Anaesthetic implications of acute and chronic alcohol abuse

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Introduction

Alcohol has been a substance of abuse for centuries. The discovery of late Stone Age beer jugs has established the fact that purposely fermented beverages existed at least as early as c. 10,000 BC. It has been suggested that beer may have preceded bread as a staple food. Throughout history, alcohol has been praised for its innumerable medicinal qualities. In the Bible, it is mentioned 191 times. Current studies and meta-analyses are still promoting moderate use of alcohol for the potential beneficial effects, but some studies have shown the contrary, where the risks of alcohol consumption seem to outweigh these benefits.

In South Africa, the proportion of the population that uses alcohol is low compared to other countries, although it has been estimated that per capita consumption among drinkers is likely to be in excess of 16.7 litres pure alcohol per year, one of the highest rates in the world. Statistics show that South Africa falls into the group of countries with the most hazardous patterns of drinking in the world with, for example, 14.3% of men admitting to binge drinking in a month in the South African national HIV prevalence, Behaviour and Communication Survey of 2005 (SABSSM II).

Acute alcohol intoxication is associated with increased mortality and morbidity arising from intentional and non-intentional injuries. It is also associated with unsafe sexual practices and increased risk of contracting a sexually transmitted disease. In Cape Town, Durban and Port Elizabeth, 39% of trauma patients had breath alcohol concentrations greater than or equal to 0.05 g/100 ml. Levels of alcohol were particularly high for transport- and violence-related injuries, with 73% of patients with violence-related injuries in PE and 46% of patients with transport-related injuries in Cape Town having levels above the legal limit for driving (0.05 g/100 ml). Findings from the first Demographic and Health survey of 1998 show that up to 28% of male drinkers and 10% of female drinkers might have an alcohol use disorder.

Definition and diagnosis

Alcohol use disorder (AUD) is defined as the repetitive, long-term ingestion of alcohol in ways that impair psychosocial functioning and health, leading to problems with personal relationships, school, or work. Alcohol use disorders include alcohol dependence, alcohol abuse, alcohol intoxication, and alcohol withdrawal.

AUD is formally diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. The DSM-IV describes two primary AUDs: alcohol abuse (harmful alcohol use) and alcohol dependence, which is characterised by the craving of alcohol, the inability to stop drinking, the development of withdrawal symptoms after a period of abstinence, and tolerance to alcohol.

Screening patients using the CAGE and AUDIT (Table I) screening tests seems to be a very sensitive (85–95%) and specific (72–95%) way of demonstrating AUD, with the AUDIT consistently scoring higher on sensitivity. The AUDIT has also been validated when answered by proxy.

Blood alcohol concentration may be helpful in diagnosing acute alcohol intoxication, but it can be negative in up to 45% of trauma patients with a risky alcohol history. Other tests that might be of some value are γ-glutamyltransferase (GGT) and carbohydrate deficient transferrin concentrations.

We as anaesthesiologists are in a unique position to incorporate screening tools for AUD in our routine preoperative assessments. Several studies
Table 1: The AUDIT test

