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BMJ Case Reports

TITLE OF CASE

Severe lactic acidosis associated with oral linezolid

SUMMARY

We present the case of a person with cystic fibrosis on long-term oral linezolid treatment for *M. abscessus* lung infection who developed severe linezolid-induced lactic acidosis resulting in deranged clotting and pancytopenia. The lactic acidosis was resistant to treatment with intravenous fluid but resolved within 20 hours of initiating continuous veno-venous haemofiltration. An unintended consequence of haemofiltration was that vascular access interfered with effective chest physiotherapy, resulting in worsened lung consolidation requiring prolonged intravenous antibiotic therapy for co-existing *Pseudomonas aeruginosa* infection. Given the potential mortality and morbidity of linezolid-induced lactic acidosis, monitoring lactate level may be clinically important but the optimum timing of monitoring is currently unclear.

BACKGROUND

Cystic fibrosis (CF) is the most common inherited condition in the UK, whereby defects in the CF transmembrane conductance regulator alter airway surface liquid and produce an environment particularly suitable for bacterial colonisation and subsequent chronic infection.[1] The resultant vicious cycle of infection and inflammation causes progressive lung damage, respiratory failure and death.[2] Typical CF pathogens include *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Burkholderia cepacia complex*. However non-tuberculous mycobacteria, in particular *Mycobacteria abscessus*, are an emerging threat.[3] *M. abscessus* is a group of rapid growing mycobacteria associated with accelerated lung function decline among people with CF.[4] Treatment of *M. abscessus*-pulmonary disease is prolonged, costly and often complicated by antimicrobial resistance, hence frequently fails to achieve culture conversion.[3] Treatment typically comprises an initial phase of intravenous and oral antibiotics, followed by a continuation phase of oral and inhaled antibiotics for up to two years or one year after culture conversion.[5]

Linezolid is a synthetic oxazolidinone with activity against *M. abscessus*. Like other antibiotics active against *M. abscessus*, linezolid has a significant adverse effect profile including myelosuppression, neuropathy and toxic epidermal necrolysis.[5] Current British Thoracic Society (BTS) guidelines recommend weekly full blood count monitoring for myelosuppression.[5] Linezolid-induced lactic acidosis (LILA) is another known adverse effect but monitoring for this is not currently part of BTS recommendations due to its rarity. Here, we present the case of an adult with CF who developed severe lactic acidosis whilst on linezolid as part of her *M. abscessus* continuation treatment.

CASE PRESENTATION

A female in her early 20s with CF (F508del / Class I mutation) was initially found to have *M. abscessus spp. bolletii* six years before the index admission. The *M. abscessus* was pan-resistant to all anti-tuberculous (conventional and specific) antibiotics including cefoxitin, tigecycline and amikacin. She experienced recurrent pulmonary exacerbations and her sputum was persistently positive for *M. abscessus* despite ongoing treatment for over three years. When her *M. abscessus* treatment ceased around four years earlier, she was unwell with persistent pyrexia >38°C and malaise. She was also chronically infected with *Pseudomonas aeruginosa* and her sputum sample a month before the index admission was positive for both *P. aeruginosa* and *M. abscessus.* Oral moxifloxacin and minocycline previously induced severe nausea, hence her continuation antibiotic regimen leading up to the index admission was oral linezolid 600mg twice daily, oral clofazimine 100mg once daily, oral azithromycin 500mg once daily and nebulised amikacin 500mg twice daily.

Linezolid was initiated three and a half years before the index admission at a dose of 600mg once daily and increased to 600mg twice daily six months before the index admission. Linezolid had been paused several times during intravenous antibiotic treatment, most recently ten weeks before the index admission. On that occasion, linezolid was suspended for four weeks during intravenous *M. abscessus* treatment with tigecycline, meropenem and amikacin for a pulmonary exacerbation. The intravenous antibiotics were completed six weeks before the index admission, when oral linezolid was recommenced at 600mg twice daily.

