INTOXICATIONS vs. ANTIDOTES

Are we prepared?

#BPC2022

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Dr. Anne-Marie Descamps

CEO Belgian Poison Centre

Welcome

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Jonas Moens

Belgian Poison Centre

Antidotes and the Belgian Poison Centre

Antidotes and the Belgian Poison Centre

Jonas Moens

Poison Centre

May 2022

Antidotes and the Belgian Poison Centre

- ✓ What makes something an antidote ?
- ✓ What do you need to expect from antidotes?
- Scientific, pharmacological quality
- Pharmaceutical quality
- ✓ What do you need to expect from the poison centre antidote stock?

Antidotes and the Belgian Poison Centre

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✓ What makes something an antidote ?

"A pharmaceutical with assessed mechanism of action, able to modify either the *pharmacokinetics*, the *pharmacodynamics* or both of the poison and whose administration *reliably* results in *significant* benefit "

Quoted from Prof. Bruno MEGARBANE

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Pharmacokinetics

(Evolution>>>severity)

- **Clearance**
  - **Chelators** (BAL, Penicilammine, DMSA, DMPS, Prussian Blue, Ca-EDTA -Na)
  - **Specific** (Digoxin immune Fab, viper antidote, hydroxocobalamin?)
  - **Aspecific** (Silibinin?)
- **Metabolites** (NAC, Sodium thiosulfate, ethanol/fomepizole)

Pharmacodynamics

(Severity>>>evolution)

- **Competitors**
  - **Target site** (naloxone, flumazenil,oxygen)
  - **Blood** (hydroxocobalamine?, lipid emulsion)
- **Direct effect** (pyridoxin, vitamin K, folinic acid, methylene blue, oximes, physostigmin, biperiden)

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✓ How do we expect antidotes to perform? Efficacy and urgency

Classification of antidotes according to their documented efficacy and their urgency of availability	
Classification aspect	
Efficacy in practice	I. Antidote efficacy is well-documented II. The antidote is widely used but not yet universally accepted as effective due to lack of research data; further research is needed to confirm effectiveness and/or the indications for use. III. The antidote is of questionable usefulness. More data regarding its effectiveness is needed.
Urgency of availability	A. The antidote must be available immediately (within 30min) B. The antidote must be available within 2 hr C. The antidote must be available within 6 hr

Sohn CH, Ryoo SM, Lim KS, Kim W, Lim H, Oh BJ. Kind and Estimated Stocking Amount of Antidotes for Initial Treatment for Acute Poisoning at Emergency Medical Centers in Korea. J Korean Med Sci. 2014 Nov;29(11):1562-1571

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- ✓ Available as an antidote as such in each hospital?
  - Naloxone, IV NAC, hydroxocobalamine,…
- ✓ Available as frequently used therapeutic medication
  - Insulin, penicillamine, calcium, vit k1,…
- ✓ Available as frequently used medical agent
  - Methylene blue, ethanol, glucose,…

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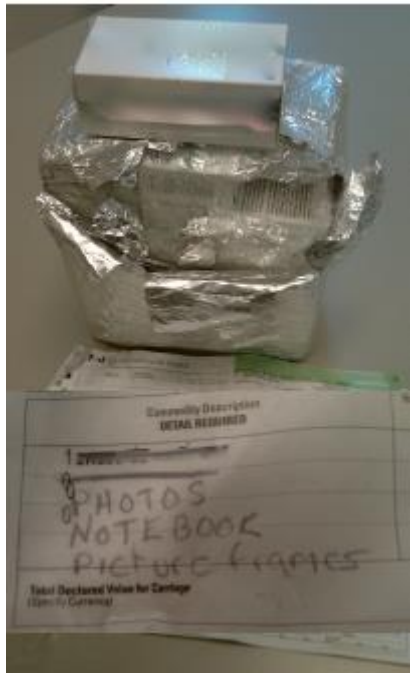
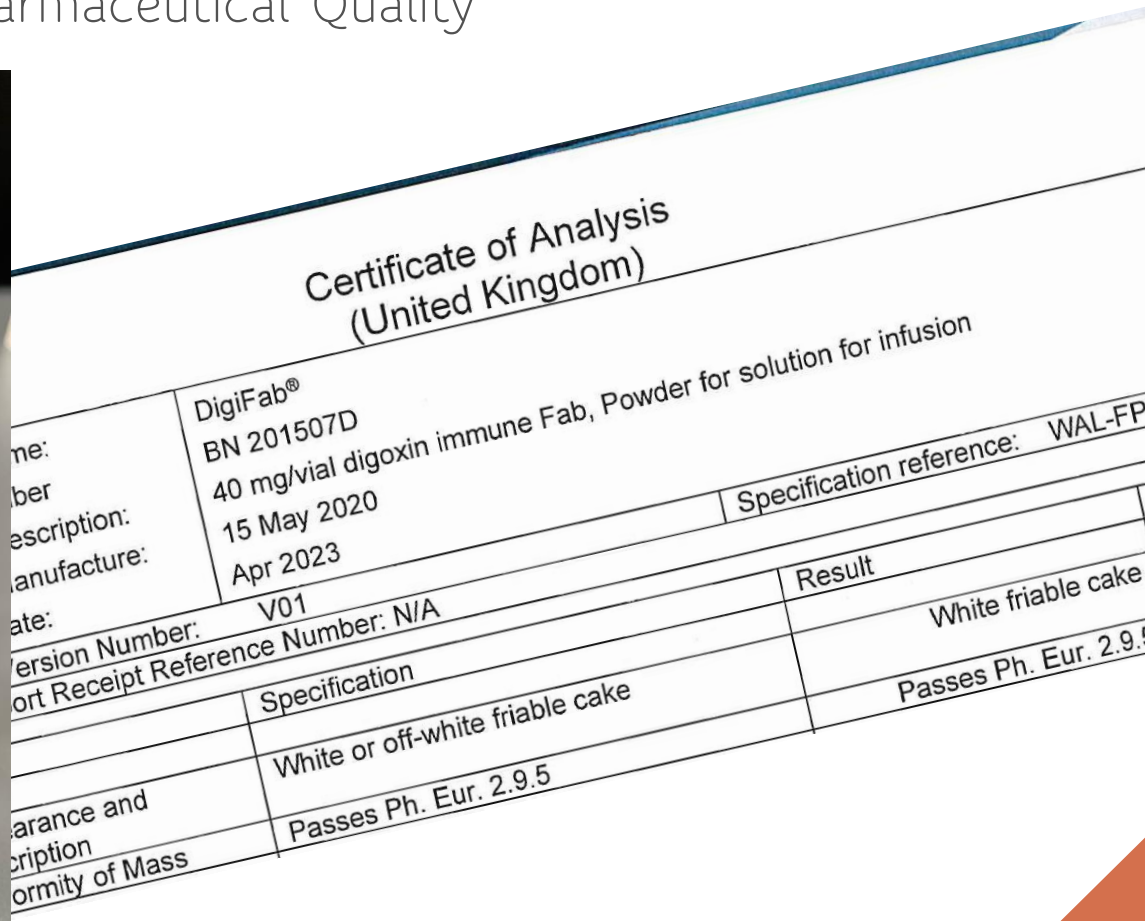
- ✓ How do we expect antidotes to perform? Pharmaceutical Quality




Certificate of Analysis
(United Kingdom)

me:	DigiFab®
ber	BN 201507D
escription:	40 mg/vial digoxin immune Fab, Powder for solution for infusion
anufacture:	15 May 2020
ate:	Apr 2023

Specification reference: WAL-FP

Version Number: V01

ort Receipt Reference Number: N/A

	Specification	Result
arance and cription	White or off-white friable cake	White friable cake
ormity of Mass	Passes Ph. Eur. 2.9.5	Passes Ph. Eur. 2.9.5

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✓ What can you expect from the poison centre antidote stock?

- Good evidence of efficacy
- Transport timeframe of two hours possible
- Good pharmaceutical quality
- Availability not guaranteed in each hospital
- Belgian endemic acute accidental intoxication

"Enough to start the treatment of one or two acutely poisoned patients before the hospital can provide itself, if necessary, with help of the poison centre or other hospitals"

Antidotes and the Belgian Poison Centre

- ✓ Biperiden
- ✓ Physostigmine
- ✓ (Digoxin-specific antibody fragments)
- ✓ 4-Methylpyrazole
- ✓ Obidoxime
- ✓ Silibinin
- ✓ Viper antidote
- ✓ Chelators:
  - Prussian blue
  - Calcium Sodium Edetate
  - DMPS
  - Penicillamine
  - DMSA
  - BAL

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- Most important BPC antidotes

  - Digoxin immune Fab (DigiFab®)

    Cardioglycosides
  - 4-Methylpyrazole (Fomepizole Serb®)

    Toxic alcohols (methanol, ethylene glycol)
  - Obidoxime (Toxogonin ®)

    Organophosphorous agents (carbamates?)

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- ✓ What can you expect from the poison centre antidote stock?
  - https://www.antigifcentrum.be/medische-professionals/antidota-belgi
  - https://www.centreantipoisons.be/professionnels-de-la-sant/antidotes
- ➢ Call 070 245 245, pending the completion of a written statement. This may be sent by fax (+32 02 264 96 46) or email medical.team@poisoncentre.be
- ➢ Transport is provided by the Poison Centre

Antidotes and the Belgian Poison Centre

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Antidotes and the Belgian Poison Centre

Prof. dr.
Peter De Paepe

"Cyanide poisoning:
case studies."

Prof. dr.
Philippe Hantson

"Methanol outbreaks,
triage and medical resources."

Dr. Kurt
Anseeuw

"Are Belgian emergency
departments prepared to
manage CBRN-victims?"

Prof. dr.
Marc Sabbe

"Towards a streamlined antidote
policy in Belgium."

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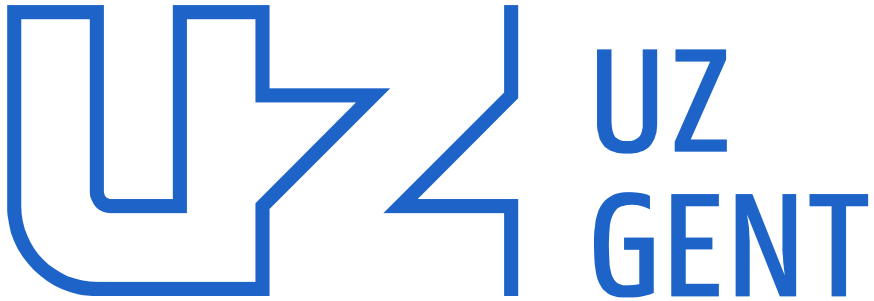
Prof. dr. Peter De Paepe

UZ Gent

Cyanide poisonings: case studies



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Prof. dr. Peter De Paepe
Chief of Department

Cyanide poisoning: Case studies

Belgian Poison Centre
12 May 2022

UZ GENT
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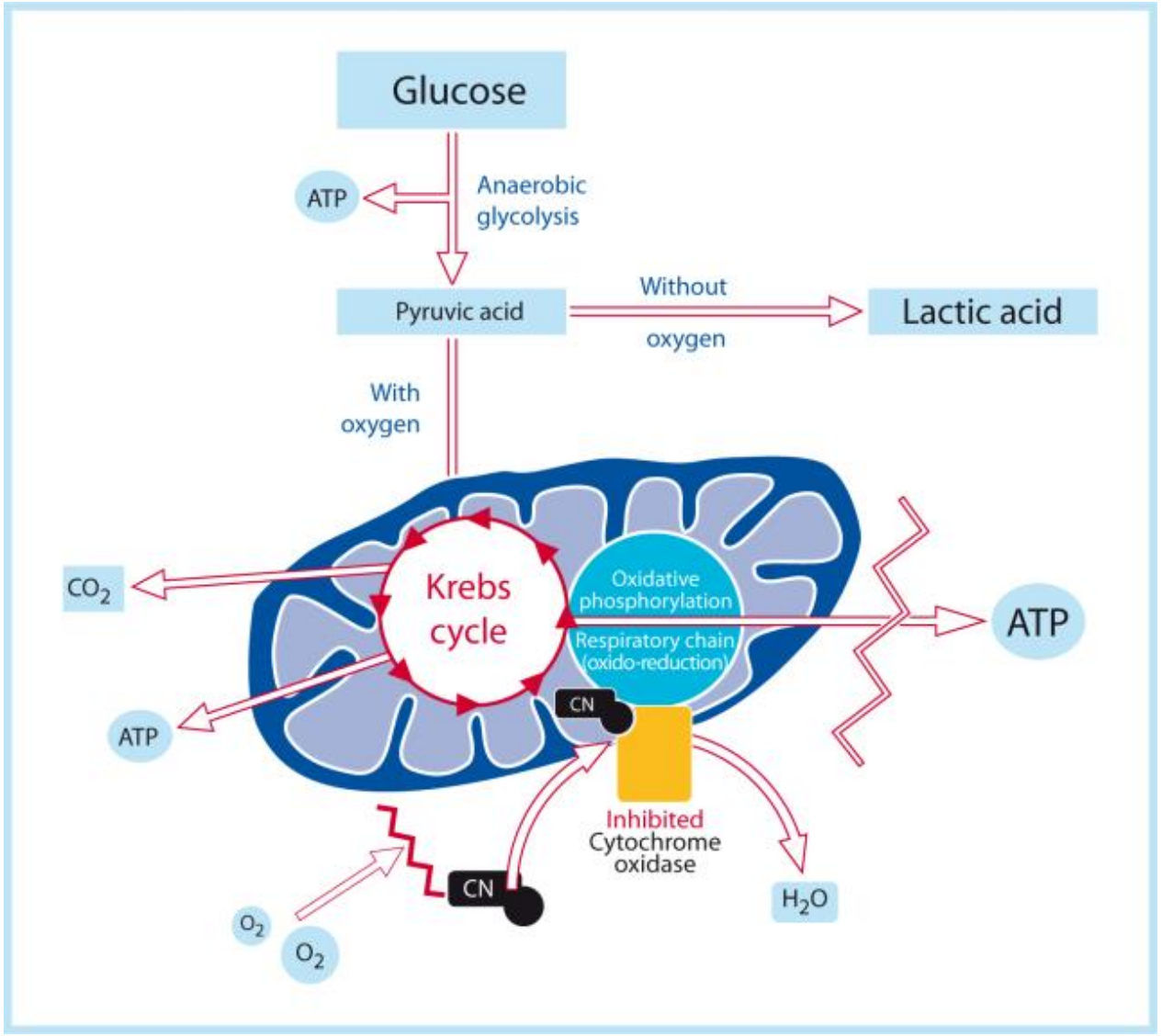
Cyanide poisoning: Chemical forms of cyanide