| Test should be scored by adding points for each answer. | Maximum total score of 40. | Score of 8 or more points toward a drinking problem. |
|-------------------------------------------------------|---------------------------|------------------------------------------------------|
| 1. How often do you have a drink containing alcohol?  | (0) Never (skip to questions 9–10) | (1) Monthly or less |
|                                                       | (2) 2 to 4 times a month    | (3) 2 to 3 times a week |
|                                                       | (4) 4 or more times a week  |                                                       |
| 2. How many drinks containing alcohol do you have on a typical day when you are drinking? | (0) 1 or 2                  | (1) 3 or 4 |
|                                                       | (2) 5 or 6                  | (3) 7, 8, or 9 |
|                                                       | (4) 10 or more              |                                                       |
| 3. How often do you have six or more drinks on one occasion? | (0) Never                   | (1) Less than monthly |
|                                                       | (2) Monthly                 | (3) Weekly |
|                                                       | (4) Daily or almost daily   |                                                       |
| 4. How often during the last year have you found that you were not able to stop drinking once you had started? | (0) Never                   | (1) Less than monthly |
|                                                       | (2) Monthly                 | (3) Weekly |
|                                                       | (4) Daily or almost daily   |                                                       |
| 5. How often during the last year have you failed to do what was normally expected from you because of drinking? | (0) Never                   | (1) Less than monthly |
|                                                       | (2) Monthly                 | (3) Weekly |
|                                                       | (4) Daily or almost daily   |                                                       |
| 6. How often during the last year have you been unable to remember what happened the night before because you had been drinking? | (0) Never                   | (1) Less than monthly |
|                                                       | (2) Monthly                 | (3) Weekly |
|                                                       | (4) Daily or almost daily   |                                                       |
| 7. How often during the last year have you needed an alcoholic drink first thing in the morning to get yourself going after a night of heavy drinking? | (0) Never                   | (1) Less than monthly |
|                                                       | (2) Monthly                 | (3) Weekly |
|                                                       | (4) Daily or almost daily   |                                                       |
| 8. How often during the last year have you had a feeling of guilt or remorse after drinking? | (0) Never                   | (1) Less than monthly |
|                                                       | (2) Monthly                 | (3) Weekly |
|                                                       | (4) Daily or almost daily   |                                                       |
| 9. Have you or someone else been injured as a result of your drinking? | (0) No                      | (2) Yes, but not in the last year |
|                                                       |                             | (4) Yes, during the last year |
| 10. Has a relative, friend, doctor, or another health professional expressed concern about your drinking or suggested you cut down? | (0) No                      | (2) Yes, but not in the last year |
|                                                       |                             | (4) Yes, during the last year |
have shown that anaesthesiologists underestimate substance abuse in patients.\textsuperscript{16} Identification of AUD in the perioperative period could decrease postoperative morbidity and mortality by pre-empting possible complications and correct diagnosis and treatment of alcohol-related problems.\textsuperscript{17,18}

**Metabolism of alcohol**

Alcohol is metabolised mainly by the group of six enzymes collectively called alcohol dehydrogenase. These convert the ethanol into acetaldehyde, an intermediate that is actually more toxic than ethanol. The enzyme acetaldehyde dehydrogenase then converts the acetaldehyde into non-toxic acetic acid.

**Clinical presentation**

**Vitamin deficiencies**

Alcohol abuse is the leading cause of thiamine (vitamin B\textsubscript{1}) deficiency in the Western world. Thiamine is a water-soluble vitamin that participates in carbohydrate metabolism. Deficiency of this vitamin leads to Wernicke’s encephalopathy, a syndrome characterised by the classic triad of encephalopathy, ophthalmoplegia and ataxia. This triad only presents in 10\% of patients with Wernicke’s and, together with the fact that presentation can be acute or chronic, the diagnosis might be difficult. Left untreated, it can lead to Korsakoff’s psychosis. What is of clinical importance here is that a metabolic stressor, such as critical illness, in conjunction with carbohydrate load typically precedes its development. Because it can be difficult to diagnose these patients, especially in acute trauma, thiamine should be given as a supplement to all patients that are at risk of developing this disorder. Parenteral supplementation is preferred because of poor enteral absorption in alcohol-dependent individuals.\textsuperscript{19}

Folate deficiency is another common hypovitaminosis occurring in AUD and is usually due to decreased dietary intake, abnormal absorption, metabolism, hepatic storage and urinary excretion. This leads to megaloblastic anaemia and impaired erythrocyte function, and could also be a co-factor in the development of postoperative infections and poor wound healing.

**Metabolic abnormalities**

**Acidosis**

Up to 25\% of patients with an alcohol use disorder will have metabolic acidosis on admission.\textsuperscript{20} Types of metabolic acidosis that are specifically linked to alcohol ingestion are alcoholic ketoacidosis, lactic acidosis and acidosis caused by ingestion of other toxic substances. The serum osmolar gap is a helpful diagnostic tool to screen for the ingestion of toxic alcohols like ethylene glycol or methanol.

Alcoholic ketoacidosis will present with nausea, vomiting, abdominal pain and, often, high anion gap. This is mainly caused by starvation and glycogen depletion, a raised NADH:NAD ratio related to alcohol metabolism by alcohol dehydrogenase, and volume depletion leading to ketogenesis. Treatment is intravenous fluid and glucose. Glucose prevents ketogenesis, stimulates insulin production and secretion, promotes oxygenation of NADH and replenishes glycogen stores.