Ten days before the index admission, the patient attended for routine review and was noted to have low grade pyrexia (37.7°C) and a slight increase in her cough resulting in mild left sided chest discomfort. The patient felt well in herself at this point and was started on oral ciprofloxacin 750mg twice daily to cover for pulmonary exacerbation from *P. aeruginosa*. Seven days later, she reported feeling more generally unwell. Ciprofloxacin was therefore switched to oral cotrimoxazole 160/800mg twice daily and her nebulised amikacin was switched to tobramycin 300mg twice daily.

At the index admission, the patient was driven by her partner for several hours from their holiday to the emergency department due to lethargy with generalised chest pain, shortness of breath, light-headedness, nausea, palpitations and loose stool. She reported no change to her chronic dry cough. She was normotensive (125/78mmHg) and saturating at 99% on room air but was tachycardic (electrocardiogram showed sinus tachycardia at 114 beats per minute), tachypnoeic (24 breaths per minute) and pyrexial (37.7°C). Clinical examination was otherwise unremarkable with no change to her chronic bibasal crackles and a soft, non-tender abdomen.

INVESTIGATIONS

On admission, inflammatory markers showed an acute rise alongside reduced renal function, deranged clotting and slight derangement of liver function (Table 1). Lactate was very elevated at 12mmol/L. Arterial blood gas showed metabolic acidosis with partial respiratory compensation (pH 7.3, CO_2 2.4 kPa, HCO_3 12 mmol/L, base excess -18mmol/L).

	Admission	10 days prior
Hb (g/L)	109	105
White cell count (x10^9/L)	22	10
Neutrophils (x10^9/L)	20	8
C reactive protein (mg/L)	51	35
Creatinine (µmol/L)	87	64
Alkaline phosphatase (IU/L)	332	174
ALT (IU/L)	74	19
AST (IU/L)	55	38
Prothrombin time (s)	14	11
Activated partial thromboplastin time (s)	42	31
Beta D-glucan (pg/mL)	42 (positive >80)	n/a
Galactomannan	ELISA negative Antigen 0.083 (positive >0.5)	n/a

Table 1 Bloods on admission compared to routine clinic 10 days prior

Computerised tomography (CT) of the thorax, abdomen and pelvis showed little change to the patient's extensive bronchiectasis compared to the most recent CT a month earlier, except some new areas of peripheral consolidation bi-basally (likely from *Pseudomonas aeruginosa* infection). Additionally, there were chronic fatty changes in the liver and pancreas but no evidence of acute abdominal pathology. Cultures of sputum, blood (peripheral and totally implantable venous access device), urine and faeces were all negative except for *Candida glabrata* in the urine. Tests for respiratory viruses, Epstein-Barr, Cytomegalovirus and Hepatitis A, B, C & E were also negative.

DIFFERENTIAL DIAGNOSIS

CF does not typically cause metabolic acidosis and is more usually associated with a slight metabolic alkalosis.[6] In this case, blood gases showed metabolic acidosis with a raised anion gap (21mmol/L) and raised lactate, suggesting the lactate caused the acidosis. Lactic acidosis results from inadequate tissue oxygenation (resulting in anaerobic glycolysis) or an alternative cause (Table 2).

Type A – inadequate tissue perfusion/oxygenation	Type B – adequate tissue perfusion/oxygenation
Global Shock (cardiogenic, distributive, hypovolaemic, obstructive), anaemia, respiratory failure, carbon monoxide Regional Ischaemia, trauma Exertional Significant exercise, seizure	Underlying disease Malignancy, liver failure, renal failure, diabetic ketoacidosis, thiamine deficiency, pancreatitis Drugs/toxins Paracetamol, aspirin, ethanol, metformin, antiretrovirals, propofol, theophylline, β-agonists, sympathomimetics Inborn errors of metabolism

Table 2 Causes of lactic acidosis[7]

Increased dietary acid load and purine intake through pancreatic enzyme supplementation can also cause metabolic acidosis which could be a factor given the high-protein diet used in CF management. However, in the absence of advanced renal disease, blood pH disturbance from dietary sources is typically not sufficient to leave the normal range[8] and would not be lactate-driven. There had also not been any significant change to diet or enzyme supplementation preceding the onset.

