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PATHCHAT

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Laboratory markers for alcohol use

DEFINITIONS AND TERMS

Alcohol use disorders (AUD) were reclassified by the DSM-5[i] in 2013. The DSM-5 replaced the DSM-IV, which differentiated *alcohol abuse* (problem drinking without compulsive use) from *alcohol dependence* (compulsive drinking). In the DSM-5, there are 11 criteria based on behaviour and physical symptoms for four groups of increasing severity:

- Impaired control (use more alcohol than intended, desire to cut down, but unsuccessful, spend a lot of time on alcohol, craving)
- Social impairment (fail obligations at home, work or school, continue drinking despite interpersonal problems, give up activities)
- Risky use (recurrent alcohol use even when physically hazardous, continue drinking despite knowledge of physical or psychological problems)
- Pharmacological criteria (tolerance, withdrawal)

Severity is classified as mild (2–3 criteria), moderate (4–5 criteria) or severe (6+ criteria) disease and can be used at time of diagnosis and for follow up. Remission (no symptoms except craving) is classified as early (3–11 months) or full (more than 12 months) remission. A psychiatric evaluation is part of the evaluation for AUD.[ii]

- *Alcoholism*: Alcohol dependence with a strong desire to drink, inability to control drinking, continued heavy alcohol use despite problems, drinking takes precedence over other activities, tolerance, and withdrawal if alcohol is reduced or stopped.[iii]
- *Withdrawal*: Syndrome of physical symptoms that occurs when blood alcohol level declines after prolonged heavy alcohol use.[ii]
- *Tolerance*: Markedly increased dose of alcohol needed for desired effect or markedly reduced effect with the usual alcohol dose.[ii]
- *Heavy episodic drinking*: More than 60 g (five or more drinks) on one occasion at least monthly. [iv]

WHO 2000[v]	Males	Females
High-risk drinking	>60 g/day (5 or more beers/day)	>40 g/day (3 or more beers/day)
Medium-risk drinking	41–60 g/day (3-4 beers/day)	21-40 g/day (2 beers/day)
Low-risk drinking	1–40 g/day (1–2 beers/day)	1–20 g/day (1 beers/day)

- A typical "drink" contains 13 g of ethanol as in one beer (330 ml, 5% alcohol), one glass of wine (140 ml, 12%) or one shot of spirits (40 ml, 40%).[iv]
- The definition of a "standard drink" varies considerably between countries: 8 g (UK), 10 g (World Health Organization (WHO), Australia, etc.), 12 g (RSA) and 14 g (USA).[iv]
- A "unit" of alcohol contains 8g of alcohol.[iii]

WHO REPORT FOR SOUTH AFRICA (2010):

	Males	Females	Both genders
Prevalence of alcohol use disorders (%)	10	1.5	6
Prevalence of heavy episodic drinking (%)	18	4	10

SCREENING FOR ALCOHOL USE DISORDERS

- In terms of the diagnostic performance of a test, good sensitivity is usually at a trade-off for poor specificity, and vice versa.
- A cut-off value separates normal and abnormal results and is chosen for optimal sensitivity and specificity.
- Sensitivity is the chance of having an abnormal result, given that an individual has the diagnosis tested for. A marker with good sensitivity will detect a

diagnosis, while a marker with poor sensitivity will miss a diagnosis. A marker with 100% sensitivity can be used to rule out the diagnosis tested for, if the result is normal.

- Specificity is the chance of having a normal result, given that an individual does not have the diagnosis tested for. A marker with good specificity is not abnormal due to conditions other than the diagnosis tested for, while a marker with poor specificity is abnormal due to many causes other than the diagnosis tested for. A marker with 100% specificity can be used to rule in the diagnosis tested for, if the result is abnormal.