61\% of patients with alcoholic ketoacidosis will have raised lactate levels. This is usually due to the presence of concomitant disorders like pancreatitis, hepatitis and rhabdomyolysis.\textsuperscript{21} Thiamine deficiency may also be a cause of lactic acidosis because of impairment of pyruvate dehydrogenase, leading to the accumulation of pyruvate which is subsequently converted to lactate.

Other non-alcohol-related causes of metabolic acidosis, like salicylate overdose or sepsis, should be excluded.

**Magnesium**

Another abnormality closely associated with alcoholism is hypomagnesaemia. The main causes are poor dietary intake and increased urinary and faecal losses.\textsuperscript{22} Replacement therapy should be considered in patients with moderate to severe deficiency, and also in patients with symptomatic hypomagnesaemia. It should also form part of the routine management of alcoholic patients with acute dysrhythmias and seizures.

Hypomagnesaemia can be a cause of hypocalcaemia because of decreased parathyroid hormone secretion. In these cases it is often unnecessary to replace calcium, but magnesium replacement should continue for 3 to 5 days.\textsuperscript{19} Hypomagnesaemia can also cause hypokalaemia after increased kaliuresis. Potassium replacement will not correct the hypokalaemia until magnesium has been corrected.

**Phosphate**

Hypophosphataemia arises as a result of increased renal excretion. This may be exacerbated during critical illness by respiratory alkalosis, catecholamines or gastrointestinal losses. Severe hypophosphataemia can lead to cardiac dysrhythmias, respiratory failure or rhabdomyolysis and should be corrected promptly.\textsuperscript{19}
Rhabdomyolysis
Up to 67% of non-traumatic rhabdomyolysis occurs in patients with alcoholism, especially after acute intoxication. The direct effects of alcohol on muscle tissue with co-existing hypokalaemia and hypophosphataemia can be involved in the pathogenesis. Patients may not have the classic symptom of muscle pain, but compartment syndrome can develop.24

Alcoholic liver disease
Alcoholic liver disease can be characterised as any one of alcoholic fatty liver, alcoholic hepatitis or alcohol-related cirrhosis.

In alcoholic fatty liver, or macrovesicular steatosis, increased acetaldehyde, due to alcohol intake, leads to a higher NADH:NAD ratio. This, in turn, increases the esterification of fatty acids. Other factors, including high levels of free fatty acids and peroxisome proliferator-activated receptor alpha (an enzyme crucial for the regulation of hepatic fatty acid metabolism) have been implicated in the pathogenesis. Alcoholic fatty liver is an early and reversible consequence of excessive alcohol consumption.

Alcoholic hepatitis is a syndrome of progressive inflammatory liver injury associated with long-term alcohol abuse. The pathogenesis is still not completely understood, although it is now increasingly clear that, besides the formation of acetaldehyde, alcohol’s effects on the liver include oxidative stress, disturbances in methionine metabolism, endoplasmic reticulum stress, inflammatory or immune responses and adipokine imbalances.23 Alcoholic hepatitis should be suspected in any patient with jaundice and a history of alcohol abuse. Signs of chronic alcohol abuse, like spider angioma, might be present, and patients may also be febrile. Laboratory tests will reveal leucocytosis and high transaminase levels, with AST more elevated than ALT. Extreme levels (more than ten times normal) are not consistent with alcoholic hepatitis. Corticosteroids have been proven to decrease mortality, although these drugs are not indicated in patients with sepsis or those with a bleeding tendency.24

It is important to remember that paracetamol doses as low as 4 g per day could induce hepatic failure, severe liver necrosis and hepatic coma in patients with known alcoholic liver disease.25

Cirrhosis occurs when damage to the hepatic parenchyma leads to activation of the stellate cell. This tissue becomes contractile and obstructs blood flow in the hepatic circulation. In addition, it secretes TGF-β, which leads to a fibrotic response and proliferation of connective tissue. Furthermore, a disturbance of the balance between matrix metalloproteinases and the naturally occurring inhibitors can take place. This will lead to matrix breakdown and replacement by connective tissue-secreted matrix. Fibrous tissue bands will separate hepatocyte nodules, which will eventually replace the entire liver architecture, leading to decreased blood flow throughout the liver. Portal hypertension is responsible for most severe complications of cirrhosis.

