Sepsis and Acute Respiratory Distress Syndrome in Alcoholic Ketoacidosis

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INTRODUCTION

Alcoholic ketoacidosis (AKA) is a syndrome characterized by metabolic acidosis with a large anion gap, malnutrition, and excessive alcohol intake in an alcoholic. AKA is commonly found in emergency units, especially in western countries, but it is seldom found in Indonesia, although the exact prevalence rate is still unknown. Acid base imbalance is different compared to metabolic acidosis with a large anion gap, and it is commonly found with metabolic alkalosis, hyperchloremic acidosis as well as respiratory alkalosis and lactic acidosis. Serum acetone was found in 96% patients. An increased alcohol level can be found and in 40% of cases with very toxic levels. Electrolyte imbalances such as hyponatremia, hypokalemia, hypophosphatemia, hyperglycemia, hypocalcemia, hypomagnesemia are also commonly found. The most common symptoms are nausea, vomiting, and stomachache. Physical examinations often show tachycardia, tachypnea, and stomachache. AKA occur commonly in alcoholics. There is no difference among different sexes or races.

The pathophysiology of AKA is very complex. Its main trigger is closely associated with low insulin levels and excessive glucagon levels due to:

1. Malnutrition/low intake, causing glycogen storage depletion.
2. NAD (Nicotinamide Adenine Dinucleotide)/NADH ratio increase, due to alcohol metabolism by alcohol dehydrogenase.
3. Low extracellular fluid.

Relative insulin deficiency occurs due to glycogen storage depletion, decreased gluconeogenesis, and the effect of α-adrenergics on epinephrine. Increased NADH/NAD ratio influences gluconeogenesis, and both malnutrition and liver function abnormality affects the glycogen storage capacity. Reduced extracellular fluid stimulates the release of contraregulatory hormones such as growth hormone, cortisols, epinephrine, and glucagons. Insulin deficiency supports lypolysis and release of free fatty acids.

Table 1. Symptoms and Signs Abnormality in AKA

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
<th>Physical abnormality</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>76</td>
<td>Tachycardia</td>
<td>58</td>
</tr>
<tr>
<td>Vomiting</td>
<td>73</td>
<td>Tachypnoe</td>
<td>49</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>62</td>
<td>Abdominal tenderness</td>
<td>43</td>
</tr>
<tr>
<td>Rapid breathing</td>
<td>20</td>
<td>Hematemesis</td>
<td>18</td>
</tr>
<tr>
<td>Tremor</td>
<td>20</td>
<td>Hepatomegaly</td>
<td>18</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>19</td>
<td>Reduced consciousness</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
<td>Hypotension</td>
<td>12</td>
</tr>
<tr>
<td>Muscular pain</td>
<td>10</td>
<td>Abdominal distension</td>
<td>5</td>
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<tr>
<td>Fever</td>
<td>8</td>
<td>Hypothermia</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>Fever</td>
<td>3</td>
</tr>
<tr>
<td>Syncope</td>
<td>4</td>
<td>Diminished bowel sounds</td>
<td>1</td>
</tr>
<tr>
<td>Weakness</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melena</td>
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AKA is treated in accordance to its pathophysiology. Saline solution is given to hinder the release of contraregulatory hormones. Glucose is given to impede ketogenesis due to stimulation of insulin production and release. Dextrose in saline solution is administered to stimulate NADH oxidation, repair the acidic state, and increase liver glycogen storage. In patients with hyperglycemia, it is better to avoid dextrose solution administration because it might aggravate hyperglycemia. Insulin may be given with the
consideration of the possibility of hypoglycemia in patients with low glycogen storage. Low dose insulin is indicated only in patients with glucose levels of more than 250 mg/L. Potassium administration is indicated in hypokalemia and normokalemia with acidemia. Routine thiamine administration is indicated to increase pyruvate dehydrogenase activity and to prevent Wernicke’s encephalopathy.

There are four types of metabolic acidosis in AKA: ketoacidosis, lactic acidosis, acetic acidosis, and indirect bicarbonate loss in urine. There are complex interactions between various types of metabolic acidosis and metabolic alkalosis. AKA does not only manifest as acidosis with large anion gap due to ketone accumulation. Only 55% patients present with acidemia, and 79% have mixed acid base imbalance. Twenty five percent of patients show primary metabolic alkalosis with large anion gap while the other 25% suffer from primary respiratory alkalosis. Metabolic alkalosis occurs mostly due to vomiting and changes in body fluid volume, whereas respiratory alkalosis occurs due to alcohol withdrawal, pain, sepsis, or severe liver dysfunction.

