia (i.e. ddI, d4T) needs to be considered carefully, weighing the risks and benefits in the individual patient.

DIAGNOSIS

Apply the rule: if you consider the diagnosis, do the laboratory investigation immediately. Delays in diagnosis may be life-threatening.

Many conditions (Table I) may result in raised lactic acid and acidosis. Hyperlactataemia/lactic acidosis secondary to NRTIs is therefore a diagnosis of *exclusion*.

Symptoms may be very nonspecific and vague, and have generally been present and getting worse for weeks and occasionally months.

Key symptoms and signs include:

- Unintentional loss of weight (LOW) (especially > 5%).
- Gastrointestinal (GIT) symptoms, including nausea, vomiting, loss of appetite, abdominal pain and hepatomegaly.
- Weakness and fatigue.
- Dyspnoea, tachypnoea without respiratory cause.
- Unexplained tachycardia.

TABLE I. CAUSES OF HYPERLACTATAEMIA/LACTIC ACIDOSIS OTHER THAN NRTIs

■ Sepsis	■ Severe cardiac failure
■ Severe anaemia	■ Severe dehydration
■ Hepatic failure	■ Thiamine deficiency
■ Renal failure	■ Other drugs (e.g. INH overdose, metformin)
■ Pancreatitis	

- Myalgia.
- Peripheral oedema.
- Peripheral neuropathy and lipoatrophy often herald the onset of symptomatic hyperlactataemia.

The diagnosis is often missed initially, with symptomatic therapy being prescribed for GIT complaints. It is essential to maintain a high index of suspicion.

Symptomatic hyperlactataemia/lactic acidosis usually occurs after patients have been on NRTIs for several months (median 9 months). Typically the patient has initially experienced resolution of HIV- and opportunistic infection-related symptoms, has gained weight in the months after starting HAART and is virologically suppressed, then experiences a deterioration with the onset of hyperlactataemia and its associated weight loss and symptoms. However, we have documented rare cases in our cohorts that have occurred after only 2 months. It is unusual for symptomatic hyperlactataemia/lactic acidosis to develop after 2 years on therapy, but we have seen exceptions to this.

Clinical assessment should include evaluation of respiratory rate, abdominal examination and assessment for peripheral neuropathy. Tachypnoea in the absence of a respiratory cause is suggestive of metabolic acidosis.

The diagnosis is made by measuring venous or arterial lactate. The blood sample should be taken without the use of a tourniquet in a sodium fluoride tube and should reach the laboratory within 20 minutes on ice. However, if the sample is centrifuged on site and serum separated the serum sample then has 24 hours to reach a central laboratory.

Point-of-care devices for lactate measurement are particularly useful for primary care and rural facilities where access to a laboratory that is able to measure lactate is difficult. These devices have been validated in ICU settings and reliably determine lactate levels within ± 1 mmol/l of the laboratory measurement.⁵ However, they have not yet been validated in a busy clinic setting. It is important that the blood used for the measurement is taken by venepuncture without a tourniquet and is not a fingerprick sample – the latter method has been shown to falsely elevate the lactate level at sites using these devices.

When doing blood gas sampling it is important to expel all residual heparin from the syringe before taking the sample. Failure to do this will cause a false lowering of pH.

Liver function tests, creatinine kinase, lipase and lactate dehydrogenase may be elevated in association with the lactate, but these do not have the necessary sensitivity or

specificity to be used as reliable diagnostic tests. It is, however, important to check lipase and liver functions in all patients with confirmed symptomatic hyperlactataemia/lactic acidosis to assess for coexistent pancreatitis and steatohepatitis. Blood gas levels should also be checked in all patients with symptomatic hyperlactataemia to confirm or exclude metabolic acidosis.

Once NRTI-associated lactic acidosis is established, it represents a profound metabolic insult. When the NRTIs are removed, it takes weeks to months to resolve.

DIFFERENTIAL DIAGNOSIS

Other causes for LOW and abdominal pain may mimic or coexist with hyperlactataemia/lactic acidosis.

Other causes for LOW to consider:

- Opportunistic infections (ask about tuberculosis symptoms).
- Lipoatrophy.
- Chronic diarrhoea with malabsorption.
- Virological failure.
- Depression.
- Malignancy.
- Undiagnosed diabetes.
- Poor diet and poor social circumstances.
- Hyperthyroidism.

Other causes for abdominal pain/symptoms to consider:

- Pancreatitis (check lipase).
- Hepatitis/steatohepatitis (check ALT/alkaline phosphatase and assess for hepatomegaly).
- Opportunistic infections or immune reconstitution inflammatory syndrome (IRIS) (e.g. abdominal TB).
- GIT intolerance of medication, especially if on concomitant TB treatment. Hyperlactataemia is often incorrectly diagnosed as this. GI intolerance to drugs rarely develops after months of therapy.
- Unrelated causes (e.g. pregnancy, diabetic ketoacidosis, appendicitis, peptic ulcer disease, pelvic inflammatory disease, urinary tract infections, pneumonia).