Pancreatitis
Alcohol is the major causative factor of acute pancreatitis in about 32% of cases. The pathophysiology is still not fully understood, but one hypothesis is that alcohol sensitises acinar cells to cholecystokinin and potentiates the effects on the activation of transcription factors such as nuclear factor κB and activating protein-1.24 Other possible mechanisms include the toxic effects of acetaldehyde in acinar cells, induction of microtubular dysfunction and oxidative stress, as well as the uncoupling of mitochondrial oxidative phosphorylation.

Acute pancreatitis should be suspected in all alcoholic patients with abdominal symptoms. Elevated levels of serum lipase and amylase may assist in the diagnosis. Up to 30% of patients with acute pancreatitis will develop complications requiring critical care management. Ranson’s criteria may be helpful in predicting morbidity and mortality. Guidelines concur that close monitoring, combined with aggressive fluid resuscitation and supplemental oxygenation, is the mainstay of supportive therapy. Enteral nutrition is preferred over parenteral nutrition, but the nasogastric vs the nasojugal route is still under debate.27 Currently, prophylactic antibiotics are not indicated in patients with acute pancreatitis.

Immune dysfunction
Patients with AUD have a three- to five-fold increased postoperative infection rate compared to non-alcoholic patients. 38% of chronic alcoholics will develop pneumonia after surgery, compared to 7% in non-alcoholic patients.

Exposure to alcohol inhibits proliferation of CD3+ T cells and blunts the number of CD4+ and CD8+ T cells.28 The preoperative ratio of T helper cells 1 to T helper cells 2 (Th1/Th2 ratio) is significantly reduced. This is predictive of infections at a later stage. A low Th1/Th2 ratio is also associated with a higher risk of prolonged treatment time, and prolonged ICU treatment in particular. It correlates with a higher incidence of postoperative complications, particularly postoperative infections.29
Alcohol-associated changes in the balance between proinflammatory and anti-inflammatory cytokines have also been reported, particularly in alcoholic patients with liver disease, where increased concentrations of plasma cytokines were found. Acute alcohol intake leads to an increase in the levels of proinflammatory cytokines IL-12 and IFN-γ, and a decrease in the anti-inflammatory cytokine IL-10. Levels of proinflammatory cytokines IL-6 and TNF-α did not differ between alcoholic and non-alcoholic patients but, in long term alcoholics IL-10 was significantly raised immediately postoperatively. IL-10 depresses the antigen-presenting capacity of monocytes/macrophages by inducing down-regulation of expression of major histocompatibility complex class II. IL-10 remains increased for up to five days postoperatively in alcoholic patients. This reduction in the IL-6/IL-10 ratio is predictive of an increased postoperative infection rate.

On day one postoperatively, the T cytotoxic cells 1 to T cytotoxic cells 2 ratio (Tc1/Tc2 ratio) plays a predictive role much like the Th1/Th2 ratio plays preoperatively. The decrease in the Tc1/Tc2 ratio is predictive of postoperative infections, especially nosocomial pneumonia. The Th1/Th2 and Tc1/Tc2 ratios tend to remain depressed for up to five days postoperatively in alcoholic patients, whereas they are increased in non-alcoholic patients. Alcoholic patients also have an altered plasma cytokine response at the onset of infection and early septic shock with lower than normal levels of the proinflammatory cytokines IL-1β, IL-6 and IL-8, and normal levels of IL-10.

The hypothesis that therapeutic interventions with low dose ethanol, morphine and ketoconazole at the hypothalamus-pituitary-adrenal axis provides therapeutic benefit by affecting the neuroendocrine-immune regulatory pathways was supported by a study done by Spies et al. in an attempt to design a perioperative approach to prevent altered T-cell immunity. Low dose ethanol also prevented postoperative hypercortisolism and alcohol withdrawal, with placebo patients displaying an increased postoperative infection rate, especially nosocomial pneumonia, followed by prolonged ICU stay.