Acute respiratory distress syndrome (ARDS) is a syndrome of acute respiratory failure due to destruction of alveolar capillary membrane barrier, causing lung edema due to increased permeability. This can occur as a complication in various internal medicine or surgical illnesses. ARDS needs to be differentiated from acute lung injury (ALI), which is a milder form of ARDS. ARDS criteria include 3 conditions, i.e., severe hypoxemia, reduced lung physiological capacity, and diffuse lung infiltrates portrayed in chest x-ray. These criteria are added with: acute onset, PaO$_2$ / FIO$_2$ 200mmHg, bilateral infiltrate in thorax x-ray, and PAOP $\leq$ 18mmHg. History of alcohol addiction may increase the risk of ARDS in critically ill patients.

Sepsis is the body’s reaction against invasion of microorganisms. Fever, hypothermia, tachypnea, and tachycardia are initial symptoms. Sepsis is a systemic inflammatory response syndrome (SIRS) that has been proven or considered to be due to bacterial infection. SIRS is diagnosed when two or more of these are found: fever of $>38^\circ$C or hypothermia of $<36^\circ$C, tachypnea of $>24$/minute, tachycardia of $>90$/minute, leukocytosis of $>12,000$/ul or leukopenia of $<4,000$/ul. More than 50% sepsis patients suffer from ARDS.

Fatty liver is divided into alcoholic fatty liver (AFL) and nonalcoholic fatty liver (NAFL). In AFL, fat is deposited in liver cells as macrovesicular steatosis, and pushes the nucleus to the cell periphery. Diagnosis is made by liver biopsy. Hepatomegaly is found in 90% of AFL. The best treatment is to discontinue alcohol consumption and to consume a high calorie high protein diet, which quickly deplete fat in the liver, and patients may recover from severe steatosis in 4-6 weeks.

CASE ILLUSTRATION

Mr. S. 40 years old, was admitted to the hospital on April 28th 2002 with a chief complaint of vomiting and reduced consciousness since 18 hours before admission.

Three days prior to admission, the patient consumed alcoholic drinks until he was drunk. When the patient reached his house, he had a headache and started to vomit (the vomit contained food and liquid), he was not able to undertake any activity, and could only rest in bed. He was not able to eat anything due to continuous vomiting. Eighteen hours prior to admission he was delirious, babbling, and unable to answer questions. He was then brought to Cipto Mangunkusumo Hospital by his family.

The patient had been an alcoholic for approximately 10 years. He consumed alcoholic drinks especially on Saturdays with his friends, mixing the alcoholic drink with energy drinks or drinks that contain ginseng. The alcohol content was usually 40% and he usually consumed 2-4 bottles.

History of frequent thirst, drinking, urination, and night urination were not found. There was no history of heart disease, high blood pressure, renal or lung diseases. There was no family history of diabetes mellitus, heart disease, high blood pressure, renal or lung diseases.

Physical examination showed the patient to be severely ill, weak, soporo-comatose. His blood pressure was 110/60 mmHg, pulse rate 120 x/minute, respiration rate 40x/minute, respiration rapid and shallow, and body temperature was 37$^\circ$C. His sclerae were not jaundiced, conjunctivae not anemic, pupils isochoric. Heart examination results were as follows: heart sounds I-II regular, gallop – murmur. Lungs: vesicular, no wheezing, rales +/- . Abdomen: flat, tense. His liver was palpable 4 fingers under the costal arch, 2 fingers under the xyphoid process, and his spleen was not palpable. His extremities were warm, edema-/-, decreased turgor.

Laboratory results were as follows: hemoglobin 18.9 g/dl, hematocryte 54%, leukocyte count 20,900/ul, platelet count 212,000/ul, ureum level 40 mg/dl, creatine level 1.4 mg/dl, blood glucose level 230. Urinalysis results: specific density 1.005, pH 6, protein +2, glucose - , blood - , ketone +2, bilirubin - , leukocyte 0-2 /large field, erythrocyte 0-2 /large field, crystal-,
bacteria -, cylinder -, epithelium -. Na 134 mEq/l, K 6.1 mEq/l, blood gas analysis pH 6.82, pCO\textsubscript{2} 13, pO\textsubscript{2} 113, HCO\textsubscript{3} <3.0, satO\textsubscript{2} 95%. Anion gap= 31 (normal value 8-12). ECG SR, NA, QRS rate 110 x/minute, ST change-, T inverted-, pathologic Q-, RVH-, LVH-. Chest x-ray: cardio-thoracic ratio < 55%, infiltrate -/