QUESTIONNAIRES

The gold standard screening questionnaire is the WHO-developed AUDIT, a 10-item questionnaire with a sensitivity of 51 to 97% and a specificity of 78 to 96%.[ii]

Questionnaire results may be unreliable when an individual is hesitant to disclose alcohol use, or has altered mental status.[vi]

LABORATORY MARKERS

Classification:

- State vs. trait: [vii]
  - State markers reflect recent drinking patterns.
  - Trait markers are inherited and identify individuals at risk or genetically predisposed to alcohol-use disorders to facilitate prevention and early diagnosis, or to predict response to treatment. These markers are being researched, are not routinely available and are beyond the scope of this publication.
- Direct vs. Indirect:[vi]
  - Direct markers measure alcohol or its metabolites, and reflect alcohol use.
  - Indirect markers reflect the effects of alcohol on the body and reflect damage caused by alcohol use.

Use of current laboratory markers:

- Current laboratory markers can be used to:
  - enhance suspicion of alcohol use disorders and must be combined with a clinical history, including from a family member, questionnaire and physical examination,
  - give objective information regarding alcohol use and changes in use over time,
  - detect heavy drinking,
  - detect relapse in known alcoholic patients.
- Diagnostic accuracy is improved by combining markers.
- In primary health care, the most efficient screening with routinely available markers is combined use of the AUDIT questionnaire, CDT and GGT.[viii]

Limitations of current laboratory markers:

- No laboratory marker is reliable enough on its own to detect alcoholism.
- Sensitivity and specificity published in the literature varies greatly depending on the population being studied (alcoholism treatment centres vs. primary health care setting).
- The ideal laboratory marker for alcohol use does not exist, which should be:
  - very sensitive to detect chronic alcohol use (screening marker) and acute alcohol use (relapse marker); and
  - very specific to discriminate heavy, hazardous drinking from social, safe drinking, and not be abnormal due to non-alcohol-related causes.

Current routinely available laboratory markers for alcohol use

Analyte	Cut off	Sensitivity	Specificity	Use	Amount and time of alcohol use to cause abnormal marker	Time to normalise with absti-nence	Comment
Ethanol (direct)	0.05 g/dl (SA legal limit when driving)	-	-	• Detect acute alcohol use • Detect tolerance (>0.15 g/dl without intoxication or >0.3 g/dl at any time) • Calculate number of drinks ingested (need weight, blood-alcohol level, drink volume and drink alcohol percentage)	For blood alcohol >0.05 g/dl after one hour: >2 beers in 70 kg person	Hours, depends on dose	• Short detection time limits use • Widmark formula is based on a bolus alcohol load of one type of alcohol on an empty stomach
GGT-CDT (indirect)	Male 4.18 Female 3.81	89 96	98 97	Detect heavy drinking among: heavy drinkers (n=165); moderate drinkers (n=51); abstainers (n=35) *(Finland)*	>40 g/day (3 or more beers/day) for one month	2–3 weeks	• GGT-CDT is calculated by a mathematical formula that weighs GGT and %CDT. • Increased sensitivity without affecting specificity. • Detects more alcohol abusers than CDT or GGT alone. • Performance is similar whether or not heavy drinkers are contrasted with abstainers or moderate drinkers, which is useful for screening. • Correlates with the amount of alcohol used. • Use of MCV, ALT or AST as a third component did not add value • Liver disease in heavy drinkers did not influence GGT-CDT performance.
%CDT (indirect)	2.35 2.47	94 93	97 97	• Most useful to monitor abstinence in alcoholics • Detect heavy drinking for at least one week in alcoholics • Detect %CDT above 97.5% on HPLC reference method (n=100 normal, n=100 increased)	50–80 g/day (4–6 beers/day) for at least one week in alcoholics	2–4 weeks	• %CDT: Transferrin is a protein that carries iron in blood. Normal transferrin has four carbohydrate chains. With excessive alcohol use, forms of transferrin that contain no, one or two carbohydrate chains (collectively known as CDT) increase. • CDT and total transferrin are measured and the %CDT is calculated. • %CDT should be reported rather than absolute CDT to correct for fluctuations in total transferrin levels. • In alcoholics that relapse, lower use can lead to rapid re-elevation. • Most accurate single serum marker for chronic alcohol use and recent heavy drinking that is readily available. • Main strength is specificity. • Single episodes of acute alcohol intoxication do not elevate CDT. • Decreased sensitivity to detect alcohol abuse in females. • False positive results may occur due to non-alcoholic liver disease (primary billiary cirrhosis, chronic active hepatitis, chronic Hepatitis C, hepatocellular carcinoma), or carbohydrate deficient glycoprotein syndrome (rare). • %CDT methods include immunoassays, capillary electrophoresis and HPLC. • Results and cut-off values from different methods cannot be used interchangeably. • Cut-offs listed here are for the N-Latex immuno-nephelometric assay (INA) currently in use at Ampath.

