

Case report

The more you give, the worse it gets

A 33-year-old, female nonsmoker presented to our unit with 2 days of worsening breathlessness associated with sore throat, nonproductive cough, wheezing and chest tightness. She was a homemaker with three children, of whom the eldest had asthma. Further questioning revealed a pattern of intermittent and variable symptoms frequently triggered by exposure to cold and dust, with clear symptom-free intervals. Four of her episodes required outpatient visits for nebulisation in the preceding 2 months, resulting in transient control of her symptoms. Despite this, she was not on maintenance therapy and had only self-administered continuous doses of inhaled salbutamol prior to current presentation. She had no other chronic medical illnesses, was not on any prescribed medications and denied taking supplements or illicit substances.

On physical examination, she was conscious and orientated but spoke in short phrases, demonstrated audible wheezing and was visibly tachypnoeic, with a respiratory rate of 40 breaths per min. She had a blood pressure of 175/125 mmHg, heart rate of 110 beats per min, oxygen saturation (SpO_2) of 94% under room air and temperature of 36.5°C. Lung auscultation revealed generalised polyphonic wheeze with reduced air entry bilaterally. As all potential cough-inducing respiratory testing was suspended due to the COVID-19 pandemic in our local setting, her peak expiratory flow rate (PEFR) was not evaluated throughout the admission [1]. A plain chest radiograph was performed in the emergency unit (figure 1).

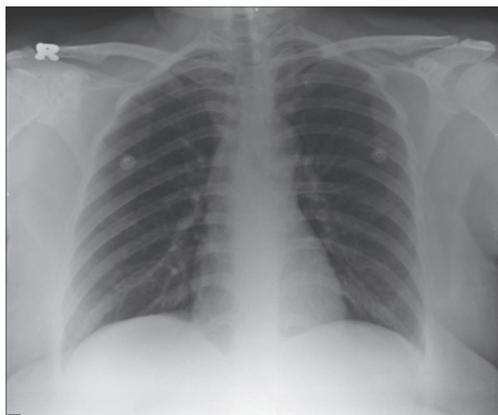


Figure 1 Plain chest radiograph on admission. Anterior-posterior projection, sitting position.

Task 1

Describe the plain chest radiograph in figure 1.

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Laboratory investigations revealed normal haemoglobin level with slightly raised total white cell and platelet counts. Renal and liver function tests were normal. Most serum electrolytes were within the normal range except for low serum phosphate and magnesium levels. The initial laboratory investigations are presented in table 1. Arterial blood gas on room air revealed pH of 7.37, oxygen tension (PO_2) of 91.7 mmHg (12.2 kPa), carbon dioxide tension (PCO_2) of 31.5 mmHg (4.2 kPa),

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 @ERSpublications

Persistent tachypnoea despite resolution of bronchospasm in a patient with acute asthma exacerbation after administration of inhaled short acting β_2 -receptor agonist should alert the clinician to this potential diagnosis. <https://bit.ly/385VU2Q>



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Table 1 Initial laboratory investigations

Parameter	Value	Normal range
Haemoglobin, g·dL ⁻¹	14.3	12.0-15.0
Total white cells, ×10 ⁹ per L	13.6	4.0-10.0
Platelets, ×10 ⁹ per L	412	150-410
C-reactive protein, mg·L ⁻¹	13.1	0.0-5.0
Erythrocyte sedimentation rate, mm·h ⁻¹	42	2-12
Serum sodium, mmol·L ⁻¹	138	136-145
Serum potassium, mmol·L ⁻¹	4.5	3.5-5.1
Serum chloride, mmol·L ⁻¹	106	98-107
Serum calcium, mmol·L ⁻¹	2.10	2.1-2.5
Serum magnesium, mmol·L ⁻¹	0.88	0.85-1.05
Serum phosphate, mmol·L ⁻¹	0.68	0.74-1.52
Urea, mmol·L ⁻¹	2.7	2.5-7.2
Creatinine, µmol·L ⁻¹	65	53-97
Total bilirubin, µmol·L ⁻¹	5.2	3.4-20.5
Alanine transaminase, U·L ⁻¹	24	0-55
Aspartate transaminase, U·L ⁻¹	61	5-34
Alkaline phosphatase, U·L ⁻¹	60	40-150
Total protein, g·L ⁻¹	80	64-83
Serum albumin, g·L ⁻¹	39	35-50
Serum globulin, g·L ⁻¹	41	34-50

HCO₃⁻ 18.4 mmol·L⁻¹ with base excess of -5.1 mEq·L⁻¹ and a raised anion gap of 18.1 mmol·L⁻¹. Serum lactate was 4.40 mmol·L⁻¹.