Based on the above, at the emergency unit, the following problems were established in the patient:

- Alcoholic ketoacidosis was established based on a long history of alcoholism (since youth), a history of drinking alcohols 3 days prior to admission, a physical examination showing soporomatoase, kussmaul breathing, laboratory examination showing blood acetone +1, urine ketone +2, anion gap = 31, and blood gas analysis indicated severe metabolic acidosis. Treatment using the diabetic ketoacidosis protocol was scheduled.
- Renal insufficiency was established based on a history of reduced intake for 3 days, laboratory results showing a blood urea level of 40 mg/dl and a blood creatinine level of 1.4 mg/dl. Ureum, creatinine, creatine clearance test, and renal ultrasound examination were scheduled.
- Hyperkalemia was established based on a blood potassium level of 6.1 mEq/l. Repeated potassium examination and hyperkalemia correction using sodium bicarbonate were scheduled.
- Hepatomegaly was established based on a liver palpable 4 fingers under the costal arch and 2 fingers under the xyploid process. This might be caused by alcoholic fatty liver and possibly viral or toxic hepatitis. Examinations for ALT, AST, cholinesterase, liver function test, liver viral serologic marker, liver biopsy, and liver ultrasound examination were scheduled. The patient received temporary therapy of 3x1 tablet of hepatoprotector.

**Disease Progression**

At the emergency unit, the patient was treated using the protocol for diabetic ketoacidosis. He was given antibiotics (1x2 g of ceftriaxone) and 3x100 ug of intravenous vitamin B1. During the first two hours he was given fluid therapy 2500 cc of 0.9% NaCl solution. Acidosis correction using sodium bicarbonate 250meq was planned. On the third hour, his blood glucose was 210 mg and his potassium level 6.1. Three lines of infusion was given. 2 lines NaCl 0.9% and 1 line of insulin drip 1 U/hour. On the fourth hour he was soporous. His blood glucose dropped to 84 mg, and thus the single NaCl 0.9% line was replaced with 500 cc/6 hours of D5%, and the insulin drip was reduced to 1 u/hour. On the 14th hour, his consciousness improved to somnolence. His blood gas analysis was pH 7.08, pCO\textsubscript{2} 10, pO\textsubscript{2} 138, HCO\textsubscript{3} 3.0, Na145 mEq/l, K3.2mEq/l, blood glucose 117mg/dL. He was given 300 mEq drip of sodium bicarbonate and 50 mEq of KCl in 500 cc 0.9% NaCl solution in 6 hours. The insulin drip and D5% infusion were sustained. One-thousand-calorie liquid diet was given. Twenty four hours diuresis was 3050 cc. On the 35th hour at the emergency unit, he was transferred to the 4th floor of inpatient ward B in the following condition: fully conscious, stabile hemodynamics, with a blood gas analysis of pH 7.3, pCO\textsubscript{2} 14, pO\textsubscript{2} 102, HCO\textsubscript{3} 6.9, O\textsubscript{2} saturation of 97% and three lines infusion with insulin drip of ½ U/jam, 500 cc of D5% /6 hours and 50 mEq of KCl in 500cc 0.9% NaCl /6 hours and 3 L of oxygen/ minute through a nasal cannule.

In the ward (on May 1\textsuperscript{st}, 2002) physical examination showed that the patient was severely ill, between fully conscious and apathetic, nasogastric tube showing transparent-greenish liquid, his blood pressure 110/60 mmHg, pulse rate 120 x/minute, respiration rate 32 x/minute, body temperature 39° C. Lungs: bronchial respiratory sound, wheezing +/-, rales +/, bowel sounds + (diminished), epigastic pain on palpation +. Laboratory tests demonstrated a Hemoglobin level of 14.5 g/dl, Ht 41%, leukocyte 13400 ul, platelet count 165,000/ul, ureum 40 mg/dl, creatinine 1.4 mg/dl, blood sugar 146 mg/dL, Na 144 mEq/l, K 3.2 mEq/l, blood acetone +, urine ketone +2, anion gap + (diminished), epigastic pain on palpation +. Laboratory tests demonstrated a Hemoglobin level of 14.5 g/dl, Ht 41%, leukocyte 13400 ul, platelet count 165,000/ul, ureum 40 mg/dl, creatinine 1.4 mg/dl, blood sugar 146 mg/dL, Na 144 mEq/l, K 3.1 mEq/l, blood gas analysis pH7.43, pCO\textsubscript{2} 14, pO\textsubscript{2} 102, HCO\textsubscript{3} 6.9, O\textsubscript{2} saturation of 97% and three lines infusion with insulin drip of ½ U/jam, 500 cc of D5% /6 hours and 50 mEq of KCl in 500cc 0.9% NaCl /6 hours and 3 L of oxygen/ minute through a nasal cannule.