- HCN
- CN salts (e.g. NaCN, KCN, CNCl)
- Nitriles
- Nitroprusside
- Cyanogenic plants

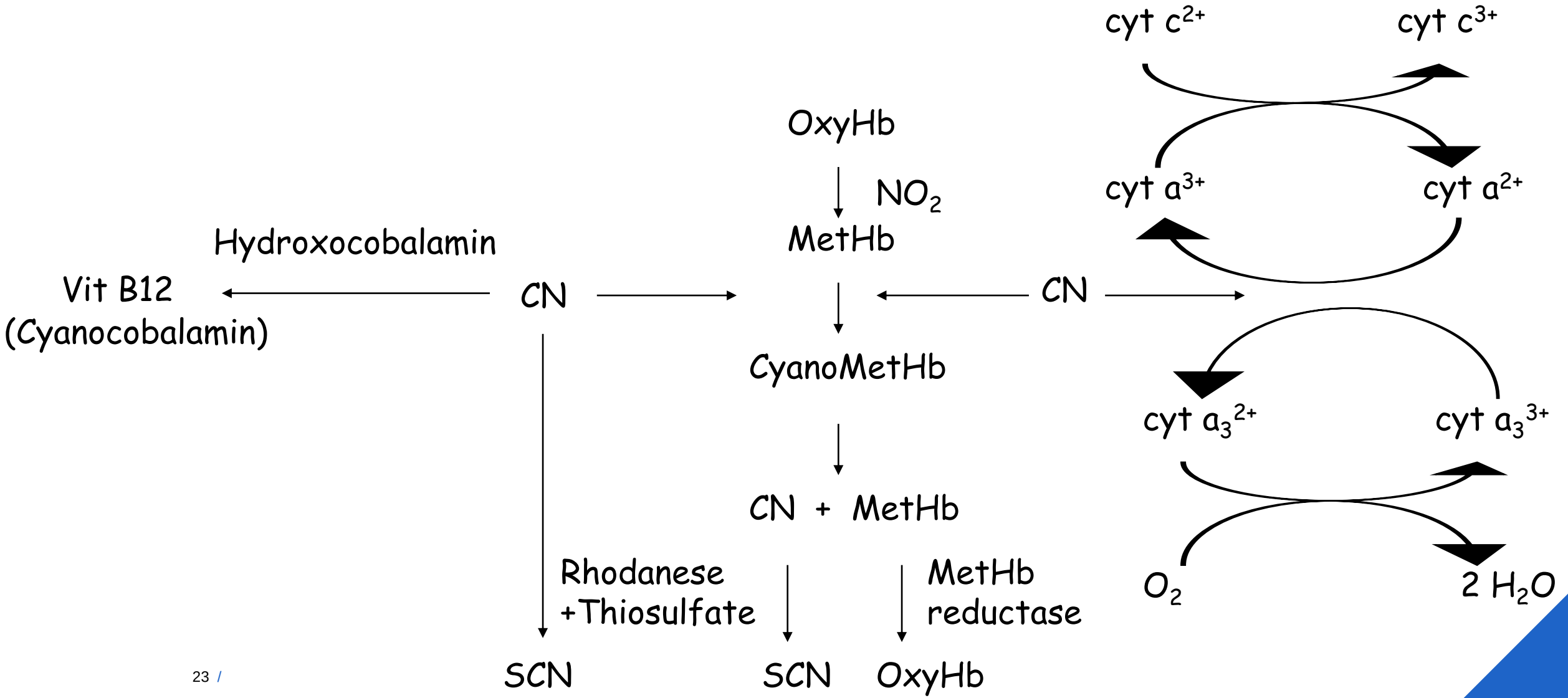
Cyanide poisoning: Sources of exposure

- Fire-related (mainly domestic fires)
  - e.g. wool, silk, polyurethane, polyacrylonitriles, synthetic rubber
- Industrial
  - e.g. metal extraction in mining, electroplating in jewelry production, photography, plastics and rubber manufacturing, pesticides
- Medical
  - e.g. sodium nitroprusside
- Diet
  - e.g. cassava root, pits and seeds from bitter almond, apricot, peach, pear, apple
- Suicide and homocidal/terrorist acts

Cyanide poisoning: Pathophysiology



Cyanide poisoning: Detoxification



Cyanide poisoning: Onset of symptoms

- Seconds → HCN (>> inhalation)
- Minutes → CN salts (>> ingestion)
- Hours → Cyanogenic compounds
  - Nitriles (ingestion, inhalation, dermal)
  - Nitroprusside (i.v.)

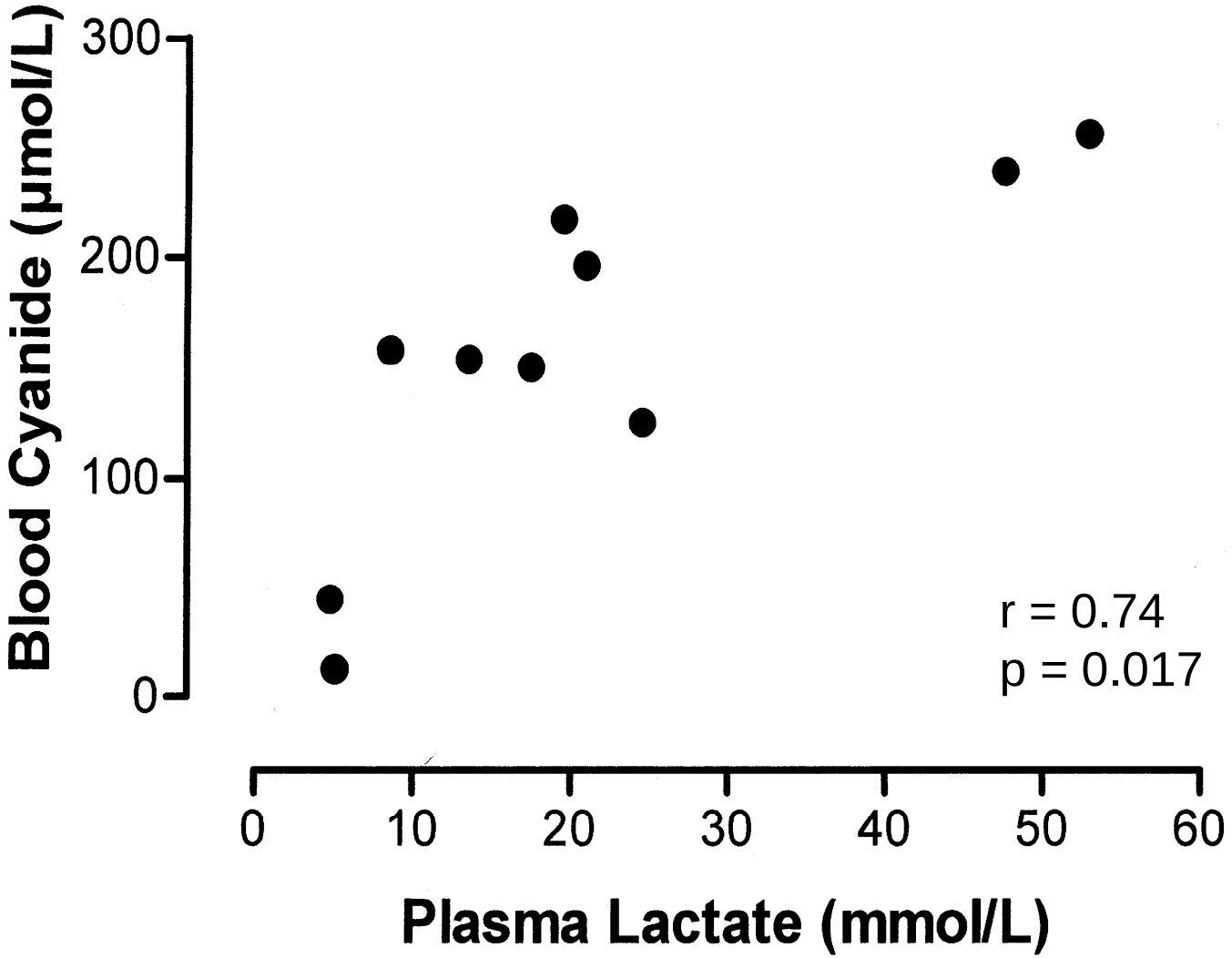
Cyanide poisoning: Clinical presentation

Neurological	Respiratory	Cardiovascular	Metabolic
Dizziness	Hyperpnea	Hypertension	↑ Blood glucose
Restlessness	Central apnea	Tachycardia	↑ Lactate
Anxiety	Pulmonary edema	Shock	Metabolic acidosis
Confusion		Bradycardia	Rhabdomyolysis
Coma		Cardiac arrest	Renal failure
Seizures			

Cyanide poisoning: Diagnostic testing

- Making the diagnosis requires a high index of suspicion based on history and clinical presentation
- Aspecific findings
  - ↑ Anion gap metabolic acidosis
  - ↑ Lactate
  - ↑ SvO2
  - ECG: rhythm disturbances, ST segment abnormalities
- Blood CN concentration
  - Not routinely available

Cyanide poisoning: Diagnostic testing



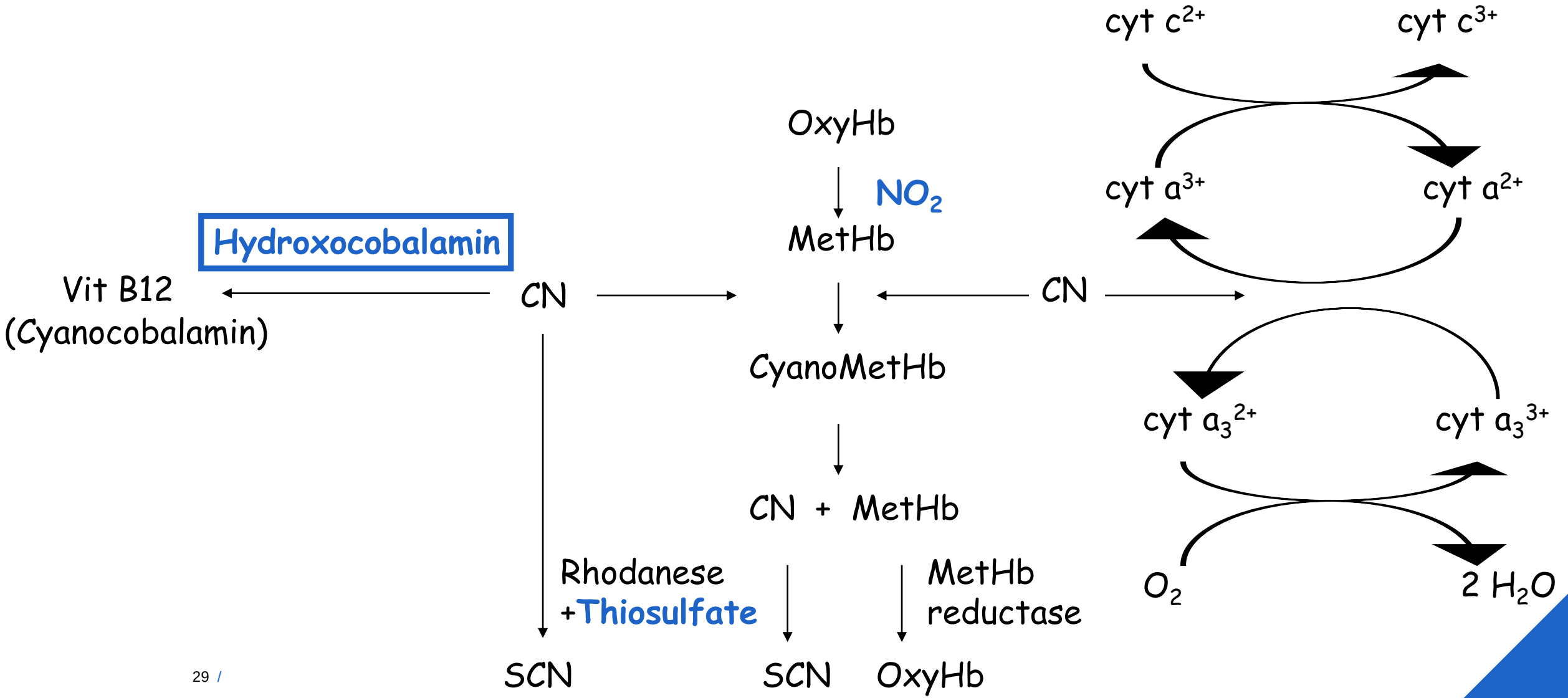
Sensitivity : 94 %
Specificity : 70 %
PPV: 64 %
NPV: 98 %