The alcoholic lung
Recent research cites alcoholic lung disease as comparable to liver disease in terms of alcohol-related mortality. One of the central changes relating to chronic alcohol ingestion is decreased concentration of glutathione, an antioxidant, throughout the alveolar fluid lining of the lung and also in type II pneumocytes. Pulmonary glutathione deficiency results in abnormal surfactant synthesis and secretion, increased type II cell apoptosis, increased basal expression of transforming growth factor β (TGFβ), and changes in alveolar-capillary barrier function and permeability.

Alcoholic patients are at greater risk to develop ARDS than their non-alcoholic counterparts. In patients with septic shock, alcohol abuse increases the incidence of ARDS from 31% to 70%. In ARDS survivors, alcohol abuse is also associated with an increased duration of mechanical ventilation and prolonged ICU length of stay.

Because of impaired alveolar immune function, individuals with a history of chronic alcohol abuse are more likely to develop severe or lethal bacterial pneumonia. AUD is also associated with an increased risk of bacteraemia and empyema, extended recovery time, a higher frequency of cavitary disease and persistent pulmonary infiltrates on chest X-ray.

In these patients, pneumonia is often caused by atypical organisms, particularly Gram-negative organisms like Klebsiella pneumoniae. Possible reasons for this can be higher colonisation rates, poor oral health and a higher risk of aspiration in alcoholic patients.

Alcoholic cardiac dysfunction
Chronic alcohol ingestion leads to alcoholic cardiomyopathy and is characterised by cardiomegaly, disruptions of myofibrillar architecture, reduced myocardial contractility, decreased ejection fraction and increased risk of stroke and hypertension. This syndrome is frequently asymptomatic. Several mechanisms have been postulated for alcoholic cardiomyopathy, including oxidative damage, accumulation of triglycerides, altered fatty acid extraction, decreased myofilament Ca2+ sensitivity and impaired protein synthesis, but neither the mechanism nor the actual toxin responsible has been satisfactorily explained. The specific toxins may be alcohol, acetaldehyde, the first and major metabolic product, and fatty acid ethyl esters. Acetaldehyde can directly impair cardiac contractile function, disrupt cardiac excitation-contraction coupling, and contribute to oxidative damage and lipid peroxidation. Heavy ethanol consumption leads to increased risk for sudden cardiac death and cardiac arrhythmias. Atrial fibrillation (AF) after binge drinking is a well known entity, and chronic alcohol abuse has been associated with 34% increased risk of developing AF. In patients with coronary heart disease, alcohol use was associated with increased mortality.

Left untreated, with no changes in drinking behaviour, patients with alcoholic cardiomyopathy can develop signs and symptoms of heart failure. This distinct form
of congestive heart failure is responsible for 21-36% of all cases of non-ischaemic dilated cardiomyopathy in Western society. Without complete abstinence, the 4-year mortality for alcoholic cardiomyopathy is close to 50%.

Thiamine deficiency can lead to a high output cardiac failure (wet beri-beri), due to vasodilatation and decreased vascular resistance from vasomotor depression and augmented venous return.

**Haemostatic disturbances**

Evidence in the literature suggests both platelet activation and platelet inhibition by alcohol. A unifying hypothesis is that platelets are partially activated by ethanol, with incomplete degranulation allowing for continued circulation of platelets with impaired function. Alcohol has also been shown to directly inhibit bone marrow platelet production. Evidence exists showing that alcohol intake decreases fibrinogen, factor VII, and vWF levels. In addition, alcohol has been found to increase fibrinolysis by increasing tissue plasminogen activator activity. The effect of alcohol on platelets, coagulation factors, and the fibrinolytic system is likely to contribute to the proposed cardiovascular protective effects of alcohol, but can lead to increased bleeding times, with postoperative bleeding and excessive haemorrhage in traumatically injured patients.

**Drug interaction/metabolism**

Alcohol acts as a central nervous system depressant by specifically altering the function of several ligand-activated ion channels, including N-methyl-D-aspartate (NMDA), serotonin (5-HT₃), glycine and GABAₐ receptors. Because of the similarity in mechanism of action, it is easy to explain the phenomenon of lower requirements of induction agents, opioids and inhalational anaesthetic agents during acute alcohol intoxication.