Other causes of tachypnoea and tachycardia, with or without the above:

- Respiratory conditions.
- Cardiac conditions.
- Anaemia.
- Sepsis.
- Diabetic ketoacidosis.
- Hyperthyroidism.
- Hypoperfusion due to diarrhoea, vomiting or inadequate fluid intake.

CONFOUNDERS

There are several causes of lactic acidosis other than NRTIs that need to be considered before the diagnosis is made (see Table I).

HIV-infected patients frequently present with infective gastroenteritis with diarrhoea and vomiting. If severe this may result in profound dehydration with poor tissue perfusion and a raised lactate level. In this situation once the patient is resuscitated with fluids the lactate will normalise. If the lactic acidosis is incorrectly attributed to the NRTIs in this situation an inappropriate interruption and switch in therapy may result. This may compromise future HAART options.

Similarly, septicaemia and other bacterial infections (e.g. pneumonia) may result in lactic acidosis that will resolve with fluid resuscitation, appropriate antibiotics and other supportive therapies.

However, to complicate matters further opportunistic infections and bacterial sepsis may unmask mitochondrial toxicity and precipitate a presentation with hyperlactataemia/lactic acidosis. Even with adequate fluid resuscitation and appropriate treatment for their infection these patients have persistently raised lactate levels. The presence of an infection therefore does not exclude the fact that the lactic acidosis is contributed to by the NRTIs.

PREVENTION

Recognising the syndrome before the person becomes acidotic is the most effective prevention, and symptoms tend to occur long before severe laboratory abnormalities are present. The mortality and morbidity of the condition dramatically increases in the presence of acidosis. The mortality rate with lactic acidosis is 30 - 60%. A practical approach is to educate patients to report any loss of weight, abdominal pain or vomiting lasting more than a few days, excessive fatigue, lipoatrophy or peripheral neuropathy symptoms (see addendum – patient education poster, p. 15). Weights should be monitored at every clinic visit, and when they drop by > 5% the lactate level should be measured, even if no other symptoms are present. Any patient with a severe or rapidly progressive NRTI-induced neuropathy (typically due to d4T or ddI) should also have the lactate level measured.

There is evidence that reducing the dose of d4T is associated with less toxicity (including hyperlactataemia) and equal efficacy. Patients developing other d4T-induced side-effects (e.g. peripheral neuropathy) should have their dose reduced (e.g. from 40 mg bd to 30 mg bd for those weighing > 60 kg, and from 30 mg bd to 20 mg bd in those < 60 kg) or switched to AZT. Another preventive strategy is to start women with a BMI > 28 on NRTIs with a lower risk of hyperlactataemia (3TC, ABC or TDF – but in the South African public sector AZT rather than d4T in the first-line regimen) or to switch them to these NRTIs if they gain weight to a BMI > 28 on HAART. This is a particularly high-risk group.

It is prudent to avoid using ddI and d4T in the same HAART regimen as this combination carries the highest risk for mitochondrial toxicity. This combination should only be used if there are no other options available.

Routine lactate measurement in asymptomatic patients is not recommended, as the correlation with the development of

symptoms is poor. Up to 25% of patients on NRTIs have asymptomatic hyperlactataemia with mild elevations in lactate levels, but only a minority will develop symptoms. Elevated lactate levels in the absence of symptoms are not a good predictor of symptomatic hyperlactataemia.

MANAGEMENT

Once the diagnosis is confirmed (raised lactate and *exclusion* of other causes), the following guidelines are suggested. Different facilities will have different treatment and monitoring options.

Stop the regimen even before the diagnosis is biochemically confirmed if you have a high index of suspicion. Do not stop the NRTIs alone – stop the entire regimen. It is better to interrupt a regimen for a short period than to continue a toxic regimen in the presence of suspected lactic acidosis.

The treatment guidelines presented below are largely based on anecdotal experience with the condition, by local and international clinicians and other published guidelines.^{4,6-8} There are no prospective studies on the treatment of hyperlactataemia/lactic acidosis, and caution and common sense is urged by the guideline authors in all cases. These guidelines are based on the experience in South Africa being that most cases of symptomatic hyperlactataemia/lactic acidosis are caused by d4T in first-line therapy. We strongly urge that you consult an experienced treater in all cases, especially if d4T is not the offending drug.

