METHANOL POISONING

PROTOCOL

INTERSECTION DOCUMENT

2023

MSF EMACC-WG

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MEDECINS SANS FRONTIERES

1. BACKGROUND

Methanol is a common organic alcohol constituent of many commercially used for many purposes: as a solvent in inks and dyes, in chemical synthesis and as a transportation fuel. Methanol toxicity is a common problem in many parts of the world, especially among members of lower socioeconomic classes and can cause outbreaks of mass poisonings. Outbreaks often occur when methanol (which can be cheaply purchased) is added to alcoholic drinks, in order to dilute them. The main spike of victims typically appears over a few days with a "tail" of patients who can keep being poisoned for weeks or even months. As patients with methanol poisoning often need intensive medical care, outbreaks can rapidly overwhelm medical facilities, and ministries of health. Staff often does not have the capacity to diagnose and treat them properly. Outbreaks frequently occur all over the world with hundreds, possibly thousands, dying every year from methanol poisoning. In 2016, more than 50 incidents were registered globally; more than 100 in 2017 and 2018.

Methanol is not toxic itself but is metabolised to the highly toxic formic acid/formate complex (see figure 01) which can cause metabolic acidosis, neurologic sequelae (including blindness), and even death. Formic acid is the primary toxic metabolite responsible for the metabolic derangements, ocular disturbances, and brain damage observed in methanol poisoning. The toxicity of formic acid/formate increases with increasing acidosis. Poisoning may occur after oral ingestion, inhalation, or even dermal absorption. As little as 30 mL of pure methanol has been reported to cause fatalities, and 10mL to cause blindness. The treatment is focused on blocking the enzyme (ADH) with either ethanol or fomepizole, buffer the metabolic acidosis with bicarbonate, and where available use renal replacement therapy to remove methanol, formate and correct the metabolic acidosis. Folic- (or folinic-) acid should also be given to enhance the endogenous metabolism of formate.

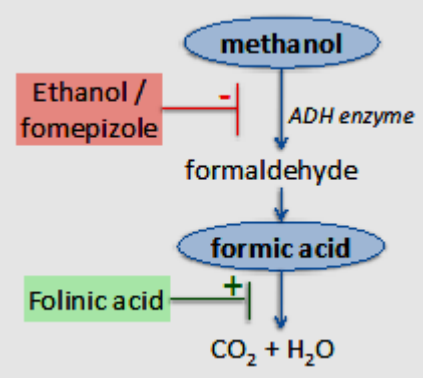


Figure 01 – Methanol metabolism

2. DIAGNOSIS

2.1 HISTORY

A detailed history is very important: "Can this be methanol?": Intake of bootleg alcohol, history of other cases in the environment/surroundings with confirmed or suspect methanol poisoning (seriously ill, fatalities, blindness etc.), mass poisoning.

2.2 SYMPTOMS

Symptoms appear after >12-24 hrs or longer (depending on concomitant ethanol). If shorter: unlikely to be methanol[1].

- Signs of intoxication: The patients often complain of a severe/unusual "hangover" with drowsiness, concentration problems and dizziness. Methanol itself does not cause drunk-like symptoms (unlike ethylene glycol), but a potential mix with ethanol may produce drowsiness, dizziness (but then other signs of toxicity would be absent).
- Respiratory signs: Hyperventilation (RR > 20-25) gradually develops as the metabolic acidosis ensues but may disappear in the late stages because of decompensating patient (poor prognostic feature).
- GI-signs: nausea/vomiting, epigastric pain.
- Visual disturbances: from blurred vision, diminished visual acuity up to loss of vision.
- Neurologic signs: Gradually reduced level of consciousness eventually progressing to coma.

[1] Concomitant ethanol ingestion may delay onset of manifestations of methanol ingestion. Alcohol dehydrogenase more rapidly metabolizes ethanol, delaying the production of the toxic metabolites of methanol.

