Kingdom Of Cambodia
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Methanol Poisoning

Cambodian National Guidelines for diagnosis and treatment

Developed by

CDC Cambodia

In collaboration with

World Health Organization (WHO)
Medécins sans Frontiéres (MSF/Doctors without Borders)
Oslo University Hospital (OUH)
The Methanol Poisoning initiative (MP*i*)

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Preface

The present National Guidelines on Methanol Poisoning has been made possible by a collaboration between several institutions: The Cambodian Ministry of Health/The Communicable Disease Control department (CDC), Calmette Hospital, Kratie Provincial Hospital, Médecins Sans Frontières (MSF/Doctors without Borders), the World Health Organization (WHO), Oslo University Hospital (OUH), and The Methanol Poisoning initiative (MP*i*; A collaboration between OUH and MSF).

Methanol poisoning is a global health threat killing thousands globally, as well as leaving patients blinded and/or with permanent brain damage. While this highly toxic substance also occurs regularly in Cambodia, it affects not only the patients but also their families and whole societies, as the breadwinner often is the one being killed or disabled. The diagnosis is typically difficult, and the patients may easily be overlooked. Based on these concerns, an expert group were put together in order to make systematic, scientifically based guidelines that could be implemented in areas with various – and often limited - available means of diagnosis and treatment.

It is with great enthusiasm I see this novel work developing in the Kingdom of Cambodia, which I also hope can be a model for other countries in the South East Asian region. It is, however, important to recognize that the job is not accomplished with the development of these guidelines: Now is the time for implementing the knowledge into daily practice.

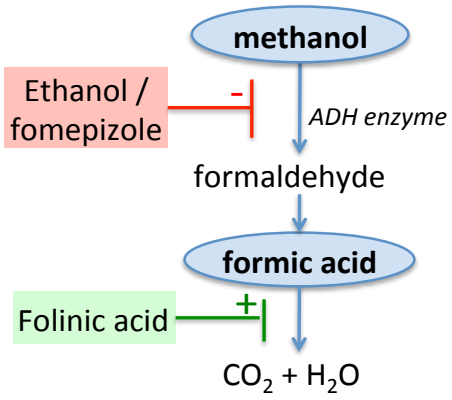
My sincere acknowledgements go to the teams of the Communicable Disease Control department and the national- and regional hospitals of Cambodia that have seen the necessity of developing these guidelines. I also want to thank WHO and MSF for their coordinating role, and the Methanol Poisoning initiative (MPi) and Oslo University Hospital for bringing in world leading expertise to put this all together. I hope this guideline along with the implementation of trainings and adapted risk communications will save lives and health, and thereby benefit the patients and their families in the years to come.

Prof. Eng Huot
Secretary of State

Name List of participants

Methanol poisoning at a glance

Background/Mechanisms of toxicity



Methanol is an alcohol without color and hardly any smell. Methanol is not toxic by itself, but it is metabolized to the highly toxic formic acid/formate (see fig): The treatment is focused on blocking the enzyme (ADH) with either ethanol or fomepizole, buffer the metabolic acidosis with bicarbonate, and use dialysis to remove methanol, and formate and correct the metabolic acidosis. Folinic acid may also be given to enhance the endogenous (own) metabolism of formate.

All of the above should be initiated as early as possible, but any of these treatments are important –
Use what you have available!

If a patient is transferred for dialysis: Start antidote (and bicarbonate if signs of acidosis) before transport

Diagnosis:

- **History *(detailed history is very important: Can this be methanol?)*:** Intake of illegal/bootleg alcohol or alcohol of unknown origin, others in the environment with confirmed or suspect methanol poisoning (seriously ill, fatalities, blindness etc.). ***Symptoms appear after >12-24 hrs*** (if shorter time from drinking to symptoms: Unlikely to be methanol).

- **Symptoms**: ***hyperventilation*** (respiration frequency (RF) >20-25/min)/dyspnoea, visual disturbances (all kinds of), GI-symptoms (frequently vomiting, but also gastric pain etc.), chest pain, severe/unusual "hangover" (feeling very sick 1-2 days after drinking).