During observation in the ward we established the problems as: sepsis, post alcoholic ketoacidosis, pneumonia with hypoxia, acute respiratory distress syndrome, RBBB, renal insufficiency, and hepatomegaly. We also considered pancreatitis and planned to test amylase and lipase. Other scheduled examinations were LFT, SGOT, SGPT, CHE, serial blood gas analysis, blood acetone, urinalysis, and repeated ureum creatinine tests. We also planned to conduct acid fast bacteria test from sputum, microorganism/resistance, sputum culture, and serial ECG /8 hours. The patient was limited to bed rest and was given 8 L of O\textsubscript{2} /minute using face mask, infusion with TFE 1000 1 bag/12hours, 0.9% NaCl and D10% 1 bag/day, as well as 3x1 g of cefotaxime, 1x1 amp of vitamin B\textsubscript{1}, 1x2 amp of furosemide (if blood pressure >100 mmHg), and 1 cc of β 2 agonist inhalation /6 hours. The pneumonia and ARDS were treated with 3x1 amp of dexamethasone and blood gas was monitored closely. Diuresis was 2200 cc/24 hours.

After one day in the ward (on May 2\textsuperscript{nd}, 2002), physical examination showed the patient to be severely ill,
The patient was moved to the ICU of Cipto Mangunkusumo hospital on May 2nd, 2002 at 4 pm.

The First Day at the ICU

The patient was severely ill, with a level of consciousness improving from apathy to comatosens-apathy, with stable hemodynamics, blood pressure of 110/70 mmHg, pulse rate of 88 x/minute, respiratory rate from 48 x/minute upon admission improving to 24 x/mnt, temperature from 41°C to 36.5°C, CVP +5, fluid balance +725 cc, a blood gas analysis indicating metabolic acidosis with respiratory compensation, but then proceeding to metabolic acidosis with respiratory compensation with a tendency of hypoxia, a pO$_2$ of 69.3 and a O$_2$ saturation of 92.9%. The patient was treated with 8 L of O$_2$/minute using a re-breathing bag, infusion, 1x2 g of cefoperazone, 2x1 amp of ranitidine, 3x1 amp of novalgin, 1x1 amp of vitamin B1 and a liquid diet of 4x 250 cc.

The Second Day at the ICU

The patient was generally severely ill, with full consciousness, stable hemodynamics, a blood pressure ranging around 100-130/60-80 mmHg, pulse rate 85-140 x/minute, respiratory rate 28-32 x/minute, body temperature 36.5 - 41°C, CVP +7, fluid balance +850 cc/day, infusion Aminosteril 5% 1000 cc, Triofusin1600 500 cc, 0.9% NaCl 2000 cc, RL 1000 cc, with added 1x120 mg of gentamycine, 500 cc liquid diet, and other treatments continued. The arising problem was copious mucoid sputum production. PO$_2$/FiO$_2$ = 123 mmHg.

The Third Day at the ICU

The patient was severely ill, fully conscious, with a blood pressure of 100/60 mmHg, a pulse rate of 132 x/minute, a respiratory rate of 32 x/minute, a body temperature of 39.5°C, and CVP +4.5. At 12 o’clock his consciousness decreased to apathy, his blood pressure dropped to 90/60 mmHg, his pulse rate 150 x/minute, and his respiratory rate 40 x/minute. In one hour his blood pressure dropped and was no longer palpable and he stopped breathing. CPR was performed and he was intubated and connected to ventilator. His blood gas analysis showed a pH level 7.066, pCO$_2$ 20.1, pO$_2$ 103.5, HCO$_3$ 13.4, and O$_2$ saturation of 98.8%.