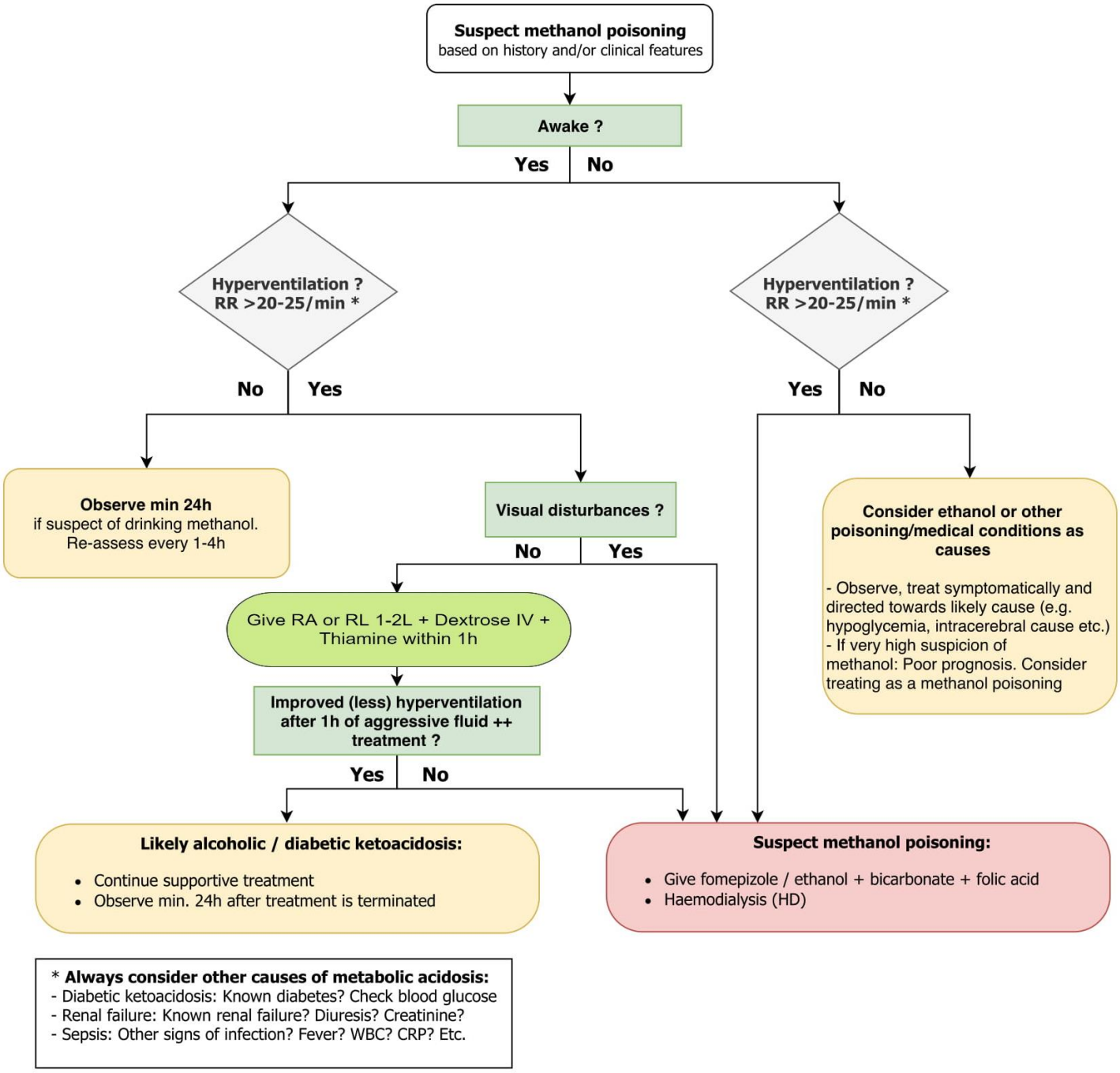


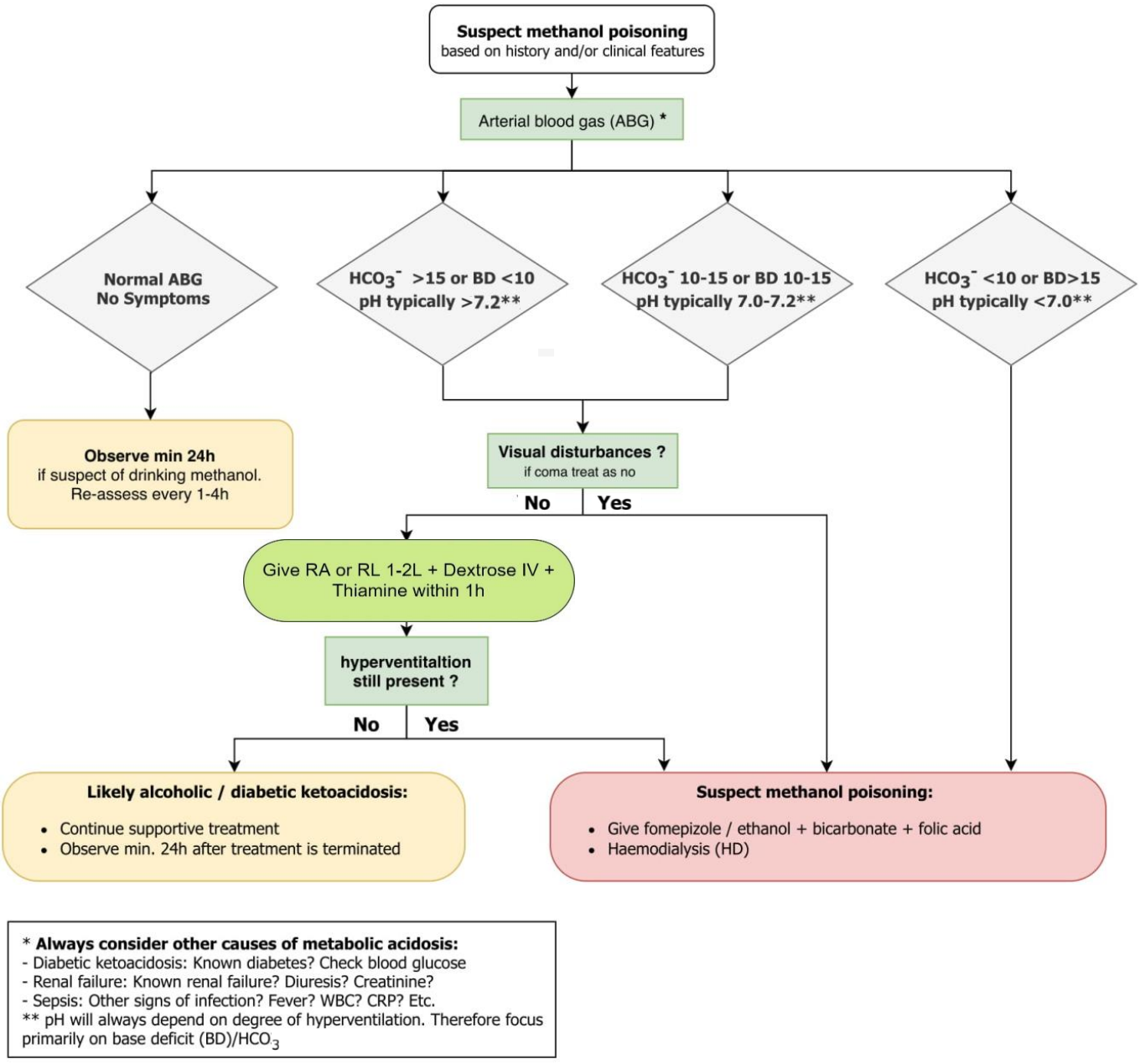
Figure 02 – Diagnosis algorithm for methanol poisoning without ABGs

2.3 FINDINGS

- Arterial blood gas: Metabolic acidosis[2] (unless concomitant ethanol intake or recent intake (<6-12 hours)) with increased anion gap not explainable by lactate. Increased osmolal gap [3] (osmolality from ABG ***cannot be used***) as long as there is more non-metabolised methanol in the blood (if not, this can be normal).
- Formate analysis (if available) is highly sensitive and specific - increased serum-formate can be detected several hours before symptoms start.

[2] If no formate is produced from methanol poisoning, no symptoms occur, i.e. Any patient with a metabolic acidosis because of a methanol poisoning must have traceable formate.