- **Lab diagnosis**: Diagnosis can be supplemented by the use of a *blood gas analysis* (see flow-chart 2 below), by the specific analysis of the toxic metabolite *formate* (see flow-chart 3 below) or by analysing for methanol itself.

Management of suspected methanol poisoning (no blood gas analysis (ABG) available – based on clinical signs and symptoms only. See also flow-chart 1):

A. **Asymptomatic patients**: Observe for up to 24 hours (depending on level of suspicion).
B. **Hyperventilation, no visual disturbances, conscious**. Adequate blood pressure/pulse: Give 1-2L of iv fluids (e.g. NaCl 0.9%) + thiamine (e.g. 100mg or 250mg) + glucose (e.g. 1000 mL of 50mg/mL (5%)) within 30-60 min. If acidosis is corrected/improved (less or no hyperventilation): likely alcoholic or diabetic ketoacidosis, not methanol poisoning. If *not* improved after 1 hr: Give ethanol/fomepizole and bicarbonate. Transport to dialysis facilities if possible. Observe min. 24 hours after treatment is terminated (see "Suggested dosing").
C. **Hyperventilation, visual disturbances, conscious:** Give ethanol/fomepizole, bicarbonate, folic acid, transport to dialysis facilities if possible. Observe min. 24 hours after treatment is terminated (see "Suggested dosing").
D. **Hyperventilating, unconscious:** Give ethanol/fomepizole, bicarbonate, folic acid, transport to dialysis facilities. Observe min. 24 hours after treatment is terminated (see "Suggested dosing").
E. **Normoventilating/slow breath, unconscious:** Likely poor prognosis if methanol poisoning. Be careful with ethanol in case this is a ethanol intoxication instead: Treat symptomatically, or as a methanol poisoning *if definite suspicion*.

Management of <u>suspected</u> methanol poisoning (when blood gas analysis (ABG) is available – based on patient blood gases. See also flow-chart 2):

A. **Asymptomatic patients, normal blood gas**: Observe for up to 24 hours (depending on level of suspicion).
B. **HCO_3>15 or BD<10, pH typically >7.2:** 1-2L iv NaCl 0.9% + thiamine (e.g. 100mg or 250mg) + glucose (e.g. 1000 mL of 50mg/mL (5%)) within 60min. If acidosis is corrected/improved: likely alcoholic/diabetic ketoacidosis, not methanol poisoning. If <u>*not*</u> improved after 1 hr: Give ethanol/fomepizole and bicarbonate. Transport to dialysis facilities if possible. Observe min. 24 hours after treatment is terminated (see "Suggested dosing").
C. **HCO_3>10 or BD<15, pH typically 7.0-7.2:** 1-2L iv NaCl 0.9% + thiamine (e.g. 100mg or 250mg) + glucose (e.g. 1000 mL of 50mg/mL (5%)) within 60min. If acidosis is corrected/improved: likely alcoholic/diabetic ketoacidosis, not methanol poisoning. If <u>*not*</u> improved after 1 hr: Give ethanol/fomepizole and bicarbonate. Transport to dialysis facilities if possible. Observe min. 24 hours after treatment is terminated (see "Suggested dosing").
D. **HCO_3<10 or BD>15, pH typically <7.0:** Give ethanol/fomepizole and bicarbonate, hemodialysis, folic acid. Observe min. 24 hours after treatment is terminated (see "Suggested dosing").
**Lower threshold of starting bicarbonate + ethanol in group C than B if acidosis worsening.*

Treatment:

A. Give **antidote** (***ethanol*** orally or intravenously *or* ***fomepizole)*** <u>**without delay**</u>.
For dosing: See below