Task 2

What is the provisional diagnosis?

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A diagnosis of severe acute exacerbation of bronchial asthma was made. The P_{CO}₂ was slightly lower than the expected level of 35.6±2 mmHg (4.7±0.2 kPa) as calculated by Winter's formula, suggesting respiratory overcompensation [2].

Task 3

What would be the initial treatment for this patient?

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Initial resuscitation in the emergency department consisted of 200 mg intravenous hydrocortisone and 5 mg nebulised salbutamol, followed by another 5 mg nebulised salbutamol and 0.25 mg ipratropium. In view of raised serum lactate (4.40 mmol·L⁻¹), 500 mL intravenous 0.9% normal saline was administered. Upon reassessment, her vital signs stabilised with reduction of heart rate to 88 beats per min, blood

pressure of 143/85 mmHg, saturation of 100% under room air and respiratory rate of 20 breaths per min. She was able to speak in full sentences with improved air entry on lung auscultation. However, repeat arterial blood gas analyses showed worsening metabolic acidosis with pH of 7.30, P_O₂ 85.5 mmHg (11.4 kPa), P_{CO}₂ 20.0 mmHg (2.6 kPa), HCO₃⁻ 9.7 mmol·L, base excess -14.1 mEq·L⁻¹ and lactate of 8.21 mmol·L⁻¹ with calculated anion gap of 26.8 mmol·L⁻¹. Clinically, she was well hydrated, as evidenced by a capillary refilling time <2 s, good skin turgor and noncollapsible inferior vena cava on ultrasound assessment. Urgent plasma paracetamol (<4.00 mg·L⁻¹) and salicylate level (<0.36 mmol·L⁻¹) were not detectable.

Task 4

What is the most likely explanation of the worsening high anion gap lactic acidosis?

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Type A lactic acidosis was unlikely as there were no features to suggest hypoperfusion or hypovolaemia. Furthermore, as serum lactate level continues to rise despite improved respiratory effort after resuscitation, hypophosphataemia and respiratory muscle fatigue contributing to worsening lactic acidosis were deemed less likely. Laboratory assessment also confirmed normal liver and renal function, which ruled out lactic acidosis secondary to liver and renal dysfunction. In the absence of illicit substance use or prescription medicines such as antidepressants, antiepileptics or metformin, accidental drug overdose was ruled out. Thus, the most likely diagnosis to explain the worsening high anion gap lactic acidosis was SIIA.

Task 5

What is the next most appropriate course of treatment?

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Inhaled salbutamol was immediately halted, while metered-dose inhaler (MDI) ipratropium bromide was continued *via* a valve holding chamber. Nasal prong oxygen was initiated at 2 L·min⁻¹. She was empirically commenced on broad spectrum intravenous antibiotic (ceftriaxone 2 g once daily) for occult sepsis in view of the hyperlactataemia. Maintenance fluid consisted of 2 L 0.45% NaCl solution over 24 h supplemented with 40 mL 8.2% sodium bicarbonate per pint (568.3 mL) of infusion fluid. 2 h later, repeat arterial blood gas analysis on nasal prong oxygen showed pH 7.34, P_O₂ 137.9 mmHg (18.4 kPa), P_{CO}₂ 27.3 mmHg (3.6 kPa), HCO₃⁻ 14.3 mmol·L⁻¹, base excess of -9.0 mEq·L⁻¹ and lactate of 3.90 mmol·L⁻¹ with a calculated anion gap of 22.2 mmol·L⁻¹. The serial blood gas results can be found in table 2.