[3] The osmolality must be analysed by a freezing point depression method, not the vapor-pressure method as used on ABGs, as the latter will not detect the volatile alcohols and may therefore give a false negative result.



BD: Base deficit; RA: Ringer Acetate; RL: Ringer Lactate

Figure 03 – Diagnosis algorithm for methanol poisoning with ABGs

3. DIFFERENTIAL DIAGNOSIS

Conditions to consider in the differential diagnosis of methanol poisoning include many causes of metabolic acidosis, especially ethylene glycol poisoning which shares the same treatment approach. Other common causes of metabolic acidosis:

- Sepsis: look for other signs of infection. WBC? CRP? Fever?
- Renal failure: known renal failure? Creatinine? Urine output?
- Diabetic ketoacidosis (or metformin-associated lactic acidosis (MALA)): Known diabetes? Blood sugar? Urine glucose? Metformin user? Lactate level?
- Alcoholic ketoacidosis: This is the most difficult one to separate, but 1-2L of IV fluids (Ringer Lactate or Acetate)[4] + thiamine (e.g. 100mg) + glucose (e.g. 1000mL 5mg/dL - 5% or 10mg/dL - 10%) within 30-60 minutes (and if necessary, insulin) will improve or correct the acidosis if by this cause. Whereas if a toxic alcohol the acidosis only worsens. **Do not give bicarbonate first** if you do this challenge, as it will disguise the acidosis.

[4] Prefer ideally Ringer acetate if available but avoid NaCl as it can produce a temporary hyperchloremic metabolic acidosis.

4. PROGNOSIS

Coma on admission, severe metabolic acidosis (HCO_3 <10mmol/L (<10mEq), BD>15 mmol/L, pH typically <7.0) and lack of hyperventilation despite this severe acidosis are the most prominent poor prognostic features on admission. S-methanol is not prognostic.

5. MANAGEMENT

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**.

5.1 SODIUM BICARBONATE

Metabolic acidosis during methanol poisoning causes formic acid/formate to be more toxic and decreases renal elimination. It should therefore be treated aggressively by infusing sodium bicarbonate; as soon as possible in sufficient doses (500–800 mmol; often much more), in order to potentially reverse visual deficits, correct acidosis and increase the renal elimination of formate.

- **Indications**
  - Consider immediate bicarbonate therapy in all patients with signs of severe metabolic acidosis (HCO_3<10, BD>15, pH typically <7.0).
  - Consider bicarbonate therapy, following fluid/thiamine/glucose trial first to support the diagnosis, in all patients with signs of mild or moderate metabolic acidosis (HCO_3 >10, BD<15, pH typically >7.0-7.2).
- **Dosing**
  - Sodium bicarbonate can be available in different concentrations [5]
    - 8.4% (1 mmol/ml) usually ampoules of 10mL **STD DINJSODB8A1** or 20 mL **STD DINJSODB8A2**.
    - 4.2% (0.5 mmol/ml) ampoule of 20 mL or 250 mL flasks.
    - 1.4 % in 500 ml solution.
  - Large doses may be required during the first few hours
  - Aim at full correction of the base deficit calculated with the following formula:

(0.3 x weight x base deficit (BD)) = mmol buffer (bicarbonate)

  - If base deficit >20 - give a minimum of 500 mmol over 0.5-1 hour
  - If no blood gas analysis available - Give 150-250 mmol or more infusion over 1-2 hours until hyperventilation is corrected (RR <20 /min), repeat if necessary.
  - If only oral treatment is available: Tablets of 500 mg bicarbonate (= 6 mmol), 6-10 tablets every hour until hyperventilation is corrected (RR <20 /min).

5.2 ANTIDOTES

Inhibitors of alcohol dehydrogenase include fomepizole (4-methylpyrazole) and ethanol. Antidote administration is mainly conditioned by their availability and prognosis of the poisoning.

5.2.1. FOMEPIZOLE

Fomepizole acts similarly to ethanol. It is a stronger competitive inhibitor of ADH and, in addition, does not cause hypoglycaemia, sedation/inebriation. Fomepizole is easier to administer than ethanol (dose based on patient weight only). It does not require monitoring of serum concentrations, and the patient does not become drunk. In selected cases, fomepizole can postpone dialysis needs or even make it unnecessary (but this requires long treatment).