Sepsis, including candidaemia, is one of the commonest causes of type A lactic acidosis and there was undoubtedly ongoing lung infection. Blood culture, beta D-glucan and galactomannan were negative, making systemic fungal infection unlikely. The lactate is also disproportionately high for sepsis to be the cause, particularly given the modest C reactive protein, lack of hypoxia and minimal interval CT change which suggest low infection severity. There was also no clinical or radiological evidence of intra-abdominal infection, ischaemia, or perforation to explain the lactate rise.

The patient was normotensive with no clinical evidence of distributive, obstructive or cardiogenic shock. Bloods showed mild anaemia on admission but not significantly enough to explain the degree of lactate rise. Blood gases showed no evidence of respiratory failure or carbon monoxide poisoning.

There was no history of trauma, seizure or excessive physical exertion. Although not at baseline, renal and liver function and glucose were not significantly deranged and there were no acute radiological changes consistent with pancreatitis. The nature of CF necessitates lifelong intensive medical surveillance and lactate was not chronically raised preceding this admission (e.g. 2mmol/L 11 weeks before the index admission), making an undiagnosed inborn error of metabolism less likely.

Drug causes remain and the patient had recently started ciprofloxacin. Although lactic acidosis is not a listed side effect of ciprofloxacin, it is known to cause rhabdomyolysis[9] which can cause lactate release from muscle tissue. However, this is unlikely given the absence of muscle pain. No other medication had been recently changed and none of the patient's other medications except linezolid are known to cause lactic acidosis, leaving LILA as the most likely remaining cause.

TREATMENT

On admission, linezolid and ciprofloxacin were stopped and intravenous meropenem 2g thrice daily, intravenous tobramycin 320mg once daily and intravenous fluid were started. Despite 24 hours of intravenous fluid and antibiotics, the lactic acidosis persisted. The patient was transferred to critical care at this point for continuous veno-venous haemofiltration (CVVH). Intravenous colomycin 2 megaunits thrice daily was also commenced.

OUTCOME AND FOLLOW-UP

The lactate improved rapidly with CVVH, dropping below 2mmol/L 20 hours after CVVH initiation (figure 1). The patient remained off linezolid and the lactate level remained low for the remainder of the admission.

Clotting normalised with pH correction. However, she developed progressive pancytopenia over the first four days of admission, likely due to haemodilution from intravenous fluid combined with an element of bone marrow suppression from the acute illness. It is less likely that the pancytopenia resulted directly from linezolid given it was mild on admission and worsened for five days after linezolid withdrawal. This was treated with intravenous iron and transfusion of two units of red blood cells on the fifth day of admission. Her blood counts continued to normalise thereafter and she was transferred back to the ward on the fifth day.

Regular chest physio is an essential part of CF treatment to mobilise thick respiratory secretions, reducing infection and mucous plugging. Unfortunately, the large-bore intravenous lines required for CVVH impeded this and the patient developed a worsening cough and pleuritic chest pain as a result. CT one week after admission showed significant bilateral patchy consolidation requiring prolonged intravenous antibiotics. A small subsegmental pulmonary embolus in the right lower lobe was also identified at that point which was treated with dalteparin followed by apixaban.

The patient was discharged four weeks after admission and returned to her usual functional level. There was no significant lasting lung function loss but there may be psychological trauma. Enough time has now passed since the event for her clinicians to feel comfortable consenting her for this case report.

DISCUSSION

Linezolid acts on bacteria by binding to the 23S ribosomal RNA, preventing bacterial protein synthesis. Structural similarities with 16S ribosomal RNA in human mitochondria mean cross-reactivity can occur.

This disrupts respiratory enzyme production, reducing aerobic respiration with consequential lactate production from increased glycolysis.[10]

In this case, the patient had been taking linezolid for several years without issue. It had been reintroduced at full 600mg BD dosing after a four-week gap six weeks before she became unwell, but the definitive onset of LILA is unknown because her last lactate check was 11 weeks prior to the index admission.