B. Give **bicarbonate ($NaHCO_3$)** as soon as possible intravenously.
For dosing: See below

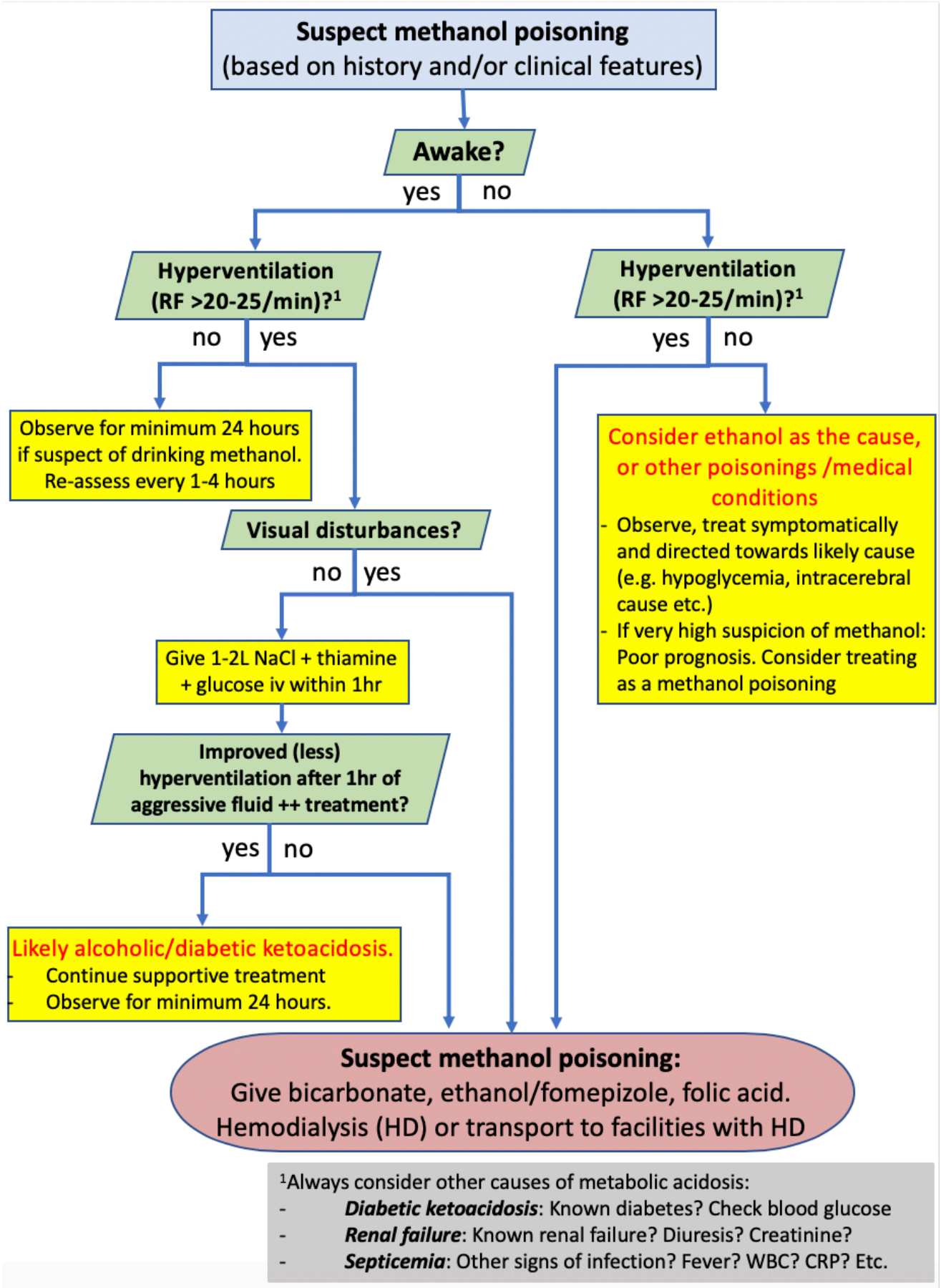
C. **Folic acid** (or folinic acid) 50mg iv. or orally (e.g. 10 tablets of 5mg) every 6 hours for 24-48 hrs.