Baud F. Crit Care Med 2002

Cyanide poisoning: Treatment

- Decontamination
- Supportive treatment
- Activated charcoal
- Antidotes
  - Methemoglobin forming agents
  - Cobalt compounds
    - Dicobalt EDTA
    - **Hydroxocobalamin (first-line agent)**
  - Sulfur donors
    - Thiosulfate

Cyanide poisoning: Antidote treatment



Cyanide poisoning: Hydroxocobalamin

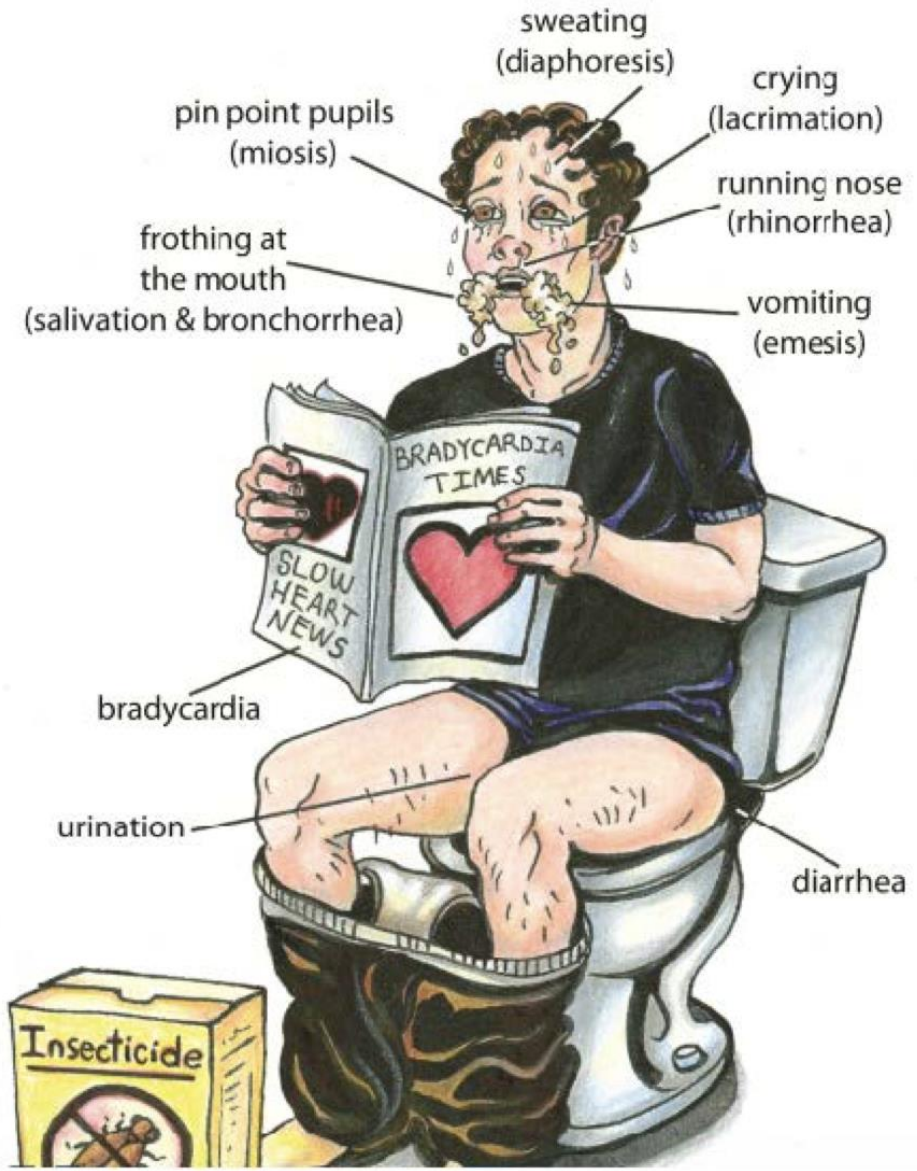
- Currently used in Europe and in the USA
- 50 g of hydroxycobalamin to bind 1 g of CN
- Dose: 5 g (70 mg/kg in children, < 5g) IV (15 min), repeated depending on severity & clinical response (10g; 140 mg/kg)
- Ability to pass through the blood-brain barrier
- Adverse effects: reddish discoloration of the skin and urine, allergic reactions

Borron SW Ann Emerg Med 2007

Cyanide poisoning: Patient case

- 30 yrs old male lab technician found comatose in his lab
- On arrival of MICU team
  - A - obstructive airway (massive bronchorrhea, salivation)
  - B - SaO2 89%, respiratory rate 9/minute
  - C - pulse rate 76/minute, blood pressure 124/76 mmHg
  - D - GCS 3/15, miosis
  - E - floor covered with many broken bottles, one intact bottle containing Aldicarb®, POCT glucose 1,27 g/L, urine loss, faecal incontinence

Cholinergic toxidrome



Cyanide poisoning: Patient case

- Heteroanamnesis: autointoxication with Aldicarb® 30 minutes before arrival of MICU team
- Treatment by MICU team
  - Safety first
  - Endotracheal intubation
  - High doses of atropine
  - Transfer to hospital

Cyanide poisoning: Patient case

- Treatment in the ED
  - Decontamination
  - Atropine + pralidoxime
- Stable vital signs
- Normal ECG and chest X-ray
- Normal arterial blood gas values

Cyanide poisoning: Patient case

- Abnormal blood results

Blood test	Result	Normal value
Osmolality (mOsm/kg)	376	275-295
Acetylcholinesterase RBC (U/L)	3920	11188-16698
Acetylcholinesterase RBC (U/L)	616	1700-5778
Osmolal gap (mOsm/kg)	30	< 10

- Positive toxicology results

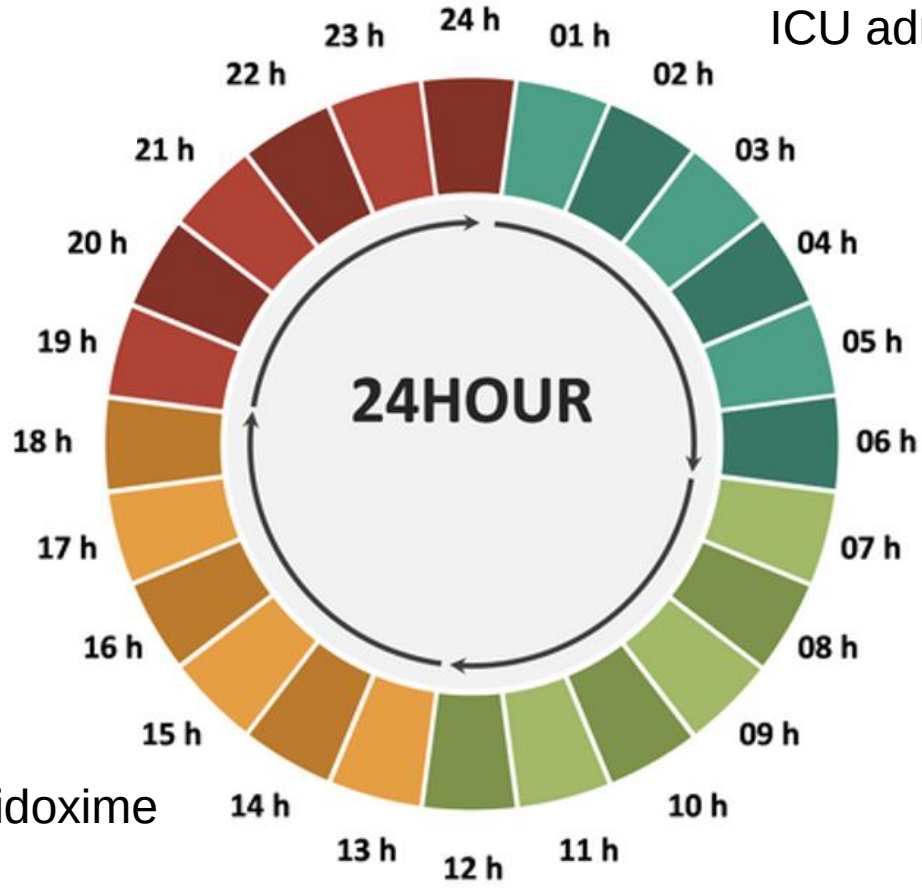
Blood test	Result
Ethanol (g/L)	2.3
Acetone	+