There is a lack of large-scale studies investigating LILA incidence, evolution and severity and if up-titrating the dosage gradually may reduce LILA risk. A study of 72 patients taking linezolid by Im et al[11] found 6.8% developed definite or probable LILA with a duration of ≥6 weeks being a significant risk factor. However, the significance of duration of treatment is controversial[12] and there have been several reports of LILA after shorter durations of treatment, particularly among those with additional risk factors for lactic acidosis such as hepatic impairment.[11] Rehman[13] describes a case of probable LILA after only two doses given for community acquired pneumonia in a patient with acute myeloid leukaemia. Most indications for linezolid only require short term therapy but tuberculosis and non-tuberculous mycobacteria are notable exceptions requiring prolonged treatment and a case of LILA presenting with dyspnoea and vomiting four months into linezolid treatment for tuberculosis was recently reported[14]. In that instance, the lactic acidosis resolved rapidly with intravenous fluid and non-invasive ventilation.

Given the importance of cross-reactivity with ribosomal RNA in LILA development, it has been hypothesised that mitochondrial genetic variation may influence susceptibility to adverse effects from linezolid.[12] Garrabou et al's[15] study of 19 patients treated with oral linezolid for one month demonstrated an association between haplogroup U, 12S and 16S ribosomal RNA polymorphisms and increased linezolid toxicity (demonstrated by reduced mitochondrial protein synthesis and clinical signs of toxicity). It also suggested haplogroup H was associated with reduced toxicity. Genetic testing before initiation of linezolid treatment (in a manner similar to genetic screening of babies before aminoglycoside treatment to prevent hearing loss)[16] may allow identification of patients in whom linezolid should be avoided or subject to enhanced lactate monitoring. However, as acknowledged by the authors,[15] that study alone is too small to establish causal link.

There is currently no definitive cure for LILA with treatment focusing on supportive measures, stopping linezolid and renal replacement therapy. Consequently, mortality once LILA is established is high at 25%.[12] Given this, alongside its uncommon but not rare incidence and that symptoms may initially be non-existent or non-specific,[17] there is an argument for monitoring lactate during linezolid treatment. However, recommending a monitoring schedule (that ensures adequate sensitivity whilst not imposing unnecessarily excessive additional burden on patients that inevitably already have significant disruption of their life from healthcare interventions) is challenging given the current lack of information about

incidence and evolution of LILA. Enhanced monitoring regimes will probably also be beneficial in those with known additional risk factors. Further large-scale studies evaluating the development and evolution of LILA are therefore required before a monitoring schedule can be recommended.

LEARNING POINTS/TAKE HOME MESSAGES

- Linezolid is an important treatment option for *M. abscessus* infection which is an emerging threat for people with CF, but there is a risk of linezolid-induced lactic acidosis (LILA)
- CVVH is an effective treatment option for LILA, but the location of large-bore intravenous lines should be carefully considered in people with CF to minimise disruption to chest physiotherapy
- Given the potential severity of LILA, lactate monitoring is clinically important but further research into risk factors, development and evolution is required before reliable monitoring schedules can be recommended

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FIGURE/VIDEO CAPTIONS

Figure 1 Arterial blood gas results during admission

PATIENT'S PERSPECTIVE

Written by the patient five years later:

Prior to admission, I could not comprehend why I felt so unwell although I had just completed an IV antibiotic course around five weeks earlier. I was vomiting, felt fatigued and had rash on my face, back and chest. My chest did not feel unwell but my body did. The warning bell was when I nearly collapsed. I knew something was seriously wrong as my heartbeat was racing and I was breathing faster than usual. I had to cut short my holiday in Newquay. Added to my worries, my parents were in Rome.

I was treated in Critical Care as the CF team ran out of treatment options. I felt powerless in this situation. My recollection of this time is a little blurry but I do know the doctors in Critical Care acted quickly and aggressively. The subsequent weeks were difficult. I suffered further complications, and recovery was long and hard. When my parents returned from Rome and found me in Critical Care, they were shocked to see how fast I had deteriorated from when they last saw me. They did not expect to see me so weak and ill.

The experience was very frightening and left a mental scar. After discharge from the hospital, there were noticeable changes such as weight and hair loss. I have now fully recovered and am thankful for the care from the CF and Critical Care Team. I am also grateful for the support of my family during recovery.

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