D. **Dialysis:**
   a. **Intermittent dialysis (IHD = high-flow dialysis/regular dialysis)** for 6-8 hours, or
   b. **Continuous dialysis (CRRT/CVVHD/CVVHDF)** for minimum 18 hours.
   c. **If dialysis is not available:** Consider transferral to dialysis unit. **Start antidote and bicarbonate if** necessary <u>before</u> transport.
   d. **If peritoneal dialysis** is available**:** Treat for at least 48 hours (lack of data to support this approach)
   e. **If limited number of dialysers:** Consider rotating the dialysers: between the patients: 1-2 hours each patient for initial stabilization– rotate – then rotate back
E. If **intubation is necessary:** The patient <u>must</u> be hyperventilated (RF >25/min) (until metabolic acidosis is corrected).

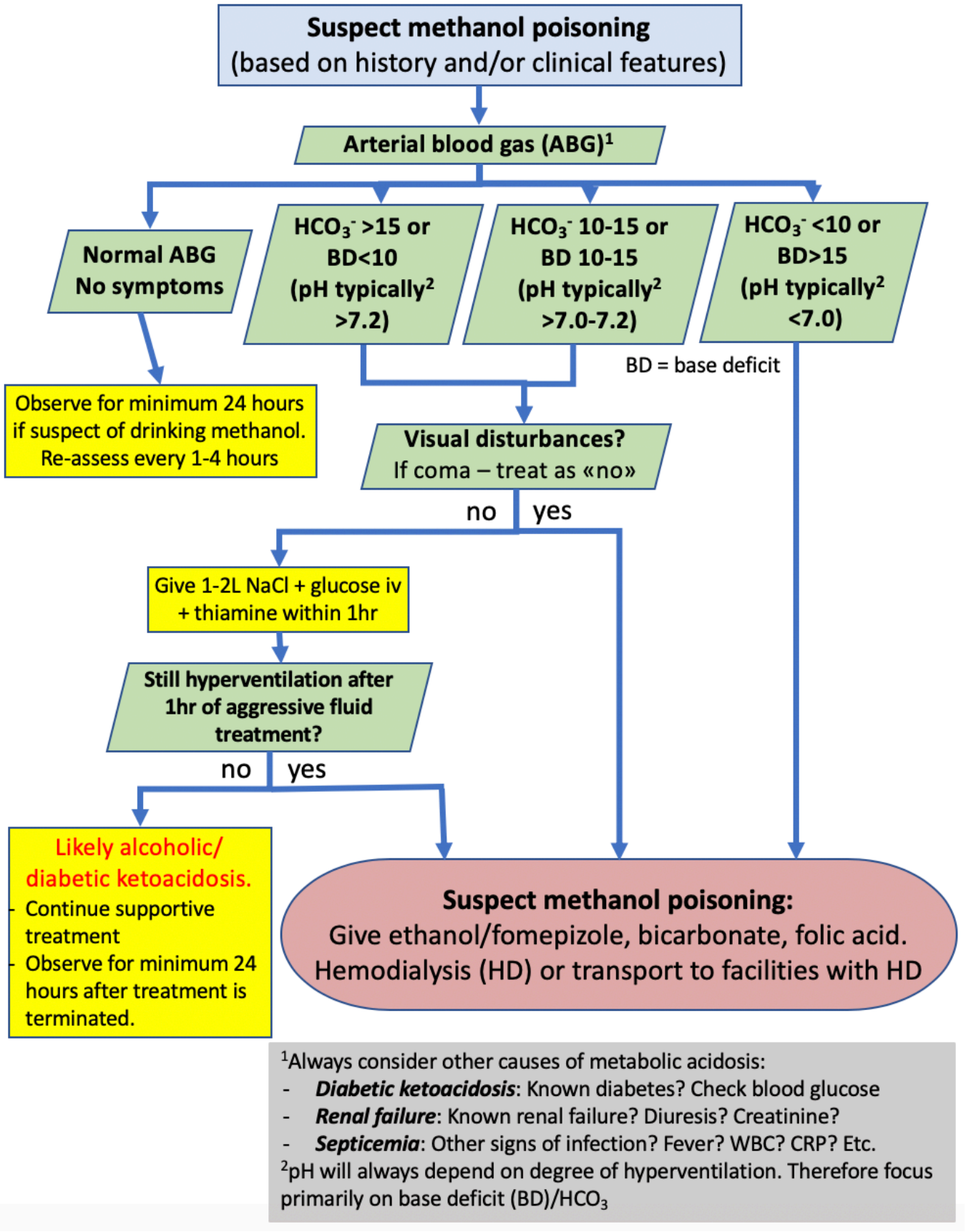
Prognostic aspects

Coma on admission, severe acidosis (pH <6.9-7.0 and HCO_3 <10/base deficit>15-20) and lack of hyperventilation indicates poor prognosis if the patient is suffering from methanol poisoning, but pure ethanol intoxication or a combination of those may be a differential diagnosis.