Cyanide poisoning: Patient case

Tachypnea, dyspnea
Severe lactic acidosis

ED admission

ICU admission



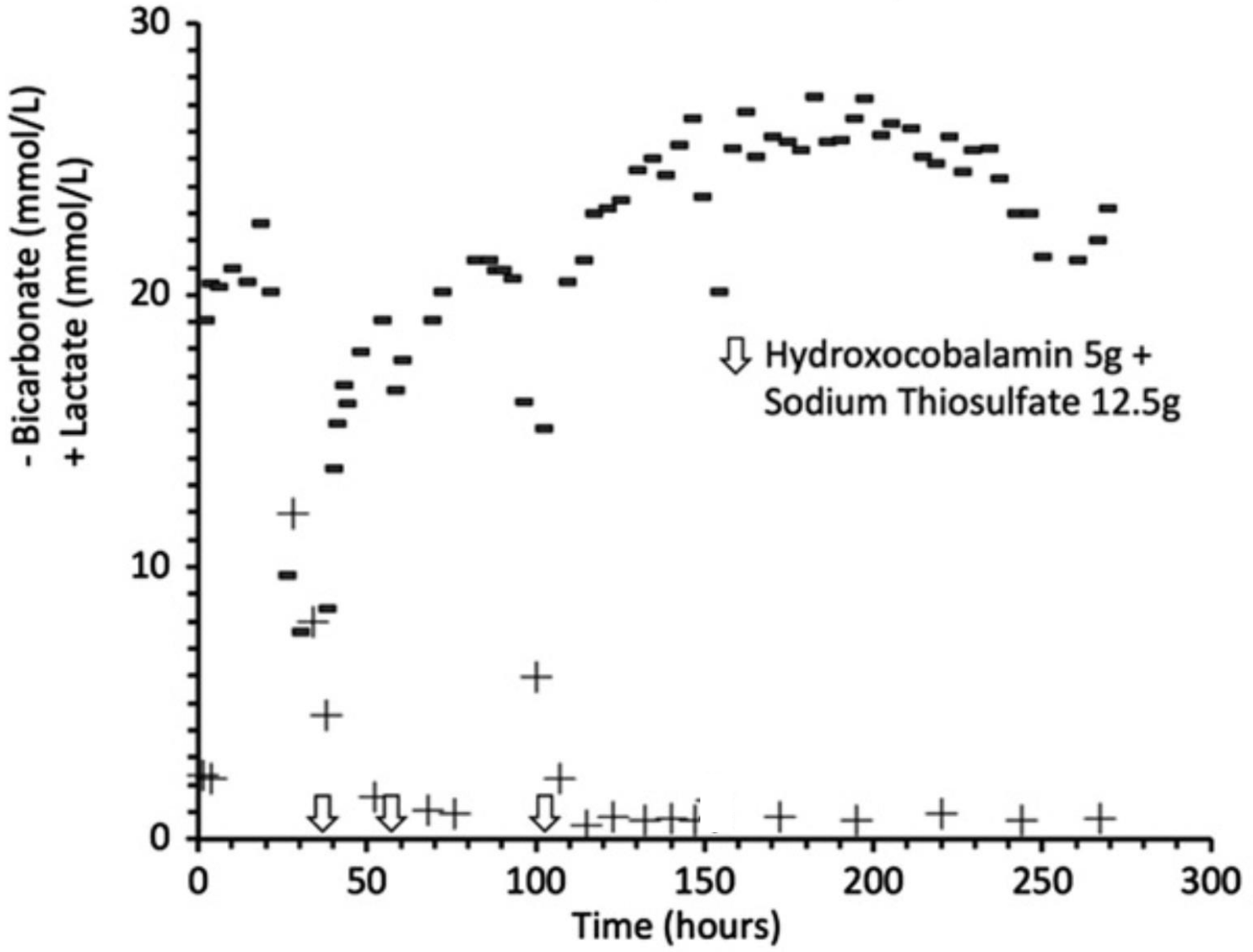
Extubation

Atropine & pralidoxime stopped

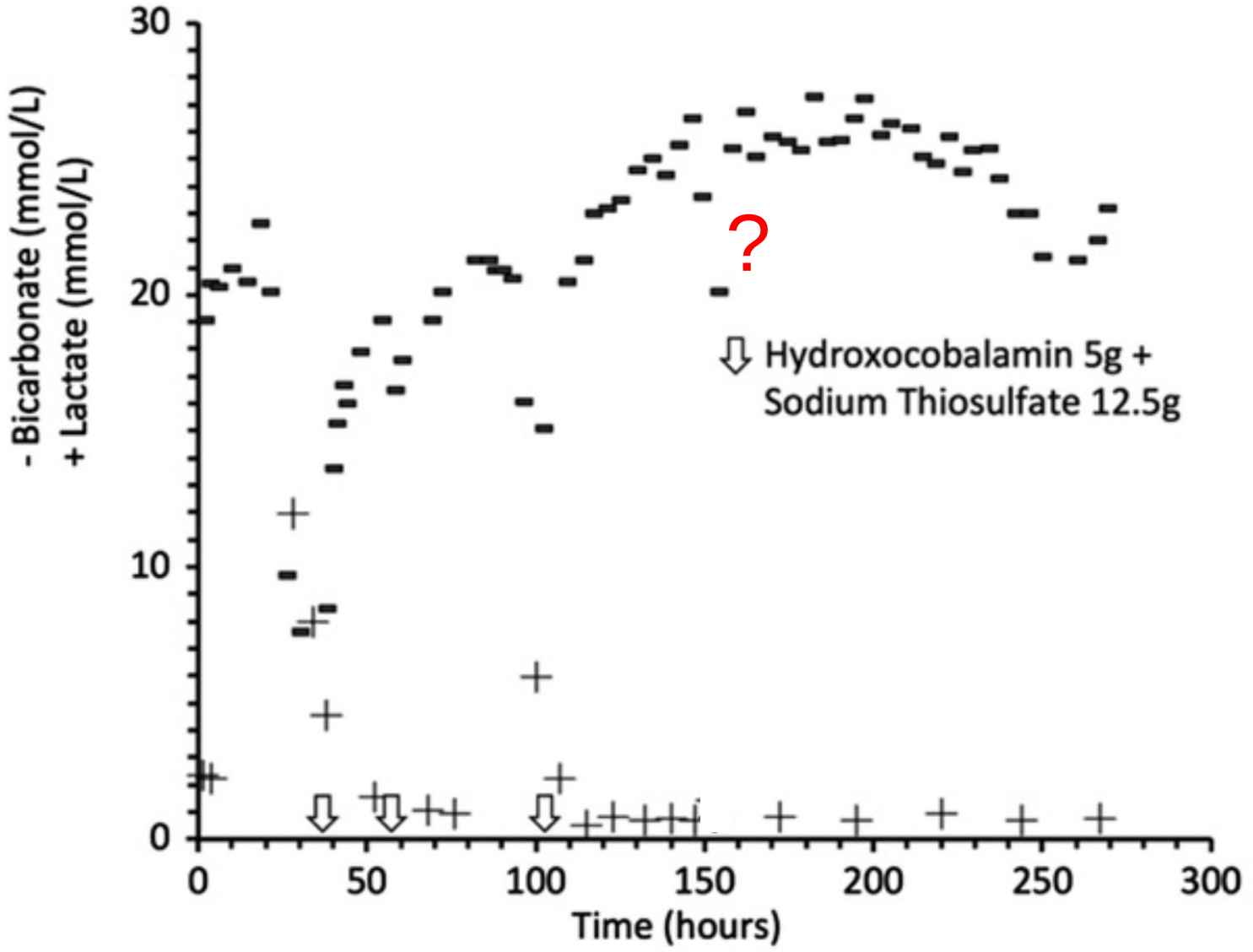
Cyanide poisoning: Patient case

- After exclusion of other causes of lactic acidosis, cyanide poisoning with a cyanogenic compound was considered
- Cyanide antidotes were given with good clinical response
- Acetone was mistaken for acetonitrile as both substances have identical retention times on GC-MS