- **Indications**

Fomepizole should be considered as first line antidote when available, in proved or suspected poisoning with criteria for antidote administration.

- **Dosing**
  - Fomepizole sulfate, **STD DINJFOME1A-** is formulated as an injectable solution 5mg/mL in a 20mL ampoule.

[5] Prefer when available 4.2% in solution 250mL (0.5 mmol/L) to avoid extreme volumes with low concentrations and large consumption with high concentrations (ampoules).

> it can be administered orally or intravenously
> Loading dose 15 mg/kg IV infusion over 30 min, THEN
> 10 mg/kg IV every 12hr for 4 doses, THEN
> increase to 15 mg/kg every 12hr after 5th dose (inducing its own metabolism)
> Dosing during haemodialysis (HD): see table 01

Fomepizole dosing during dialysis	
Maintenance dose during IHD	10 mg/kg every 4h
Maintenance dose during CRRT	10 mg/kg every 8h

IHD: Intermittent haemodialysis; CRRT: Continuous renal replacement therapy

Table 01 - Suggested fomepizole dosing regimen during haemodialysis

- **Duration**

Duration of antidote: Give antidote until 12-24 hours after dialysis is finished. If no dialysis available: Give at least 5-7 days – stop & evaluate after 24 hours; restart if new acidosis develops.

5.2.2. ETHANOL

Ethanol competes with methanol for ADH, thus preventing metabolism of methanol to its toxic by-products. ADH has a 10- to 20-fold greater affinity for ethanol than for methanol. By inhibiting the degradation of methanol, ethanol is shown to prevent the accumulation of formic acid. Due to its propensity to cause adverse effects in the patient as well as its erratic and patient specific metabolism, ethanol should be considered as second line therapy if fomepizole is unavailable.

- **Indications**

Second line antidote when available, in proved or suspected poisoning with criteria for antidote administration. Ethanol can also be considered after 24 hours of fomepizole therapy, or after discontinuation of haemodialysis (6-8 hours of intermittent haemodialysis), in the context of outbreaks and limited fomepizole stocks. Hypoglycaemia is a known, but uncommon complication, monitor blood glucose closely and administer dextrose 10% if needed.

- **Dosing**

The goal of ethanol therapy is to achieve an ethanol blood concentration of 100 – 150 mg/dl[6]. Ethanol can be administered IV or orally or via NG tube with the same rates. A 10% ethanol solution should be utilized for IV administration. Any ethanol solution can be administered orally or through a nasogastric tube, but concentrations of 40% or above should be diluted to avoid gastric irritation[7] (see dosing suggestions below). Keeping the blood concentration of ethanol between 100-150 mg/dL (if Serum-ethanol analyses are available) is difficult, especially during dialysis[8]. Under-dosing is very common. Treatment can partly be monitored with/supported by consecutive blood gases and calculation of the anion gap (blocking of methanol metabolism will reduce the acidosis and the contribution of anions by formate).

- **Duration**

Following the loading dose, ethanol therapy should be maintained until 12-24 hours after completion of dialysis. If no dialysis available: Give at least 5-7 days – stop & evaluate after 24 hours; restart if new acidosis develops and treat for 2 consecutive days (see table 02).

Ethanol dosing (IV, PO, NGT)	5% ethanol	10% ethanol	20% ethanol	40% ethanol
Loading dose	15mL/kg	7.5mL/kg	4mL/kg	2mL/kg
Maintenance dose (not regular drinker)	2mL/kg/h	1mL/kg/h	0.5mL/kg/h	0.25mL/kg/h
Maintenance dose (regular drinker)	4mL/kg/h	2mL/kg/h	1mL/kg/h	0.5mL/kg/h
Maintenance dose during HD (not regular drinker)	4mL/kg/h	2mL/kg/h	1mL/kg/h	0.5mL/kg/h
Maintenance dose during HD (regular drinker)	6mL/kg/h	3mL/kg/h	1.5mL/kg/h	0.8mL/kg/h