Flow-chart 1 Diagnostic process when blood gas is not available



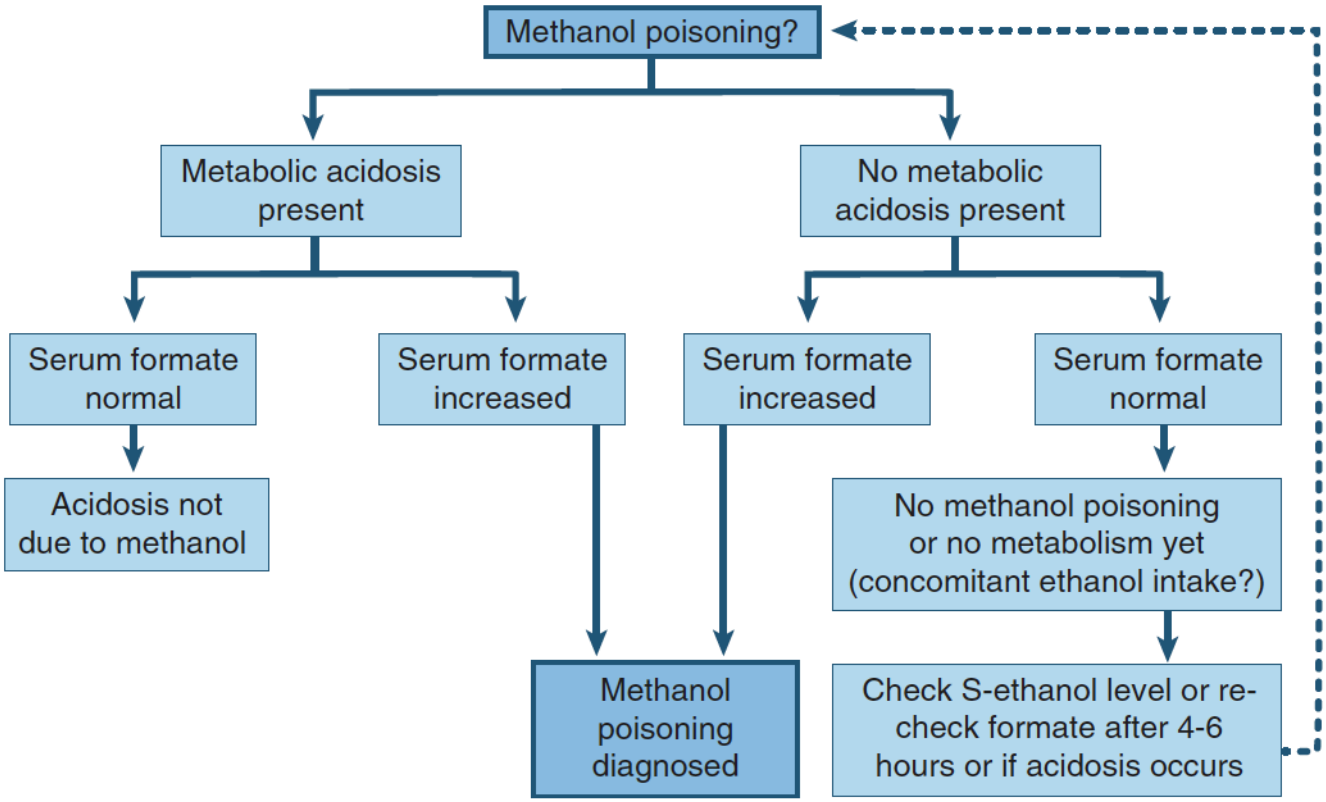
Flow-chart 2 Diagnostic process when blood gas is available



[1]Always consider other causes of metabolic acidosis:
- ***Diabetic ketoacidosis***: Known diabetes? Check blood glucose
- ***Renal failure***: Known renal failure? Diuresis? Creatinine?
- ***Septicemia***: Other signs of infection? Fever? WBC? CRP? Etc.