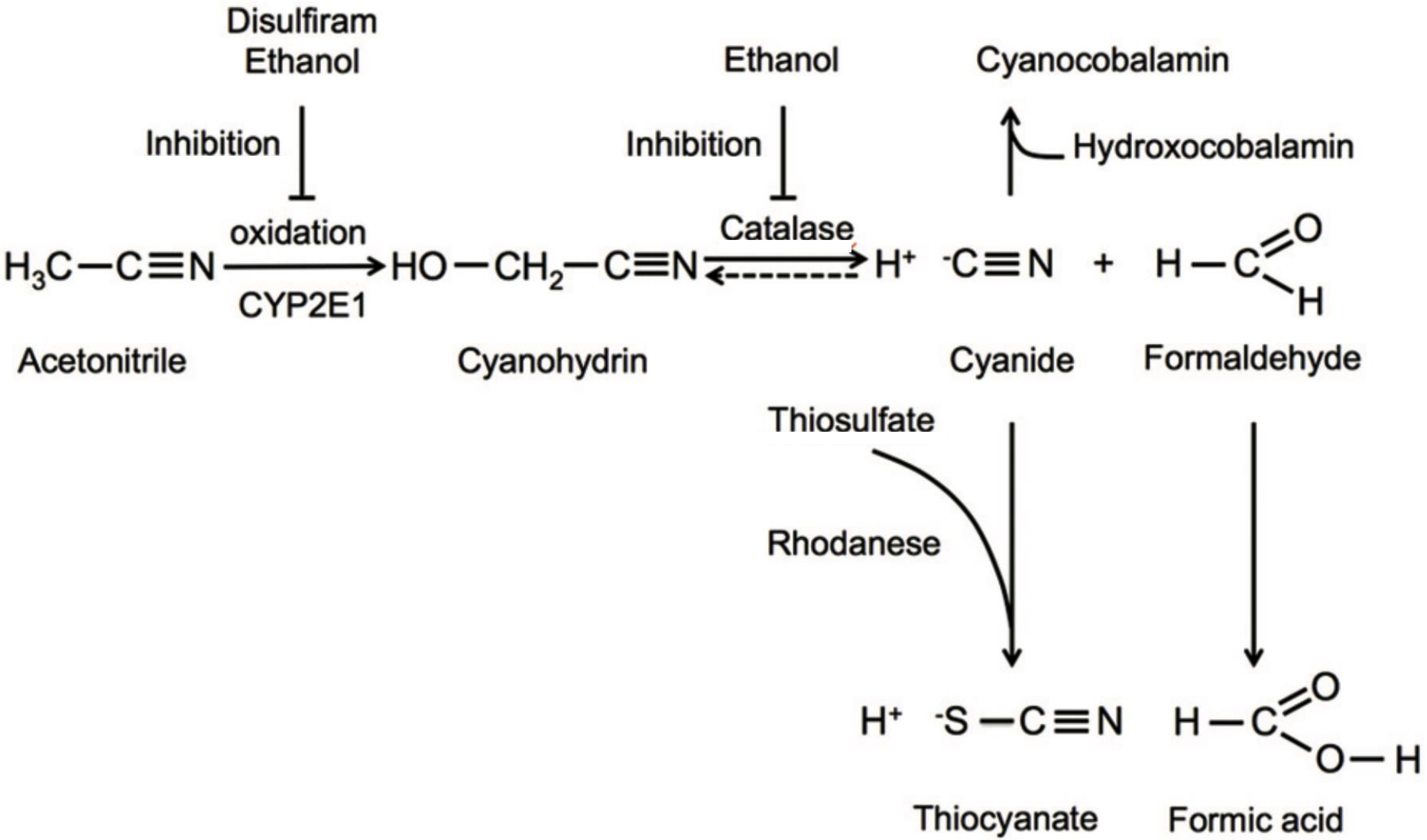
Cyanide poisoning: Patient case



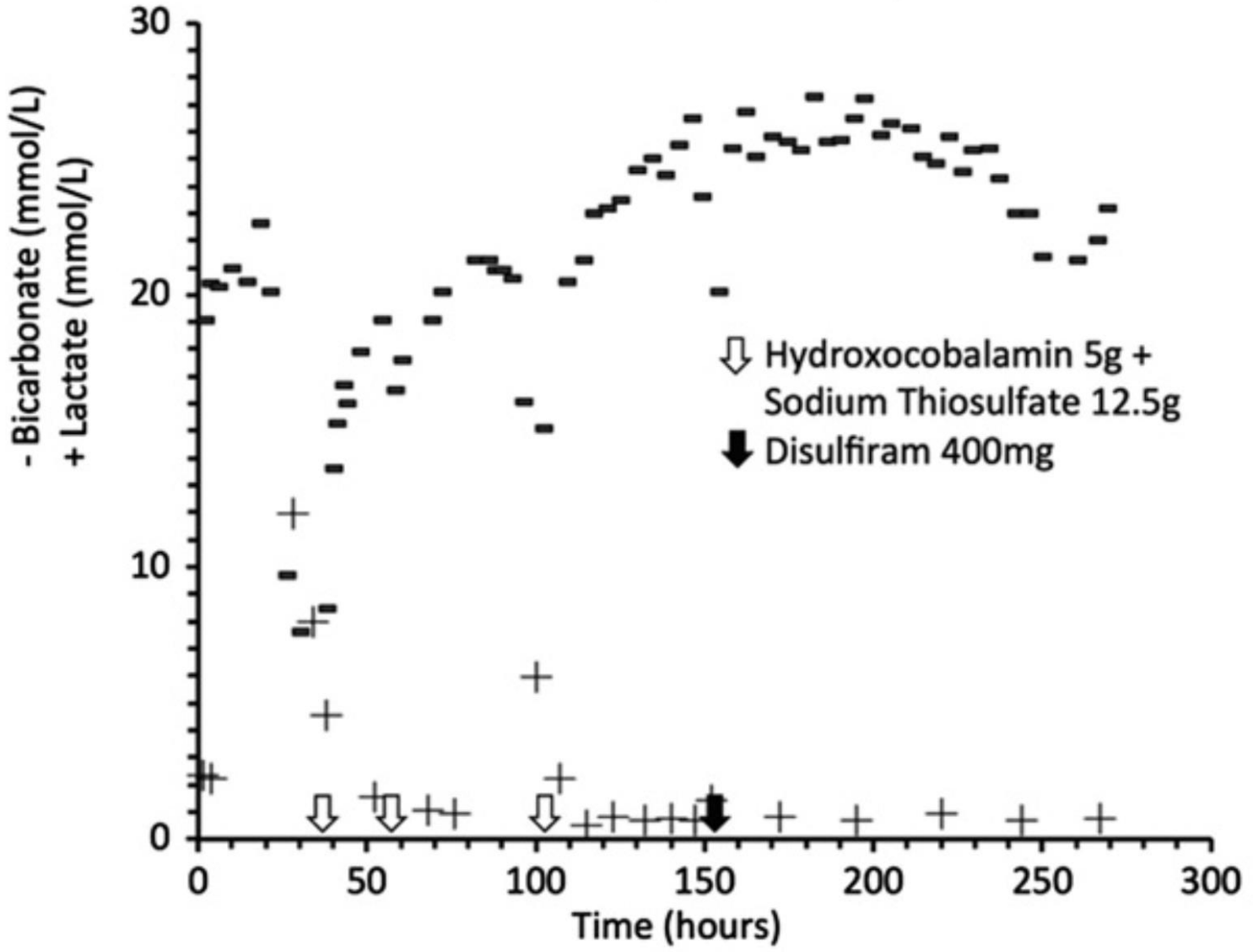
Cyanide poisoning: Patient case



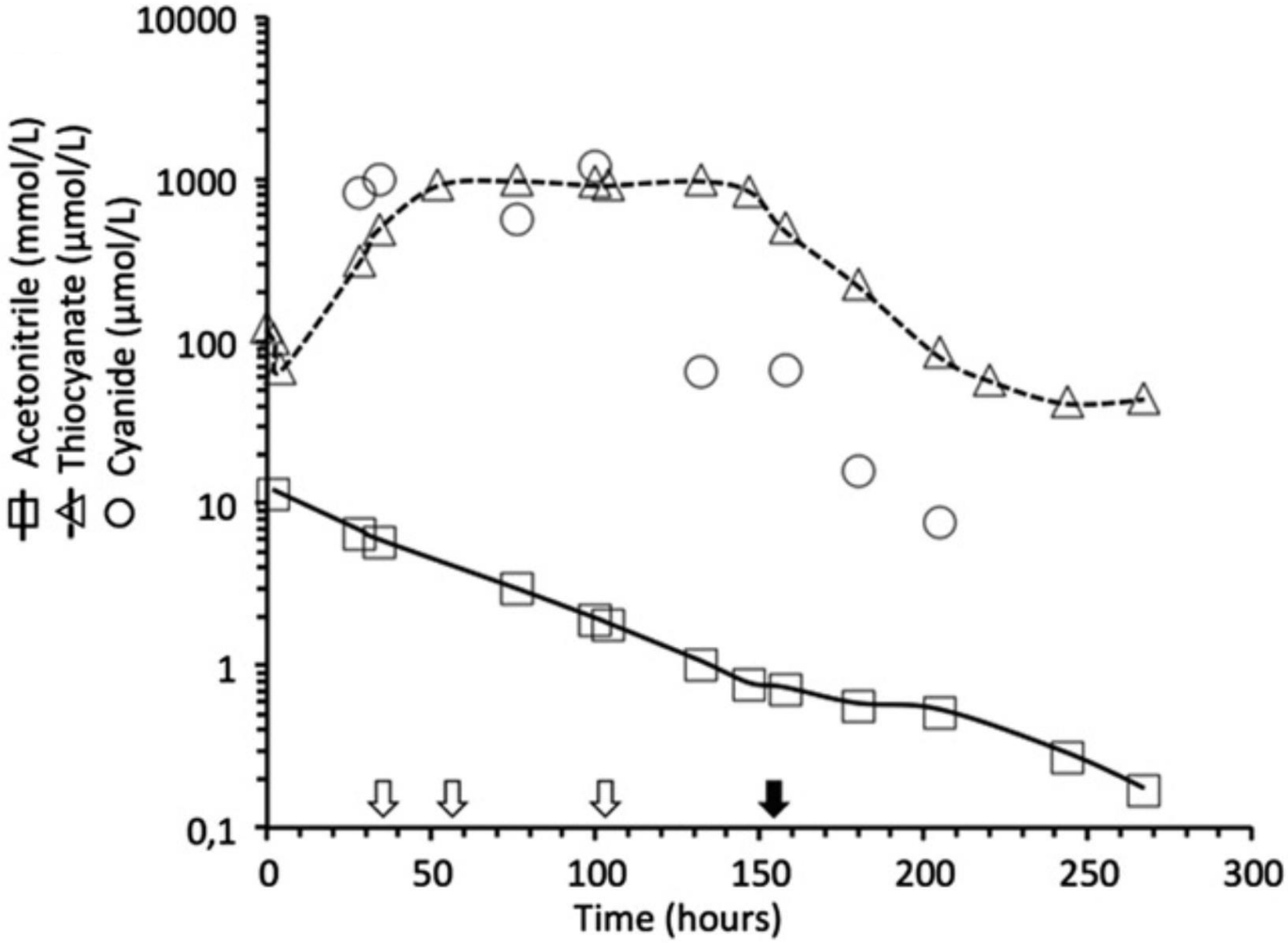
Cyanide poisoning: Patient case



Cyanide poisoning: Patient case



Cyanide poisoning: Patient case



Cyanide poisoning: Patient case

- ICU course was further complicated by a pneumonia
- Patient finally made an uneventful recovery
- Transfer to the psychiatry ward on day 11
- Patient was familiar with the toxic effects of both carbamates and acetonitrile
- Patient admitted having also ingested acetonitrile in case the suicide attempt with the carbamate would fail

CLINICAL TOXICOLOGY, 2016
http://dx.doi.org/10.3109/15563650.2015.1101770

Taylor & Francis
Taylor & Francis Group

BRIEF COMMUNICATION

Disulfiram inhibition of cyanide formation after acetonitrile poisoning

Peter De Paepe[a,b], Pieter Colin[c], Pieter Depuydt[d], An-Sofie Decavele[e], Julie De Smet[c], Koen Boussery[c], Christophe Stove[f], Dominique Benoit[d], Alain Verstraete[e], Jan Van Bocxlaer[c], and Walter Buylaert[a]

[a]Department of Emergency Medicine, Ghent University Hospital, Ghent, Belgium; [b]Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium; [c]Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium; [d]Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium; [e]Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium; [f]Laboratory of Toxicology, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium

ABSTRACT

Context Cyanide poisoning may be caused by acetonitrile, a common industrial organic solvent and laboratory agent. **Objective** To describe the potential use of disulfiram in treating acetonitrile poisoning in a human clinical case and to further study its effect in human liver microsomes *in vitro*. **Case details** A 30-year-old man initially presented with a cholinergic toxic syndrome following ingestion of aldicarb. Toxicological analysis revealed coingestion of ethanol. He subsequently developed severe metabolic acidosis caused by the cyanogenic compound acetonitrile which was erroneously interpreted as acetone in the chromatogram. After three treatments with hydroxocobalamin (5 g i.v.) and sodium thiosulfate (12.5 g i.v.) on days 2, 3, and 5, he had transient improvement but recurrent lactic acidosis. Treatment with disulfiram was associated on day 7 with resolution of metabolic acidosis and slowing of the decrease in acetonitrile concentration. He recovered from acetonitrile toxicity completely. The time course of acetonitrile, thiocyanate, and cyanide concentrations suggested that disulfiram inhibited cyanide formation. **Results** In vitro experiments with human liver microsomes showed the cyanide concentration was significantly lower after incubation with acetonitrile and disulfiram than acetonitrile alone (a mean 60% reduction in cyanide level). **Discussion** Although disulfiram was given late in the course of the poisoning it is possible that it contributed to the recovery.

ARTICLE HISTORY
Received 13 July 2015
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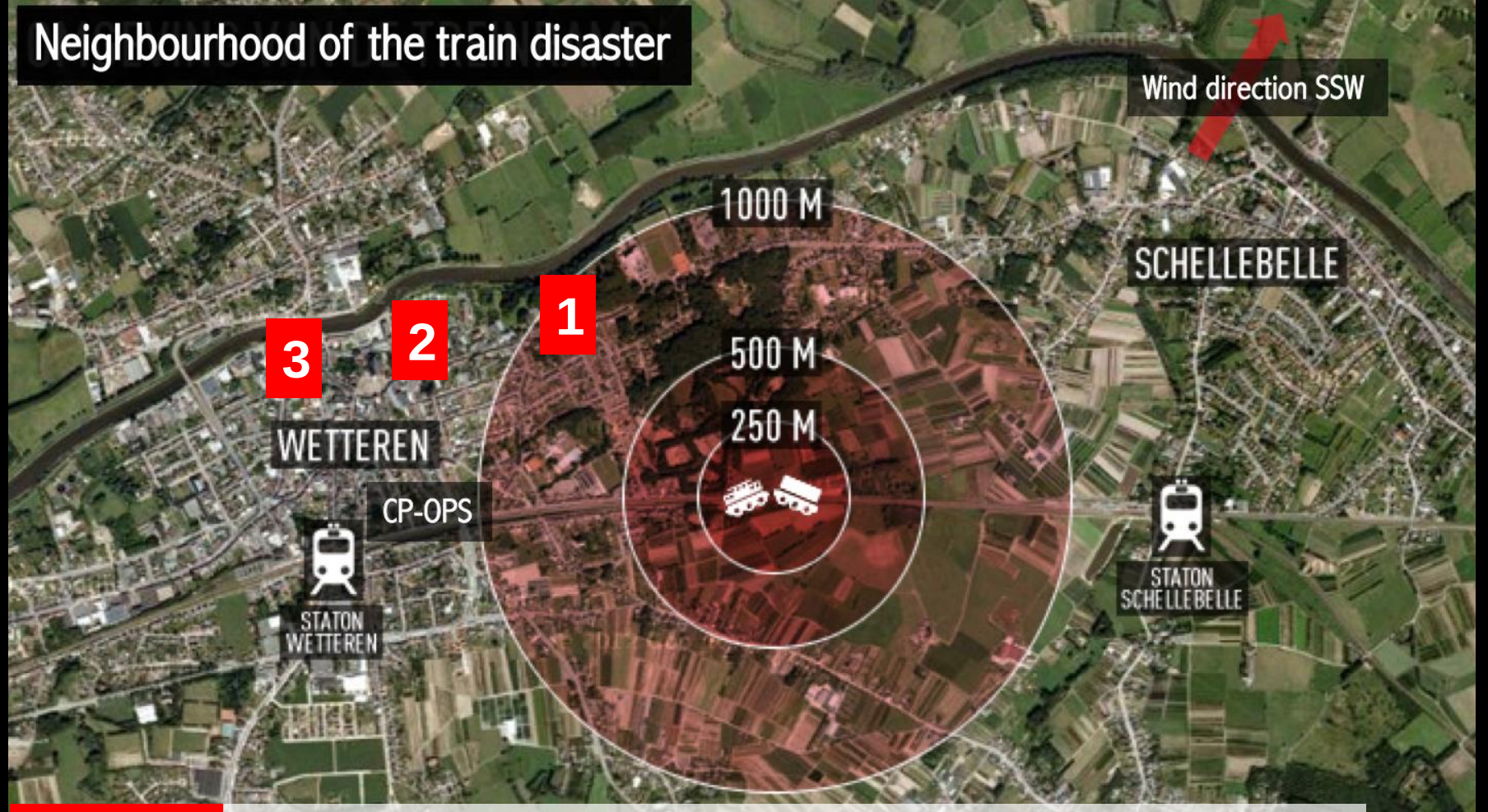
Published online
30 November 2015

KEYWORDS
Acetonitrile; antidote; disulfiram; hydroxocobalamin; poison; sodium thiosulfate; toxicology

The Wetteren acrylonitrile disaster

May 4th 2013

- >2,000 residents evacuated
- 438 ED admissions
- 8 severely poisoned
- 1 person died



1	09:30	78 yrs old woman found comatose (evolution to cardiac arrest) 4 other inhabitants unwell
2	12:30	50 yrs old woman found comatose by her husband who came home after a walk and complained of mucosal irritation
3	15:00	65 yrs old man found deceased together with his dead dog

Although acrylonitrile is heavier than air it can ascend in the sewer system of houses that have either no or a failing isolation from the main sewer system.

RWZI

Conclusion

- Always maintain a high degree of suspicion when dealing with (auto-) intoxications
- When the clinical course is atypical, the involvement of substances other than the primary toxin should be considered
- Decontamination, removal from the site of exposure, and oxygen are essential with personal protection for responders
- Patient management is based on history, clinical presentation, simple lab tests
- Toxicology test results usually are not timely for diagnostic purposes
- Hydroxocobalamin is the preferred antidote in cyanide poisoning
- Considering the mechanism of toxicity during treatment of suspected poisoning is important

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Prof. dr. Philippe Hantson

UCL

Methanol poisoning: outbreaks, triage and medical resources

Methanol poisoning: outbreaks, triage and medical resources

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Department of Intensive Care and Louvain Centre for Toxicology and Applied Pharmacology, Université catholique de Louvain, Brussels, Belgium

UCL Université catholique de Louvain

Louvain Centre for Toxicology and Applied Pharmacology

Declarations of interest

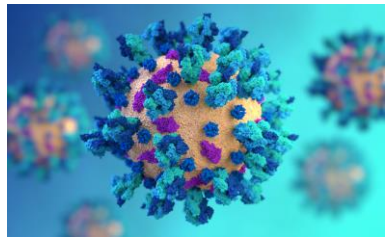
- Lecturer or scientific advisor in some meetings or symposia supported by OPI or SERB

Background

- Epidemic outbreaks are not uncommon, especially in poor income countries, and are probably under-reported
- Case fatality rates usually exceed 30%, with significant morbidity in survivors
- Reasons for poor prognosis are multiple:
  - The most important: delay in seeking or obtaining effective medical care
  - In some countries, ethanol consumption is prohibited (illicit manufacture)
  - Signs and symptoms of early methanol poisoning are often nonspecific
  - Symptoms are misdiagnosed for ethanol intoxication
  - Knowledge of pathophysiology of methanol poisoning, diagnosis and treatment may be limited
  - Triage is complicated: patients with early presentation, poorly symptomatic, but at high risk of severe toxicity and requiring optimal therapy >< patients with late presentation, severe toxicity, and poor outcome regardless of the treatment