HD: haemodialysis

Table 02 - Suggested ethanol dosing regimen

[6] Infusion rate need to be increased by 50 % - 100% if patient is a regular drinker and/or under haemodialysis

[7] Commercially available alcohols should be used with caution in MSF contexts. Rule of thumb: Beer contains 5%; wine 12-14%; spirits 40-45% ethanol

[8] Ethanol therapy might prove difficult to achieve and maintain goal ethanol serum concentrations, due to its individual differences of metabolism

5.3 FOLIC ACID

Folic or folinic acid is an adjunctive agent in methanol poisoning and may be useful to enhance folate-dependent metabolism of formic acid to carbon dioxide and water, thus reducing toxic metabolites of methanol.
In patients with ethanol-related hypoglycaemia, especially those who are malnourished or alcoholics, pre-treatment with thiamine (Vitamin B1) can be useful[9].

- **Indications**

Folic acid should be administered for at least 24-48 hours to enhance folate-dependent metabolism of formic acid to carbon dioxide and water.

- **Dosing**
  - PO: Folinic acid (or folic acid, Vitamin B9) – 50 mg (10 tablets of 5mg) every 6 hours at least 24-48 hours.
  - IV: Folic Acid or Folinic Acid 1 mg/kg (usually 50 mg) every 4-6 hours, IV in 5% Dextrose over 30-60 minutes.

5.4 RENAL REPLACEMENT THERAPY

The small molecule size, low volume of distribution (V_D), and low protein binding of methanol and formic acid, make them readily dialyzable. When available, renal replacement therapy: intermittent haemodialysis (IHD) or continuous renal replacement therapy (CRRT), is an effective modality to remove methanol and metabolites and to correct the metabolic acidosis. Peritoneal dialysis can be used, but efficiency is lower compared to the previous mentioned methods and not well documented.

- **Indications**
  - New visual disturbances (concomitant metabolic acidosis or detected methanol level).
  - Severe metabolic acidosis (HCO_3<10 or BD>15, pH typically <7.0-7.1).
  - > 30mL of methanol ingested (or 1g/kg).
  - Serum methanol level greater than 16 mmol/l (50 mg/dl).
  - The slow elimination of methanol during antidote treatment must always be considered when indication is discussed.
- **Modalities**
  - **IHD**

IHD using a high blood flow (300-400 mL/min) – high dialysate flow (750-1000 ml/min) can be the first-choice extracorporeal modality because of its common availability, the rapidity of toxin removal, and the low molecular weight of the common agents of poisoning. IHD sessions need to be extended beyond the 4 hours (up to 6-8 hours) to allow elimination of all the methanol. Ideally duration of therapy could be guided with methanol analysis or osmolality calculations, but in their absence, a duration of 6-8 hours should be administered.

  - **CRRT**

Although CRRT gives better longer-term solute clearances (over the course of several days), it is less efficient in the short term and does not provide the rapidity of elimination and correction of acidosis afforded by intermittent dialysis. The main advantage of CRRT is its applicability in hemodynamically unstable patients (CRRT during 16 - 18 hours).