Mild hyperlactataemia and minimal symptoms (lactate 2.5 – 5 and no metabolic acidosis – standard bicarbonate > 20)

The NRTI regimen should be switched to agents that are less likely to cause lactic acidosis (3TC, ABC or TDF if available – in the South African public sector switch from d4T to AZT in the first-line regimen) and the lactate rechecked within 3 days and then weekly until normalised. If symptoms are severe or the lactate continues to rise, or symptoms get worse despite the switch, HAART should be stopped and an expert treater consulted regarding the decision as to which HAART to restart when the lactate level has normalised.

If the lactate cannot be monitored in the way described, treatment should be stopped and treatment restarted when the lactate level has normalised and symptoms have resolved, following the guidelines below.

Moderately severe hyperlactataemia/moderate metabolic acidosis (lactate 5 – 10 and/or standard bicarbonate 15 – 20)

These patients should stop HAART, be observed as an inpatient for 1 – 2 days, and given oral vitamins (vitamin B complex 2 tablets bd and thiamine 100 mg bd), be well hydrated (orally or IV) and have sepsis/opportunistic infections excluded. The lactate level should be rechecked, and when it is falling the patient can be discharged for outpatient follow-up provided he or she is clinically stable. HAART should only be

recommenced when lactate and bicarbonate have normalised (this may take months), and the decision regarding what regimen to restart should be discussed with an experienced treater.

The choice as to what to recommence is one of:

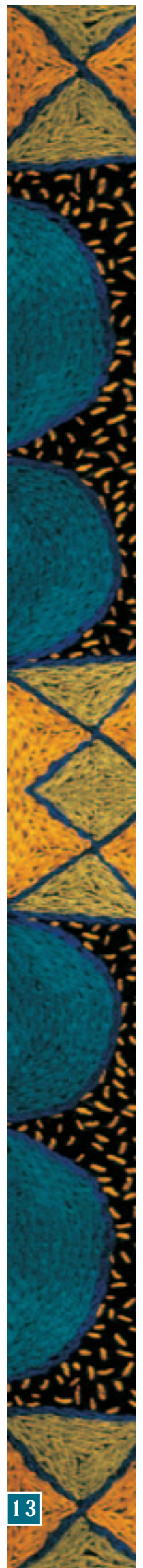
1. AZT, 3TC and non-nucleoside reverse transcriptase inhibitor (NNRTI) with lactate monitoring at 2 weeks, 4 weeks and then monthly for a further 2 months and at any time symptoms recur. This is not an option if the patient had metabolic acidosis (standard bicarbonate < 20). It is important to note that there is limited evidence for the safety of recommencing AZT in this setting.⁶
2. TDF/3TC/NNRTI or ABC/3TC/NNRTI with lactate monitoring as above.
3. NNRTI with Kaletra (Kaletra dose here is 4 capsules bd due to NNRTI induction of Kaletra metabolism). Lactate monitoring not required.
4. Dual-boosted PI regimen (e.g. Kaletra + saquinavir). Lactate monitoring not required. This option is preferable to (3) if NNRTI resistance is documented or strongly suspected, but the option is not available in many southern African public sector programmes.

This decision is based on the prior HAART history, clinical picture, lactate level, arterial blood gas, degree of steatohepatitis at presentation and ability to monitor lactate on recommencement.

Patients with more severe disease should be recommenced on (3) (or (2) or (4) if available in the private sector), whereas those with a milder syndrome could be recommenced on (1). If a metabolic acidosis was present (1) should not be recommenced. There is no risk of recurrence of hyperlactataemia with (3) or (4), whereas with (1) there is a risk that AZT may cause relapse of hyperlactataemia (although the risk is lower than with d4T). There is less of a risk of recurrence with (2) than with (1), as ABC, TDF and 3TC have been infrequently associated with hyperlactataemia and usually when used in combination with a drug that is more likely to cause mitochondrial toxicity.

Also, the decision as to when to restart HAART is a balance between the patient's nadir CD4, their current CD4 and the severity of the hyperlactataemia/lactic acidosis. Patients with low nadirs should not have HAART withheld for too long, as they run the risk of acquiring new opportunistic infections. If lactate levels are persistently elevated in a patient with a low nadir CD4 count, a regimen without a risk of occurrence (NNRTI/Kaletra or dual-boosted protease inhibitor (PI)) should be considered and can be commenced before lactate has normalised.

Patient education is critical. Patients with hyperlactataemia/lactic acidosis being rechallenged with a safer NRTI should understand the need for regular follow-up. Patients who live far from the health care facility, have transport difficulties, are unreliable or have follow-up compromised in any way, should not have NRTIs reintroduced.