The diagnosis of alcoholic ketoacidosis was established based on history, physical examination, and laboratory results. On admission the signs and symptoms were reduced consciousness, nausea, vomiting, chronic alcoholism, and poor intake since three days prior to admission, especially in the last 18 hours. Physical examination showed a reduced level of consciousness, tachycardia, tachypnea, dehydration, hepatomegaly, and decreased turgor. Laboratory tests showed increased blood glucose, ketonemia, severe metabolic acidosis, leukocytosis, and ketonuria +2. The
The patient was treated using the diabetic ketoacidosis protocol and given a parenteral diet, also orally using nasogastric tube and 100 mg of intravenous thiamine. Some references indicated that glucose administered in alcoholic ketoacidosis would improve patients’ consciousness and general condition. But while this patient also had sepsis and ARDS, although his consciousness improved, his general condition did not improve. He still suffered from hyperthermia and some threat of respiratory failure due to ARDS. During treatment his consciousness had improved to compos - apathy but then dropped again. Blood glucose was returning to normal levels, blood ketone negative, acidosis and hyperkalemia were improving due to bicarbonate correction.

ARDS in this patient was most probably due to pneumonia and possibly because of gastric acid aspiration during vomiting, as well as due to sepsis. Chest x-rays showed aggravation of bronchovesicular image showing progressive process in the alveoli. This is in accordance with the patient’s clinical condition, i.e., progressing lung edema, copious sputum production, and hypoxia refractory to oxygen. The patient was already given adequate oxygenation, stabilization of hemodynamics and eradication of the cause of sepsis using adequate antibiotics. Steroids were administered to reduce the respiratory distress and to impede alveolar inflammation process. Its administration was terminated due to hematemesis. H2 antagonist and sucralfate were then administered.

The diagnosis of pneumonia was established based on tachypnea, rales on both sides of the lungs, leukocytosis, and images of infiltrate on the chest x-ray. Sepsis in this patient was considered due to pneumonia. ARDS was also considered, due to the presence of sepsis and alcohol intoxication. Hypoxemia, reduced lung capacity due to lung edema, and infiltrates in thoracic x-ray would possibly lead to respiratory failure. The progression of respiratory alkalosis might have been due to sepsis and ARDS. Respiratory alkalosis and ARDS would cause and aggravate respiratory failure with hypercapnia and hypoxia. This was the reason to move the patient to the ICU.

Sepsis was established due to tachycardia, tachypnea, fever, and leukocytosis. The primary infection might be pneumonia, worsened by gastric acid aspiration and inadequate antibiotics. Sepsis was considered as one of the causes of ARDS in this patient. The antibiotic that was administered was 1x2 g ceftriaxone, which was changed to 3x1 g of cefotaxime and 2x80 mg gentamycine. Cefotaxime was switched to 2x1 g cefoperazone. This switch was made due to the possibility that the sepsis was caused by pneumonia, and the fact that cefotaxime can achieve higher levels in lung tissues than ceftriaxone. Cefotaxime was maintained after the leukocytes count fell. The switch from cefotaxime to cefoperazone may be due to persistent high fever.

Urinary tract infection was based on day 2 urinalysis results and was treated with the antibiotics for pneumonia. Renal insufficiency was caused by poor intake due to nausea and vomiting. After rehydration, the patient’s ureum and creatinine were back to normal levels. Therefore, we considered this as prerenal insufficiency due to poor intake. The therapy form was adequate and balanced fluid administration. Hepatomegaly is probably due to alcoholic fatty liver, based on a history of alcoholism of approximately 10 years, frequently until becoming drunk. A definite diagnosis could be made by liver biopsy. The patient had not yet received specific therapy, and we had planned to administer hepatoprotector agents such as curcuma. References stated that alcoholic fatty liver could spontaneously improve in 4-6 weeks after cessation of alcohol consumption and a diet high in protein and calories.

CONCLUSION

The patient’s death was considered to have been caused by untreatable sepsis and ARDS causing hypoxia and eventually respiratory failure. We considered the oxygen therapy using face mask to be inadequate. The result might have been better if the patient had been mechanically ventilated earlier, using continuous positive airway pressure (CPAP), and positive end expiratory pressure (PEEP) of 25-15 mmHg, which might have assisted respiration as well as prevented alveolar collapse. The delay in ventilating patient was one of the factors that caused the aggravation, since therapy was thus inadequate. Long hypoxia might have caused multi-organ failure, particularly of the heart, resulting in compensation failure to sustain function, leading to cardiac failure followed by hypotension and an immeasurable blood pressure and pulse.

REFERENCES