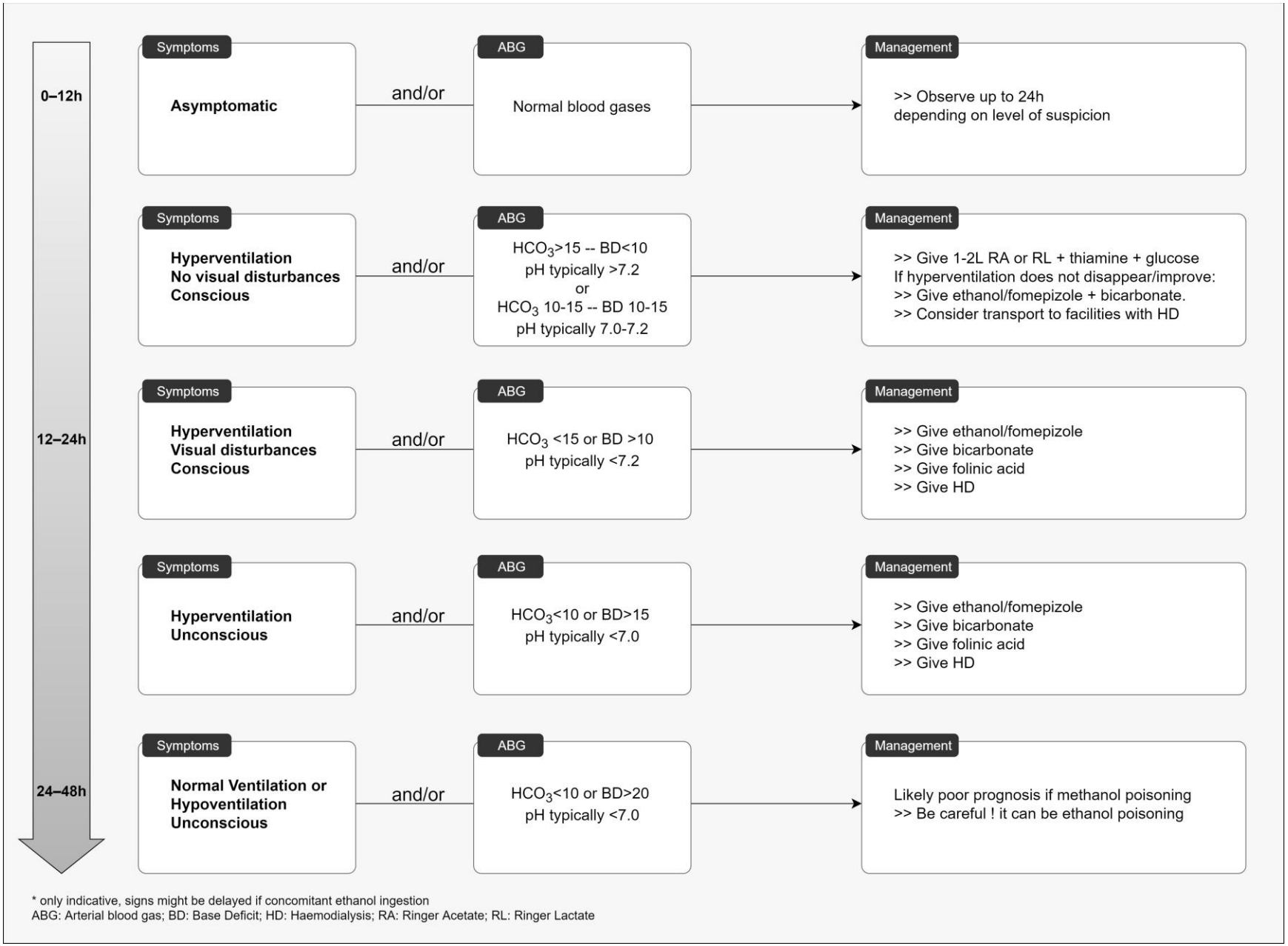
  - **End goals of RRT**
    - normalisation of acid base status,
    - resolution of hyperosmolar states,
    - decreased blood level of parent toxic alcohols (less than 25 mg/dL),
    - if no toxic alcohol level is available, treat for 6-8 on IHD and 16-18 hours for CRRT.

5.5 SUPPORTIVE THERAPY

Prompt medical care is key to avoiding complications secondary to methanol poisoning. Supportive therapy is aimed at initiating airway management, ensuring adequate circulation, correcting electrolyte disturbances, and providing adequate hydration. All these actions should be initiated as early as possible, but early antidote/epuration is essential – and should precede everything except the ABC.
If intubation is necessary: The patient must be hyperventilated (RR >25/min) until metabolic acidosis is corrected. Transfer to a unit with dialysis facilities and ICU is recommended.

[9] Thiamine– 100 mg IV; then 50-100 mg/day. Must ALWAYS precede glucose treatment to reduce the risk of Wernicke´s syndrome.

5.6 MANAGEMENT ALGORITHM



* only indicative, signs might be delayed if concomitant ethanol ingestion
ABG: Arterial blood gas; BD: Base Deficit; HD: Haemodialysis; RA: Ringer Acetate; RL: Ringer Lactate

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