Chronic alcohol abuse and, in particular, patients with alcoholic liver disease alter the pharmacokinetics of certain drugs by increasing the amount of free drug available due to lower levels of binding proteins. Drug distribution, elimination and metabolism may also be altered, with decreasing liver enzymatic function and an increase in the volume of distribution of certain drugs. This effect is dependent on specific drug metabolism and the stage of alcoholic liver disease. The effect of alcohol abuse on the dosing requirements of some commonly used anaesthetic agents is shown in Table II.

**The anaesthetic plan**

Brief suggestions to the anaesthetic approach of these patients are listed in Table III. The definitive management will, of course, be at the discretion of the anaesthesiologist with consideration of the patients’ co-morbid disease.

**To abstain or not to abstain**

All evidence in the literature suggests that a period of abstinence in the preoperative period decreases postoperative morbidity. It was found that one month of abstinence prior to surgery significantly decreases morbidity and mortality, although the morbidity was

### Table II: Interaction of alcohol with anaesthetic drugs

| Drug          | Effect in acute intoxication | Effect in chronic alcoholism |
|---------------|------------------------------|------------------------------|
| Propofol      | Decreased dosing requirement | Increased dosing requirement  |
| Thiopentone   | Decreased dosing requirement | No evidence of altered doses  |
| Etomidate     | No evidence of altered doses |                              |
| Inhalation anaesthetics | Decreased MAC | Decreased clearance of halothane |
| Opioids       | Decrease metabolism          | Beware of accumulation with repeated doses |
| Neuromuscular blocking agents | Altered pharmacokinetics | |

### Table III: The anaesthetic plan

**Preoperative**
- Extensive history, including CAGE/AUDIT
- Full physical examination, with special attention to cardiac and respiratory systems
- Chest radiograph and ECG
- Full electrolyte and biochemical profile
- Full blood count, INR and PT/PTT
- Consider local or regional anaesthetic techniques

**Anaesthetic induction**
- Altered induction agent dose
- Rapid sequence intubation if acute intoxication

**Intraoperative**
- Lower MAC of inhaled agents in acute intoxication
- Careful opioid administration
- Paracetamol dose adjustment
- Muscle relaxants with organ independent metabolism

**Postoperative**
- Always remember alcohol withdrawal syndrome (see Table IV)
- Choose analgesia carefully
still higher in the abstinence group than in non-alcoholic patients. Longer periods of abstinence may well further decrease morbidity.

**Alcohol withdrawal syndrome**

It is important for anaesthesiologists to know the symptoms, clinical signs and management of alcohol withdrawal symptoms because as alcohol withdrawal syndrome might be one of the many causes of post operative delirium. Alcohol withdrawal syndrome is a set of symptoms that can develop in alcohol-dependant individuals within 6 to 24 hours from their last drink. It typically presents after 2 to 4 days of abstinence and can persist for up to two weeks. Benzodiazepines are still considered the mainstay of treatment in these individuals. Propofol has also been used successfully, but neuroleptic agents are no more considered appropriate if used as monotherapy. Early and late signs of alcohol withdrawal syndrome are summarised in Table IV.

**Table IV: Alcohol withdrawal syndrome**

| Early signs                      | Later findings                |
|----------------------------------|-------------------------------|
| - hyperpyrexia                  | - confusion                   |
| - tachycardia                   | - agitation                   |
| - hypertension                  | - seizures                    |
| - diaphoresis                   | - psychosis                   |
| - pronounced autonomic hyper-reactivity |

**Conclusion**

AUD is a multi-system disorder that has far-reaching anaesthetic implications that are frequently misdiagnosed or under-reported. Anaesthesiologists are in a unique position to diagnose this disorder preoperatively and usually underestimate the prevalence. Knowledge of the full extent of the pathophysiology of this disease might help in preventing possible complications. Making a correct diagnosis, treating alcohol-related problems, and promotion of abstinence will decrease morbidity and mortality. Promoting abstinence in the preoperative period will decrease morbidity.

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