[2]pH will always depend on degree of hyperventilation. Therefore focus primarily on base deficit (BD)/HCO_3

Flow-chart 3: Clinical use of the formate assay (if available)



From: *Hovda KE, McMartin KE, Jacobsen D. Methanol and formaldehyde poisoning. In: Brent J, Megarbane B, Palmer R, Hatten B, Burkhart K (eds). Critical Care Toxicology, 2nd Edition. Springer Publishing, New York. 2017. 1769-86.*

Treatment - suggested dosing regimen:

- **Antidote**

Treatment with antidote should be continued for 5-7 days if no dialysis is given.
Observe and re-assess for 24 hrs after treatment is terminated to make sure no new acidosis develops:

- ***Ethanol*** (be aware of individual differences and ***frequent <u>under-dosing</u>***). ***Oral = iv dosing***
  Rule of thumb: Beer contains 5%, wine 12-14% and spirits 40-45% ethanol. Higher % can be used.

	5% ethanol	10% ethanol	20% ethanol	40% ethanol
Loading dose	15mL/kg	7.5mL/kg	4mL/kg	2mL/kg
Infusion rate (not regular drinker)	2mL/kg/hr	1mL/kg/hr	0.5mL/kg/hr	0.25mL/kg/hr
Infusion rate (regular drinker)	4mL/kg/hr	2mL/kg/hr	1mL/kg/hr	0.5mL/kg/hr
Infusion rate during HD (not regular drinker)	4mL/kg/hr	2mL/kg/hr	1mL/kg/hr	0.5mL/kg/hr
Infusion rate during HD (regular drinker)	6mL/kg/hr	3mL/kg/hr	1.5mL/kg/hr	0.8mL/kg/hr

HD = hemodialysis

- ***Fomepizole (if available)***:
  - Give 15mg/kg as a loading dose, then 10mg/kg every 12 hours. Increase dose to 15mg/kg after the 5th dose. During dialysis: IHD: Dose every 4 hours. During CRRT: Dose every 8 hrs.
  - *If fomepizole* availability is limited; Treat primarily only for the first 24 hours (two or max three doses per patient), then continue with ethanol after 24 hours

- **Bicarbonate**
  - **Calculate needs (based on ABG): 0.3 x patient weight (kg) x Base deficit = mmol HCO_3**
    Example: Patient 70kg, Base deficit (BD) 30 mmol/L: ***0.3 x 70 x 30 = 630 mmol HCO_3***

  - **If no arterial blood gas (ABG):**
    a. **<u>1000 mmol/L (Cambodia):</u>** Give 7-15 ampoules 20mL of $NaHCO_3$ 8.4% or more within 1-2 hours until hyperventilation is corrected (RF <20 /min).
    b. **<u>500 mmol/L</u>:** Give 250-500mL or more within 1-2 hours until hyperventilation is corrected (RF <20 /min).
    c. **<u>167 mmol/L</u>**: Give 1000-1500mL or more within 1-2 hours until hyperventilation is corrected (RF <20 /min).
    If only oral treatment is available: Tablets of 500 mg bicarbonate (= 6 mmol), 6-10 tablets every hour until hyperventilation is corrected (RF <20 /min).

- **Folic acid** (or folinic acid) 50mg iv. or orally (e.g. 10 tablets of 5mg) every 6 hours for 24-48 hours

When to call for assistance:
If there are patients with a strong suspicion of methanol poisoning, call the local referral hospital for advice and to discuss possibilities for intervention.
One of the most important reasons for this is the possibility to identify toxic alcohol in the environment, start early treatment ***AND*** be able to warn the public about the possible danger.

Where there is one there is usually many