Origin of methanol outbreaks

Methanol poisoning and COVID-19: an unexpected link for outbreak



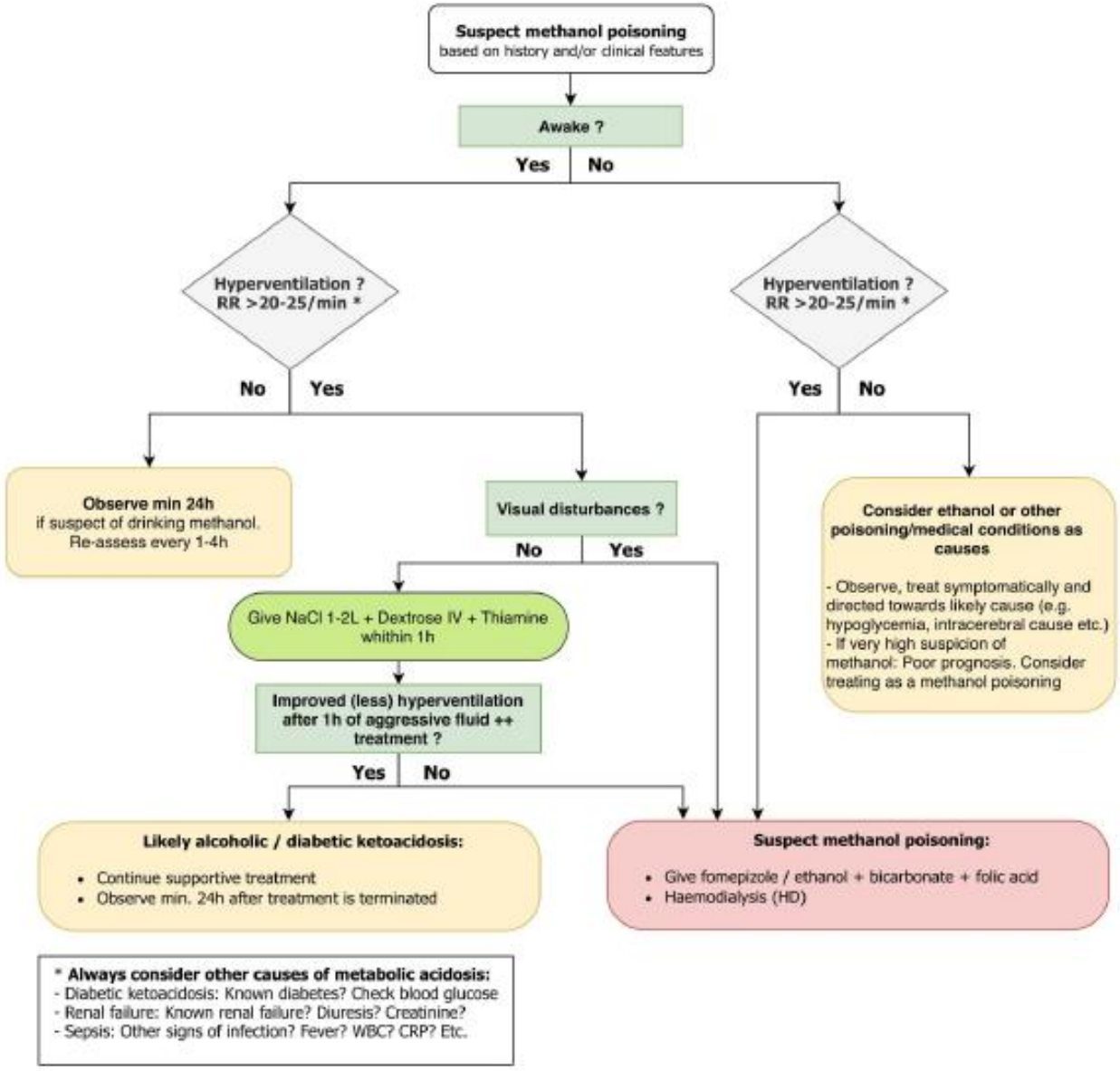
Acute pancreatitis due to **methanol** toxicity during the **COVID-19** pandemic.
Sadeghi M, Zakariaei Z, Fakhar M, Tabaripour R, Banimostafavi ES, Azadeh H.
Clin Case Rep. 2021 Oct 13;9(10):e04943. doi: 10.1002/ccr3.4943. eCollection 2021 Oct.
PMID: 34667611 **Free PMC article.**

Death by hand sanitizer: syndemic **methanol poisoning** in the age of **COVID-19**.
Holzman SD, Larsen J, Kaur R, Smelski G, Dudley S, Shirazi FM.
Clin Toxicol (Phila). 2021 Nov;59(11):1009-1014. doi: 10.1080/15563650.2021.1895202. Epub 2021 Mar 23.
PMID: 33755514

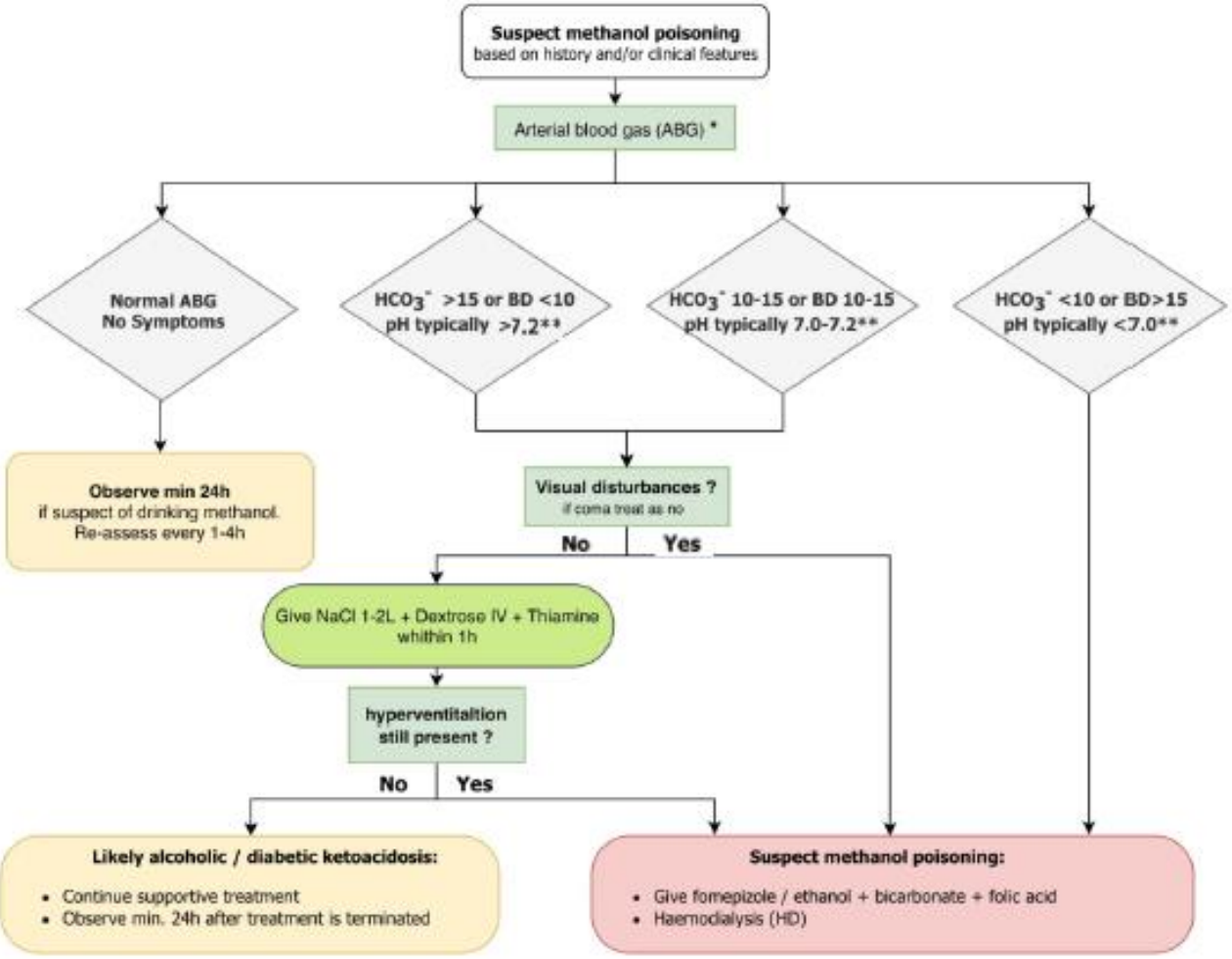
COVID-19 pandemic and **methanol poisoning** outbreak in Iranian children and adolescents: A data linkage study.
Mahdavi SA, Kolahi AA, Akhgari M, Gheshlaghi F, Gholami N, Moshiri M, Mohtasham N, Ebrahimi S, Ziaeefar P, McDonald R, Tas B, Kazemifar AM, Amirabadizadeh A, Ghadirzadeh M, Jamshidi F, Dadpour B, Mirtorabi SD, Farnaghi F, Zamani N, Hassanian-Moghaddam H.
Alcohol Clin Exp Res. 2021 Sep;45(9):1853-1863. doi: 10.1111/acer.14680. Epub 2021 Sep 6.
PMID: 34487368

COVID-19 and contamination: impact on exposures to alcohol-based hand sanitizers reported to Texas **Poison** Control Centers, 2020.
Phillips T, Schulte JM, Smith EA, Roth B, Kleinschmidt KC.
Clin Toxicol (Phila). 2021 Oct;59(10):926-931. doi: 10.1080/15563650.2021.1887491. Epub 2021 Feb 19.
PMID: 33605823

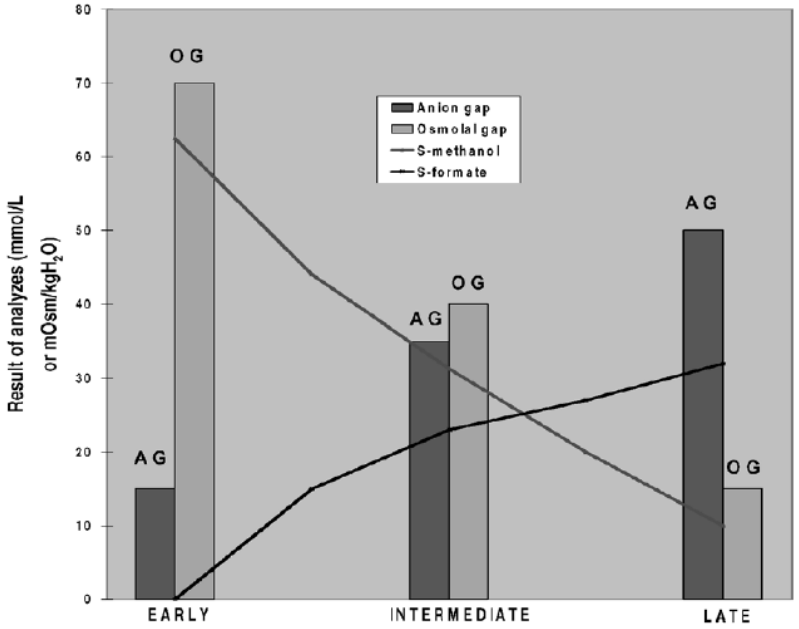
Diagnosis algorithm



Diagnosis algorithm

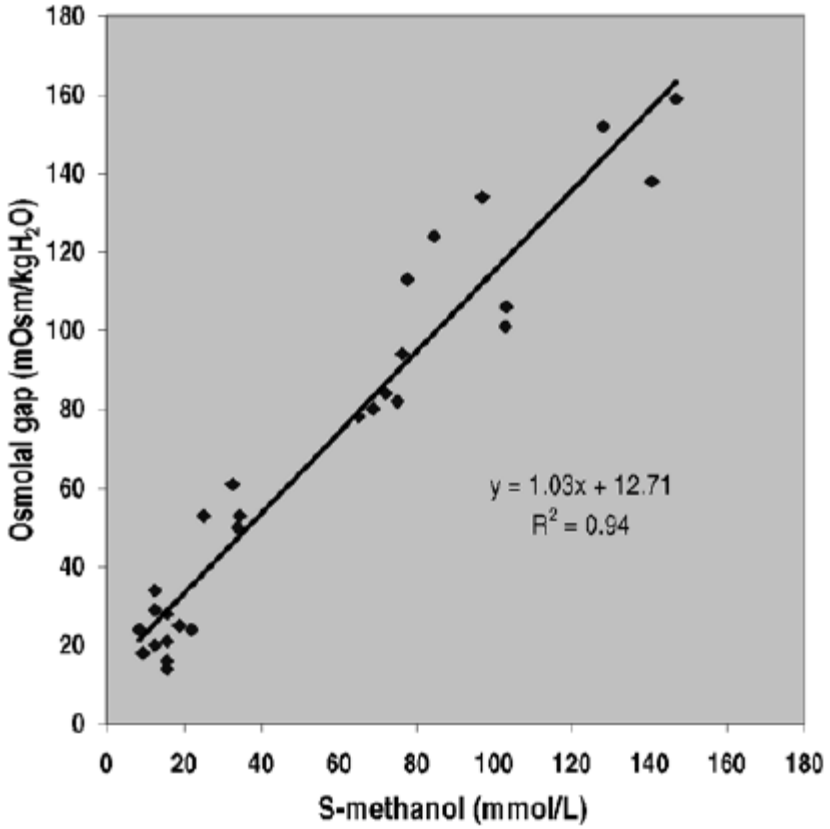


Laboratory diagnosis

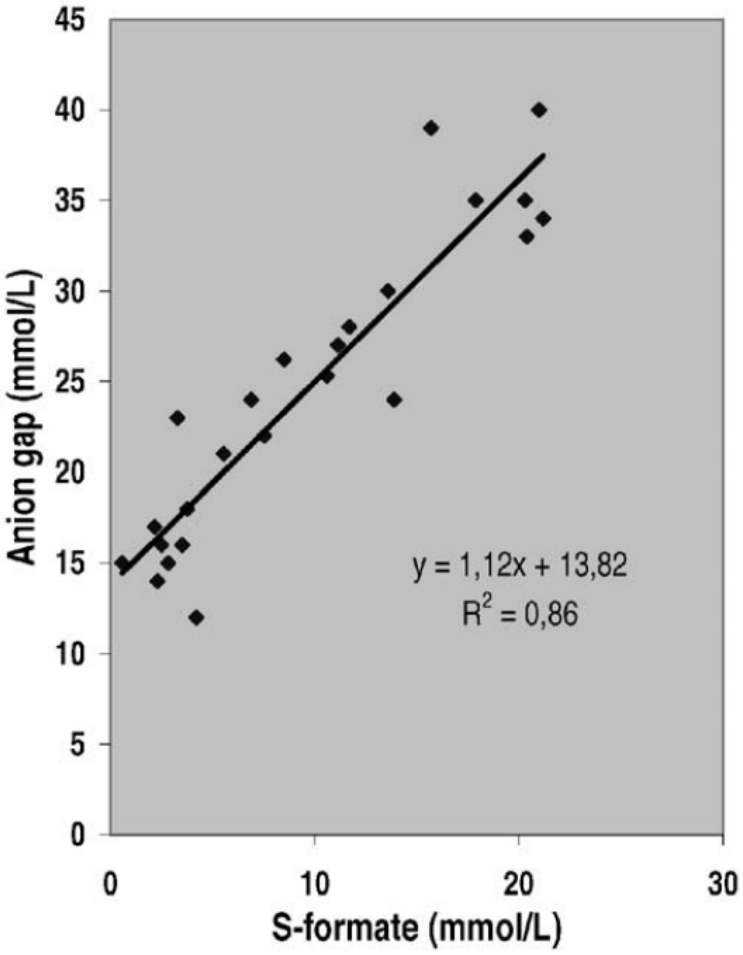


Methanol 100 mg/dl => 34 mOsm/kg H_2O
Ethanol 100 mg/dl => 24 mOsm/kg H_2O

(Hovda et al., Intensive Care Med, 2004)