Severe hyperlactataemia (lactate > 10 without metabolic acidosis) or significant lactic acidosis (raised lactate regardless of level and significant metabolic acidosis – standard bicarbonate < 15)

These patients should preferably be managed in a high-care facility as follows:

- Stop HAART
- IVI thiamine 100 mg 12-hourly and B-complex vitamins 1 amp 12-hourly.
- IVI fluids.
- Blood culture/urine culture/septic search *and* broad-spectrum antibiotic (e.g. third-generation cephalosporin or co-amoxycylav). This is important because sepsis may mimic or precipitate NRTI-associated lactic acidosis.
- Consider IVI NaHCO₃ if profound acidosis (e.g. 150 ml of 8.5% sodium bicarbonate added to a vacolitre of 5% dextrose water and infused at 80 - 100 ml per hour).
- Consider ventilation if respiratory fatigue occurs.
- Dialysis, inotropes and other supportive measures as necessary.
- Coenzyme Q, L-carnitine and other mitochondrial co-factors are used by some when available, but have very limited evidence for efficacy.
- If pancreatitis is present patients should be kept nil per mouth.
- Monitor lactate, blood gas, lipase, ALT and alkaline phosphatase.

Some of these patients demonstrate a biphasic course with initial improvement and then deterioration, often when they develop a superimposed pancreatitis.

These patients should be recommenced on Kaletra (lopinavir/ritonavir) 4 capsules bd and NNRTI or a dual boosted PI regimen (options (3) and (4) above) when lactate has normalised (this may take months). Other regimens that could potentially be used in these patients with less severe presentations are TDF/3TC/NNRTI or ABC/3TC/NNRTI with lactate monitoring on rechallenge as described above (option (2) above).

COVERING THE 'NNRTI TAIL' WITH LOPINAVIR/RITONAVIR (KALETRA)

When a HAART regimen containing an NNRTI (nevirapine or efavirenz) is stopped the NNRTI persists in the plasma for 1 - 2 weeks because of the long half-life of these drugs, unlike the NRTI component. This 'NNRTI tail' means that there is effective monotherapy with the NNRTI after the HAART is stopped, which predisposes to the development of NNRTI resistance. Provided patients are not vomiting and do not have either significant steatohepatitis or pancreatitis, it is suggested that when an NNRTI-containing regimen is stopped because of hyperlactataemia or lactic acidosis, 7 days of Kaletra (lopinavir/ritonavir) 4 tablets bd are prescribed to cover the NNRTI tail, thereby preventing effective monotherapy and the risk of NNRTI resistance developing.

PAEDIATRIC HYPERLACTATAEMIA/LACTIC ACIDOSIS

Initially paediatric symptomatic hyperlactataemia/lactic acidosis was considered very rare, but several local cases have been reported. Experience with this group is very limited, but symptoms and signs similar to those in adults seem to be present, although the differential diagnosis may be different. Management is similar to that of adults in terms of cessation of treatment and supportive measures. However, specialist advice should be sought in all cases.

PROGNOSIS

Poor prognostic markers are high lactate level, severe acidosis and coexistent pancreatitis. Patients who require ventilation and/or dialysis appear to have an extremely poor prognosis.

SWITCHING TO AZT

When d4T is switched to AZT it is frequently forgotten that monitoring for AZT haematological toxicity is required. The full blood count and differential count should be checked at baseline, then at 1, 2, 3 and 6 months, then 6-monthly. Do not start AZT in patients with a haemoglobin concentration < 8 g/dl.

THE FUTURE

Broader availability of TDF and ABC may make hyperlactataemia/lactic acidosis less common in the future. Until then, the availability of hand-held lactate monitors makes on-site diagnosis and monitoring a reality in public sector clinics. Increased access to these devices is encouraged.

Contact number. If there are any queries contact the Medicines Information Centre HIV Hotline (South Africa) (021) 406-6782.

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Guideline committee. Convenor: Graeme Meintjes; Committee: Francois Venter, Francesca Conradie, June Fabian, Gary Maartens, Douglas Wilson.

REFERENCES

1. Pallela FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; **338**: 853-860.
2. Coetzee D, Hildebrand K, Boulle A, *et al.* Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004; **18**: 887-895.
3. Simpson D, Estanislao L, Evans S, *et al.* HIV-associated neuromuscular weakness syndrome. *AIDS* 2004; **18**: 1043-1412.
4. Calza L, Manfredi R, Chiodo F. Hyperlactataemia and lactic acidosis in HIV-infected patients receiving antiretroviral therapy. *Clin Nutr* 2005; **24**(1): 5-15.
5. Brinkert W, Rommes JH, Bakker J. Lactate measurements in critically ill patients with a hand-held analyser. *Intensive Care Med* 1999; **25**: 966-969.
6. Loneragan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. *AIDS* 2003; **17**: 2495-2499.
7. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. 2005. <http://www.bhiva.org/guidelines/2005/HIV/HIV05frameset.html> (last accessed 20 February 2006).
8. Grunfeld C, Kotler DP, Mulligan K, Powderly WG, Saag MS. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr*. 2002; **31**(3): 257-275.

Addendum. Patient education poster

Symptomatic hyperlactataemia/lactic acidosis suspected