Table 2 Serial blood gas analyses and key management process

	Normal range	0 h, arterial blood on room air	2 h, arterial blood on room air	4 h, arterial blood on NPO ₂ 2 L·min ⁻¹	8 h, venous blood on room air	24 h, venous blood on room air
pH	7.35–7.45	7.37	7.30	7.34	7.29	7.34
P_{O₂}						
mmHg	80.0–100.0	91.7	85.5	137.9	42.9	29.0
kPa	10.5–13.5	12.2	11.4	18.4	5.7	3.8
P_{CO₂}						
mmHg	35.0–45.0	31.5	20.0	27.3	42.7	39.0
kPa	4.5–6.0	4.2	2.6	3.6	5.7	5.2
HCO₃⁻, mmol·L⁻¹	22.0–28.0	18.4	9.7	14.3	20.0	20.7
BE, mEq·L⁻¹	-2.0–2.0	-5.1	-14.1	-9.0	-6.3	-4.7
Lactate, mmol·L⁻¹	0.50–2.20	4.40	8.21	3.90	2.00	2.50
Anion gap, mmol·L⁻¹	4.0–12.0	18.1	26.8	22.2	16.5	10.8
Plan of action		Nebulised salbutamol 5 mg Nebulised salbutamol 5 mg + ipratropium 0.25 mg Followed by MDI salbutamol 200 µg hourly ×6 Intravenous bolus 500 mL 0.9% saline	Intravenous ceftriaxone 2 g immediately and once daily Intravenous 2 L·day ⁻¹ HS+40 mL 8.4% NaHCO ₃ Off MDI salbutamol		Intravenous 2 L·day ⁻¹ 0.9% saline Started on MART (budesonide/formoterol)	Off intravenous fluid

NPO₂: nasal prong oxygen; BE: base excess; HS: half saline; MART: maintenance and reliever therapy.

The patient improved gradually and was eventually started on maintenance and reliever therapy with budesonide 160 µg/formoterol 4.5 µg, two puffs twice daily and as needed, *via* dry-powder inhaler on the ward. 8 h after admission, venous blood gas analysis showed further improvement, with serum HCO₃⁻ 20 mmol·L⁻¹ and serum lactate of 2.00 mmol·L⁻¹. Blood, sputum culture and nasopharyngeal swab for SARS-CoV-2 PCR were negative. The patient was discharged well 48 h after admission.

Discussion

Acute exacerbation of asthma is a potentially life-threatening condition that requires prompt action with close monitoring. Management of asthma exacerbation consists of early introduction of systemic corticosteroids, controlled oxygen therapy and repetitive administration of inhaled SABA [3]. Although highly effective, SABA are not without side-effects, due to increased β-adrenergic drive. Commonly reported side-effects of SABA include tremor, palpitation, tachyarrhythmias, anxiety and hypokalaemia. SILA is rare and has been

reported not only in salbutamol overdose but also in therapeutic range doses [4].

The proposed mechanism of SILA lies in the hyperadrenergic state it induces [5]. Salbutamol-induced hyperadrenergic drive promotes glycolysis, glycogenolysis and gluconeogenesis, which leads to overproduction of pyruvate. Under normal aerobic circumstances, pyruvate is metabolised aerobically through the Krebs cycle and oxidative phosphorylation. However, once this pathway is saturated, pyruvate is shunted and metabolised through the anaerobic pathway into lactate [6]. This hyperadrenergic state also enhances lipolysis, resulting in free fatty acids that inhibit the entrance of pyruvate into the Krebs cycle *via* inhibition of pyruvate dehydrogenase, thus shunting pyruvate into the anaerobic pathway [6, 7]. Moreover, systemic corticosteroid use frequently induces a state of hyperglycaemia, which potentially provides more substrate for lactic acid production [5]. Corticosteroids also enhance β₂-receptor sensitivity, perpetuating the vicious cycle of a hyperadrenergic state and increased lactate production [7].

Lactic acidosis is generally classified into type A and B [8]. The more common type A lactic

acidosis is associated with tissue hypoxia and hypoperfusion, while the normovolaemic type B is usually associated with drugs or other metabolic derangements such as a hyperadrenergic state [8]. Assessment of lactate to pyruvate ratio (L/P) can be helpful in distinguishing type A from B lactic acidosis. A high L/P ratio signifies impaired tissue oxygenation (type A) while a normal L/P ratio occurs in nonhypoxic states when pyruvate fails to be metabolised at the mitochondrial level (type B) [9, 10]. As pyruvate level was not assessed in our case due to technical difficulties, a hypoxic mechanism leading to lactic acidosis cannot be precisely ruled out. Nevertheless, we postulate that our patient had a predominant type B lactic acidosis as she was not hypoxic during presentation, as evidenced by a PO_2 of 91.7 mmHg (12.2 kPa). Furthermore, there were no clinical features to suggest hypoperfusion, serum lactate also continues to rise despite improvement of respiratory distress. Our hypothesis is also in consistent with a study of paediatric patients admitted to the intensive care unit with severe exacerbation of asthma and concurrent lactic acidosis, in which the majority (88%) of them were found to have a L/P ratio <25 , indicating a type B lactic acidosis [11].