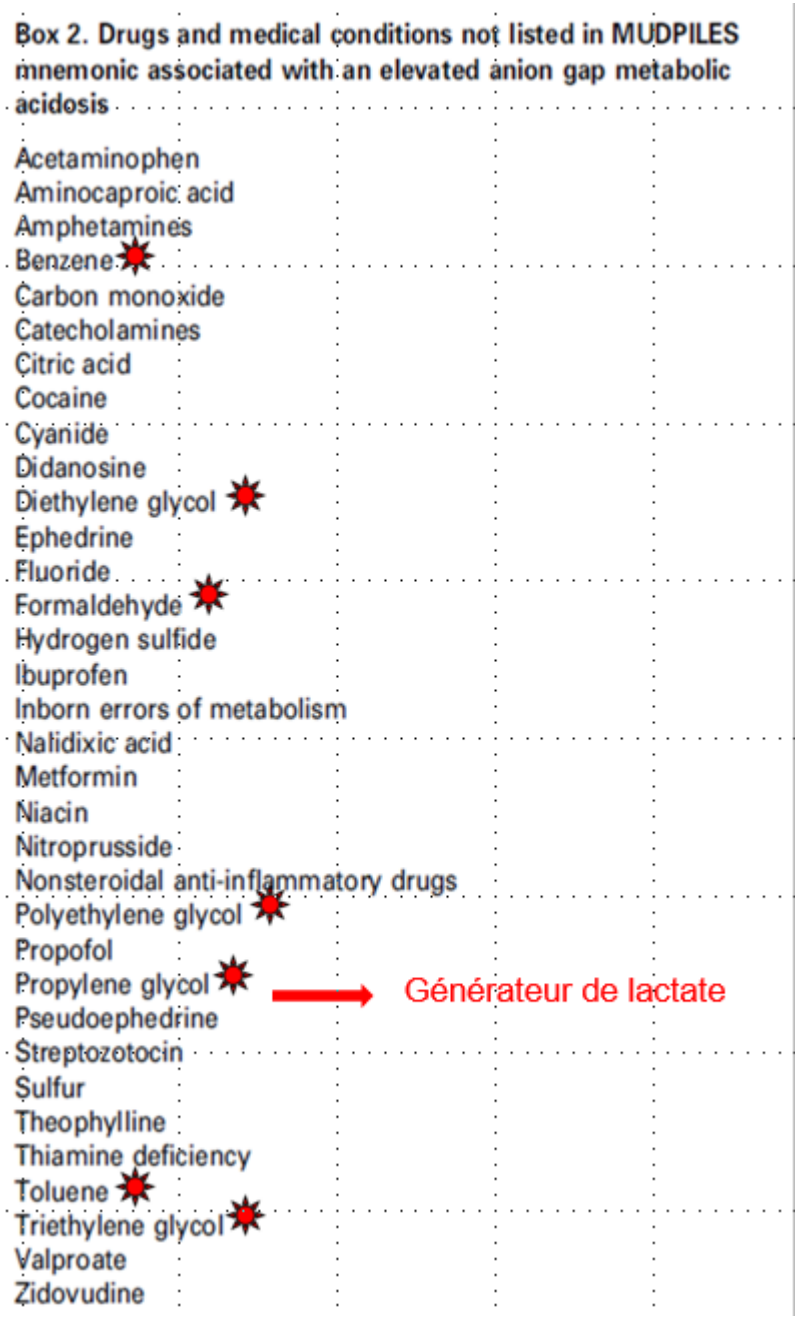
Osmolal gap



Anion gap

Difficulties in differential diagnosis

- Other toxic alcohols ingestion: ethylene glycol (di-, or tri-ethylene glycol, isopropanol, propylene glycol…)
- Other causes of metabolic acidosis: diabetic ketoacidosis, but also alcoholic ketoacidosis



Difficulties in differential diagnosis: mind the gaps!

Box 1. Toxins and disease states associated with an elevated anion gap metabolic acidosis

Methanol
Uremia
Diabetic ketoacidosis, alcoholic ketoacidosis, starvation ketoacidosis
Paraldehyde, phenformin
Iron, isoniazid
Lactic acidosis
Ethylene glycol
Salicylates

Box 5. Toxins associated with an elevated osmol gap

Mannitol
Alcohols: ethanol, ethylene glycol, isopropanol, methanol, propylene glycol
Diatrizoate
Glycerol
Acetone
Sorbitol

From Chabali R. Diagnostic use of anion and osmolal gaps in pediatric emergency medicine. Pediatr Emerg Care 1997;13:204; with permission.

- Difficulties occur when anion or osmol gaps are at the limit of « normal range »

Bedside diagnostic test for formate: promising

- Enzymatic methods for methanol determination in serum and urine are complex and interferences possible with ethanol
- With late presentation, methanol may have disappeared from blood
- Formate analysis represents a potential diagnostic tool!
- High specificity and sensibility, allows to exclude the responsability of methanol in metabolic acidosis of unknown origin
- Formate test strip with a dry-reagent and colorimetric test device
- Semi-quantitative method, 2 min analysis time
- Promising tool for methanol outbreaks

(Hovda et al., Scand J Clin Lab Invest, 2015)

Difficulties in differential diagnosis: some recent exemple

- 46-yr-old chronic abuser woman admitted to the ED with altered consciousness, no clear history from relatives
- GCS 14/15, ABP 75/50 mmHg, RR 32/min
- Lab results: glucose 40 mg/dL, pH 6,95, pCO2 16 mmHg, HCO3 6 mmol/L, lactate 27 mmol/L, serum osmolality 306 mOsm/kg ketone bodies (-)
- What is the next step?
- Anion gap: 37 mmol/L, Osmol gap: 12 mOsm/kg
- Is toxic alcohol ingestion possible?
- Toxicological screening: ethanol, ethylene glycol, methanol, isopropanol: negative!
- What do you suggest?
  - Supportive therapy
  - Antidotal therapy: ethanol or fomepizole?
  - Hemodialysis?

Difficulties in differential diagnosis: some recent exemple

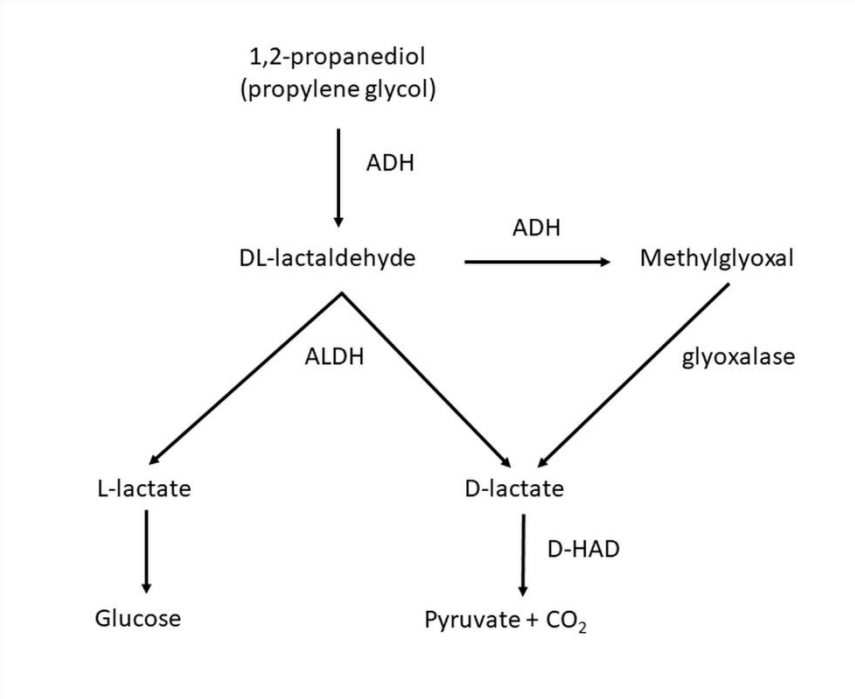
	Day 1 4:00 pm	Day 1 7:00 pm	Day 1 8:00 pm	Day 1 10:00 pm	Day 2 0:30 am	Day 2 4:00 am	Day 2 8:00 am	Day 2 12:00 am
Arterial pH *(7.35-7.45)*	6.95	7.16	7.21	7.36	7.45	7.39	7.37	7.41
Serum bicarbonate (mmol/L) *(22-28)*	6	6	7	14	20	14	14	20
Anion gap (mEq/L) *(8-12)*	37	39	32	20	-	9	19	15
Serum osmolality (mOsm/kg) *(280-300)*	306	310	-	-	-	310	-	-
Osmolal gap (mOsm/kg)	12	19	-	-	-	36 (2**)	-	-
Urine ketone bodies	Absent	-	-	-	-	-	-	-
Serum ethanol (mg/dL)	0	0	-	80	50	130	-	-
Serum L-lactate (mmol/L)* *(0.5-2.0)*	27	25	19	11.7	6.8	10.8	10.0	5.8
Serum creatinine (mg/dL) *(0.6-1.30)*	2.80	-	-	0.89	-	0.79	-	-

*determined on Radiometer ABL 800

**adjusted for a serum ethanol level of 130 mg/dL

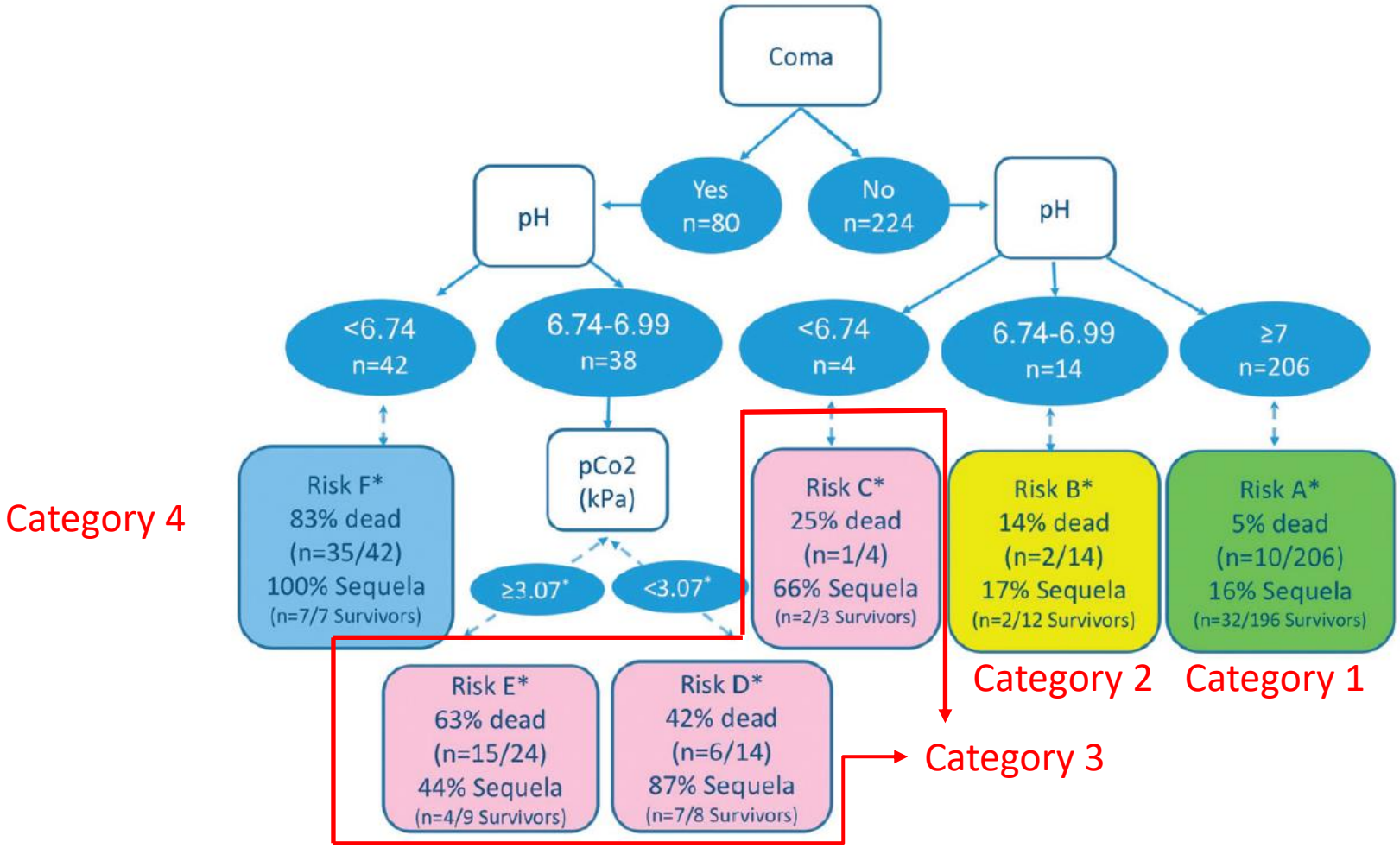
Difficulties in differential diagnosis: some recent exemple

- What we did: Treatment first! –bicarbonate, hemodialysis, and ethanol *ut aliquid*…
  - The clinical condition improved together with correction of metabolic acidosis!
- Further investigations
  - L-lactate: real or false? (false increase possible with glycolate interference)
  - D-lactate? Yes, also present in blood and urine!
  - Ketone bodies (-): but high β-hydroxobutyrate in urine!
  - Urine: propylene glycol 108 mg/L
- Final diagnosis
  - Mixed alcoholic ketoacidosis and PG toxicity
  - Treatment:
    - Supportive, glucose + insulin for KA
    - Ethanol or fomepizole + HD for PG



Prognostic factors: a clue for triage?