Analyte	Cut off	Sensitivity	Specificity	Use	Amount and time of alcohol use to cause abnormal marker	Time to normalise with absti-nence	Comment
GGT (U/l) (indirect)	Male 85 Female 65	30 23	92 94	Detect heavy drinking in the general population (1 022 males, 583 females) *(USA)*	>70 g/day (>5 beers/day) >55 g/day (>4 beers/day) >40 g/day (>3 beers/day) in chronic alcoholics	2–5 weeks	GGT is a liver enzyme. • Most commonly used marker. • Increase in absence of other causes should raise suspicion of excessive drinking. • Rapid fall with abstinence is highly suggestive that suspicion is correct. • Does not increase with binge drinking in non-alcohol abusers. • False negative: no longer increased in some chronic drinkers. • Rarely increases in individuals <30 years old. • False positive results may occur due to a wide range of medication (hormones, anticonvulsants), generalised liver damage, non- alcoholic fatty liver disease, any cause of biliary damage or stasis, hepatic congestion (CCF), pancreatitis, Diabetes Mellitus, obesity, smoking, hyperlipidemia, hyperthyroidism or severe trauma.
MCV (Fl) (indirect)	96	45	94	Marker of chronic alcoholics with sustained heavy drinking Detect heavy drinking among: heavy drinkers (n=165) moderate drinkers (n=51) abstainers (n=35) *(Finland)*	>60 g/day (>4 beers/day) for at least a month	2–4 months	• Mean corpuscular volume (MCV) is the size of the red blood cells. • Good specificity (very few tee-totallers and social drinkers will have increased MCV). • Easily obtained. • Use encouraged when considering chronic alcohol abuse and dependence. • Poor screening marker for alcohol abuse; main weakness is low sensitivity. • Poor marker of acute ethanol intake. • Takes several months to reflect changes in drinking. • May continue to rise after use stopped in alcohol dependence. • Cannot monitor abstinence or relapse. • False positive results may occur due to Vitamin B12 or folate deficiency, hypothyroidism, haemolytic disease, non-alcoholic liver disease, age, smoking or medication (anticonvulsants, azathioprine or zidovudine).
AST/ALT (indirect)	>2	Low	90	• Detect alcohol-induced liver damage. • Distinguish alcohol induced from non-alcohol induced liver disease.	-	-	Indicates advanced alcoholic liver disease rather than heavy alcohol consumption

i DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5
ii Vonghia L et al. 2014. Diagnostic challenges in alcohol-use disorder and alcoholic liver disease. *World Journal of Gastroenterology* 20(25):8024–8032
iii Sharpe PC. 2001. Biochemical detection and monitoring of alcohol abuse and abstinence. *Ann Clin Biochem* 38:652–664
iv Babor TF et al. 2001. AUDIT 2nd ed. World Health Organization
v World Health Organization. 2000. International Guide for Monitoring Alcohol Consumption and Related Harm
vi Tavakoli HR et al. 2011. Review of current clinical biomarkers for the detection of alcohol dependence. *Innov Clin Neurosci* 8(3):26–33
vii Hashimoto ERI et al. 2013. Consensus paper of the WFSBP task force on biological markers: biological markers for alcoholism. *The World Journal of Biological Psychiatry* 14:549–564
viii Miller RF et al. 2004. Biochemical alcohol screening in primary health care. *Addictive Behaviours* 29:1427–1437