In our case, the temporal relationship between the resolution of high serum lactate level with salbutamol withdrawal supports the diagnosis of SILA. Although our patient presented with systemic inflammatory response syndrome with elevated inflammatory markers (raised total white blood cells, C-reactive protein and erythrocyte sedimentation rate), there was no clinical evidence of sepsis and she responded well to initial resuscitation. Furthermore, the patient's blood and sputum cultures were negative; hence, sepsis as a cause of worsening hyperlactataemia is very unlikely. Hyperlactataemia may also be explained by respiratory muscle fatigue from increasing respiratory effort, as well as hypophosphataemia [10, 12–14]. It is known that hypophosphataemia leads to reduced muscle ATP synthesis, resulting in muscle weakness, impairing diaphragmatic contractility and increasing haemoglobin affinity for

oxygen due to decrease in 2,3-diphosphoglycerate level [10, 13,14]. All these factors eventually lead to tissue hypoxia, perpetuating lactic acidosis in patients with asthmatic exacerbation. We postulate that respiratory muscle fatigue, as a result of respiratory distress and hypophosphataemia, contributed to the initial raised blood lactate level ($4.40 \text{ mmol}\cdot\text{L}^{-1}$) in our patient upon presentation. However, despite initial SABA administration and improving respiratory effort, serum lactate level continued to rise. This temporal relationship is highly suggestive of SILA as the predominant culprit of the subsequent worsening hyperlactataemia in our patient.

Sporadic case reports on SILA have been documented in literature [6, 7, 15, 16]. As there are no specific diagnostic criteria for this rare condition, vigilant clinical assessment and judgement is of utmost importance. The clinician should suspect SILA when a patient demonstrates persistent or worsening tachypnoea despite resolution of bronchospasm after administration of SABA. Lack of awareness of this condition may put patients at risk of the vicious cycle of worsening lactic acidosis and increasing salbutamol administration. Cautious interpretation of blood gas results and clinical correlation is paramount. To the best of our knowledge, risk factors and prevalence of SILA in the adult population have yet to be elucidated in the literature. However, among the paediatric population, 87% of moderate to severe asthma patients had evidence of raised serum lactate level $>2.2 \text{ mmol}\cdot\text{L}^{-1}$ in a prospective observational study. In that study, older age, higher blood glucose level and salbutamol administered through nebulisation were found to be independent risk factors associated with SILA [5].

SILA is a rare but recognised adverse effect of inhaled salbutamol. The use of inhaled salbutamol should not be discouraged during an asthma exacerbation as life-saving bronchodilator effects outweigh the risk of this rare adverse event. However, clinicians should be aware of this potential complication and act promptly, keeping in mind that the more you give, the worse it gets.

Answers

Answer 1

This chest radiograph in anterior–posterior projection shows mild hyperinflation as evidenced by visualisation of six anterior ribs and 10 posterior ribs above the diaphragm, with no evidence of lobar consolidation, collapse or pneumothorax.

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Answer 2

Severe acute exacerbation of asthma with compensated high anion gap metabolic (lactic) acidosis.

[<< Go to Task 2](#)

Answer 3

Repeated doses of inhaled bronchodilators consisting of short-acting β_2 -agonist (SABA) and ipratropium bromide, along with controlled oxygen therapy aiming for S_{pO_2} in the range of 93–95% and early systemic corticosteroid administration. Reassessment is required after initial treatment to assess response and the need for escalation of care.

<< Go to Task 3

Answer 4

Salbutamol-induced lactic acidosis (SILA), a type B lactic acidosis.

<< Go to Task 4

Answer 5

Reduce the hyperadrenergic state by withdrawing salbutamol administration and provide alternative treatment to address bronchoconstriction in the management of bronchial asthma exacerbation.

<< Go to Task 5

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Author contributions

S.S. Kho initiated the idea for case reporting. S.S. Kho and L.E. Nyanti prepared the final copy of the manuscript. S.S. Kho, N.A. Muhammad and M.Z. Nasaruddin were involved in the overall patient management. J.A. Abdul Rahaman supervised the whole management process and reviewed the final manuscript. All authors have read and approved the final manuscript.

Conflict of interest

None declared.

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