- From the data obtained from two recent outbreaks (Estonia, Czech Republic)



Fomepizole versus ethanol

Consensus statements on the approach to patients in a methanol poisoning outbreak

Hossein Hassanian-Moghaddam, Nasim Zamani, Darren M. Roberts, Jeffrey Brent, Kenneth McMartin, Cynthia Aaron, Michael Eddleston, Paul I. Dargan, Kent Olson, Lewis Nelson, Ashish Bhalla, Philippe Hantson, Dag Jacobsen, Bruno Megarbane, Mahdi Balali-Mood, Nicholas A. Buckley, Sergey Zakharov, Raido Paasma, Bhavesh Jarwani, Amirhossein Mirafzal, Tomas Salek & Knut Erik Hovda

- Antidotes should be administered promptly based on the high probability of methanol outbreak (1C)
- Ideally, antidote should be already started in the pre-hospital setting (1B)
- No special concern about the concurrent misuse of ethanol
- Which antidote? When fomepizole and ethanol are both available, patients with more severe poisoning (acidosis, visual disturbances, coma) should receive fomepizole (1D)
  - What about pediatric patients and pregnant women?
  - What about patients at high risk of toxicity but no current acidosis and organ damage (osmolal gap > 20-30 mOsm, methanol > 50 mg/dL)? Fomepizole with the objective to reduce the need for ICU admission? (1D)

Adverse Drug Events Associated With the Antidotes for Methanol and Ethylene Glycol Poisoning: A Comparison of Ethanol and Fomepizole

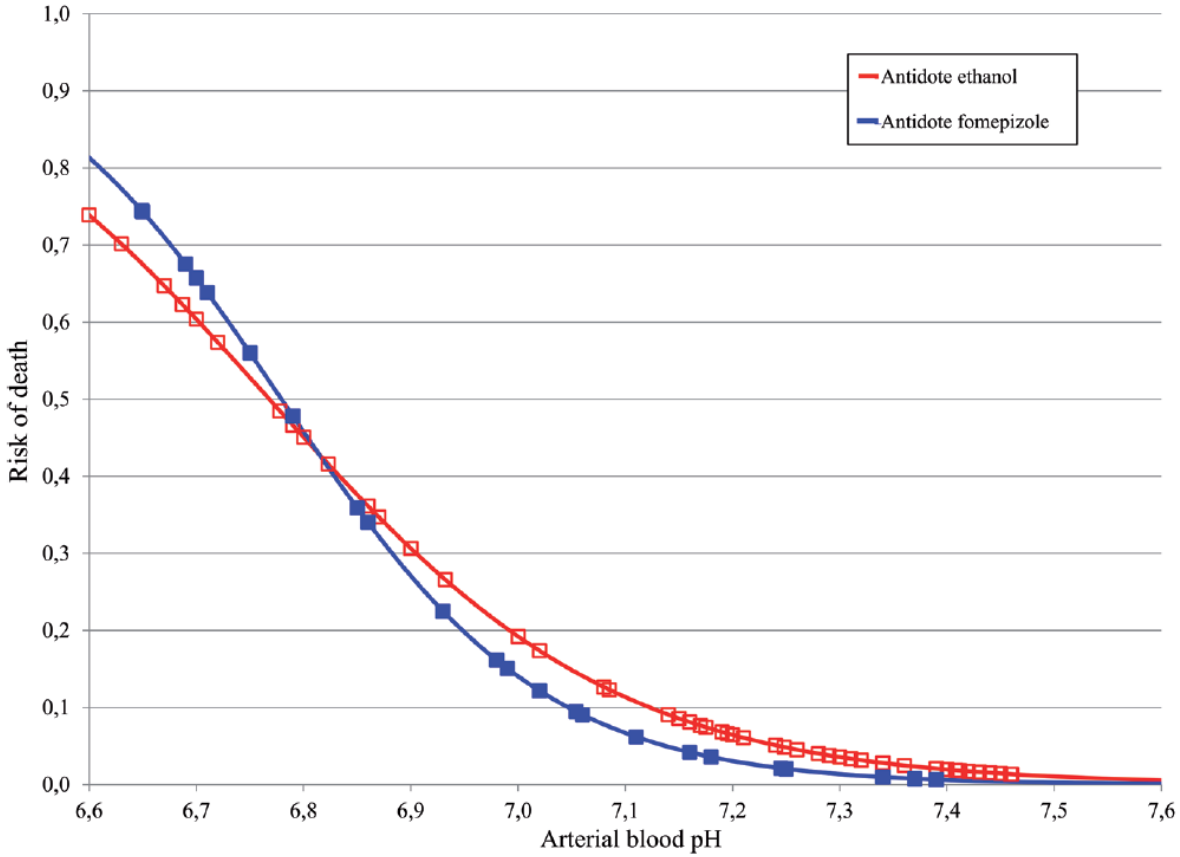
- Cohort study including patients admitted between 1996 and 2005 for M or EG poisoning, and treated with at least one dose of ethanol or fomepizole
- 172 charts analyzed: at least 1 adverse drug event in 74 of 130 (57%) ethanol-treated and 5 of 42 (12%) fomepizole-treated cases
- Median adverse drug event onset was within 3 h after the start of either antidote
- CNS symptoms accounted for most adverse drug events (48% ethanol-treated, 2% fomepizole treated)
- Severe adverse drug events occurred in 26 of 130 (20%) ethanol-treated (coma, extreme agitation, cardiovascular) and 2 of 42 (5%) fomepizole-treated (coma, cardiovascular).
- Serious (life-threatening) adverse drug events occurred in 11 of 130 (8%) ethanol-treated (respiratory depression, hypotension) and 1 of 42 (2%) fomepizole-treated (hypotension, bradycardia)
- Results suggest lower occurrence of adverse drug events with fomepizole than ethanol

(Lepik, Ann Emerg Med, 2009)

Fomepizole versus ethanol in the treatment of acute methanol poisoning: Comparison of clinical effectiveness in a mass poisoning outbreak

Sergey Zakharov[a], Daniela Pelclova[a], Tomas Navratil[ab], Jaromir Belacek[c], Martin Komarc[c], Michael Eddleston[d] & Knut Erik Hovda[e]

- 25 pts with fomepizole compared with 68 receiving ethanol. More severely acidotic (*p*= 0.001) and late-presenting (12 h; *p*=0.028) patients received fomepizole more often than ethanol, as reflected in the higher number of fomepizole-treated patients being intubated (*p*= 0.009).
- No association was found between the type of antidote and the survival in either the case series (*p*=0.205) or the quasi-control groups (*p*=0.705) in which patients were very closely matched to minimize confounding by allocation.



To cite this article: Sergey Zakharov, Daniela Pelclova, Tomas Navratil, Jaromir Belacek, Martin Komarc, Michael Eddleston & Knut Erik Hovda (2015): Fomepizole versus ethanol in the treatment of acute methanol poisoning: Comparison of clinical effectiveness in a mass poisoning outbreak, Clinical Toxicology

Practical use of antidotes

Ethanol

- Ethanol 94°, diluted in D5%
- Loading dose: 0,6-0,8 g/kg iv over 20-30 min
- Maintenance: 66-154 mg/kg.hr^{-1}
- Hemodialysis: x 2 maintenance dose
- High inter and intra-individual variability
- Ethanol blood monitoring: ideally every hour for adaptation

Fomepizole

- Loading dose: 15 mg/kg iv
- Maitenance: 10 mg/kg.hr^{-1} iv
- Hemodialysis: 1-1,5 mg/kg.hr^{-1} or 15 mg/kg every 4 hours (could by reduced by 50% for CRRT)
- Doses are probably « in excess »
- Fomepizole not approved in pregnant women and children (despite published experience), but probably safe at the same dosage

Folic/folinic acid

- No firm evidence

Extra-renal epuration

Recommendations for the Role of Extracorporeal Treatments in the Management of Acute Methanol Poisoning: A Systematic Review and Consensus Statement

We recommend ECTR is initiated in the following circumstances:

1) Severe methanol poisoning (grade 1D), including any of:
   a) Coma (grade 1D)
   b) Seizures (grade 1D)
   c) New vision deficits (grade 1D)
   d) Metabolic acidosis from methanol poisoning
      i) Blood pH ≤ 7.15 (grade 1D)
      ii) Persistent metabolic acidosis despite adequate supportive measures and antidotes (grade 1D)
   e) Serum anion gap > 24 mmol/L (grade 1D); calculated by serum $[Na^+] - [Cl^-] - [Hco_3^-]$.

2) Serum methanol concentration
   a) > 700 mg/L or 21.8 mmol/L in the context of fomepizole therapy (grade 1D)
   b) > 600 mg/L or 18.7 mmol/L in the context of ethanol treatment (grade 1D)
   c) > 500 mg/L or 15.6 mmol/L in the absence of an ADH blocker (grade 1D)
   d) In the absence of a methanol concentration, the osmolal/osmolar gap may be informative (grade 1D)

3) In context of impaired kidney function (grade 1D)

To optimize the outcomes from ECTR, we recommend:

4) Intermittent hemodialysis is the modality of choice in methanol poisoning (grade 1D). Continuous modalities are acceptable alternatives if intermittent hemodialysis is not available (grade 1D).

5) ADH inhibitors are to be continued during ECTR for methanol poisoning (grade 1D) as well as folic acid

6) ECTR can be terminated when the methanol concentration is < 200 mg/L or 6.2 mmol/L and a clinical improvement is observed (grade 1D)

ECTR = extracorporeal treatment, ADH = alcohol dehydrogenase.

Intermittent versus continuous renal replacement therapy in acute methanol poisoning: comparison of clinical effectiveness in mass poisoning outbreaks

Sergey Zakharov[1*], Jan Rulisek[2], Olga Nurieva[1], Katerina Kotikova[1], Tomas Navratil[1,3], Martin Komarc[4], Daniela Pelclova[1] and Knut Erik Hovda[5]

Table 4 Univariate logistic regression analysis of impact of different parameters including hemodialysis modality (IHD vs. CRRT) on mortality and survival with sequelae in the patients with acute methanol poisoning ($n = 81$)

Variable	Outcome							
	Mortality				Survival with long-term visual/CNS sequelae			
	OR	(95% CI)	p	R^2	OR	(95% CI)	p	R^2
HD modality (IHD vs. CRRT)	*0.231*	*0.075–0.719*	*0.011*	*0.127*	*0.261*	*0.101–0.671*	*0.005*	*0.131*
Arterial blood pH	*0.002*	*0.000–0.038*	*<0.001*	*0.419*	*0.000*	*0.000–0.010*	*<0.001*	*0.546*
GCS	*0.756*	*0.663–0.862*	*<0.001*	*0.412*	*0.768*	*0.679–0.868*	*<0.001*	*0.384*
S-creatinine	*1.027*	*1.011–1.043*	*0.001*	*0.229*	*1.041*	*1.019–1.064*	*<0.001*	*0.323*
S-glucose	*1.179*	*1.059–1.312*	*0.003*	*0.174*	*1.164*	*1.034–1.310*	*0.012*	*0.128*
S-EtOH	0.948	0.813–1.106	0.498	0.331	*0.999*	*0.998–1.000*	*0.042*	*0.123*

The alpha level used in the univariate analysis is $\alpha = 0.05$

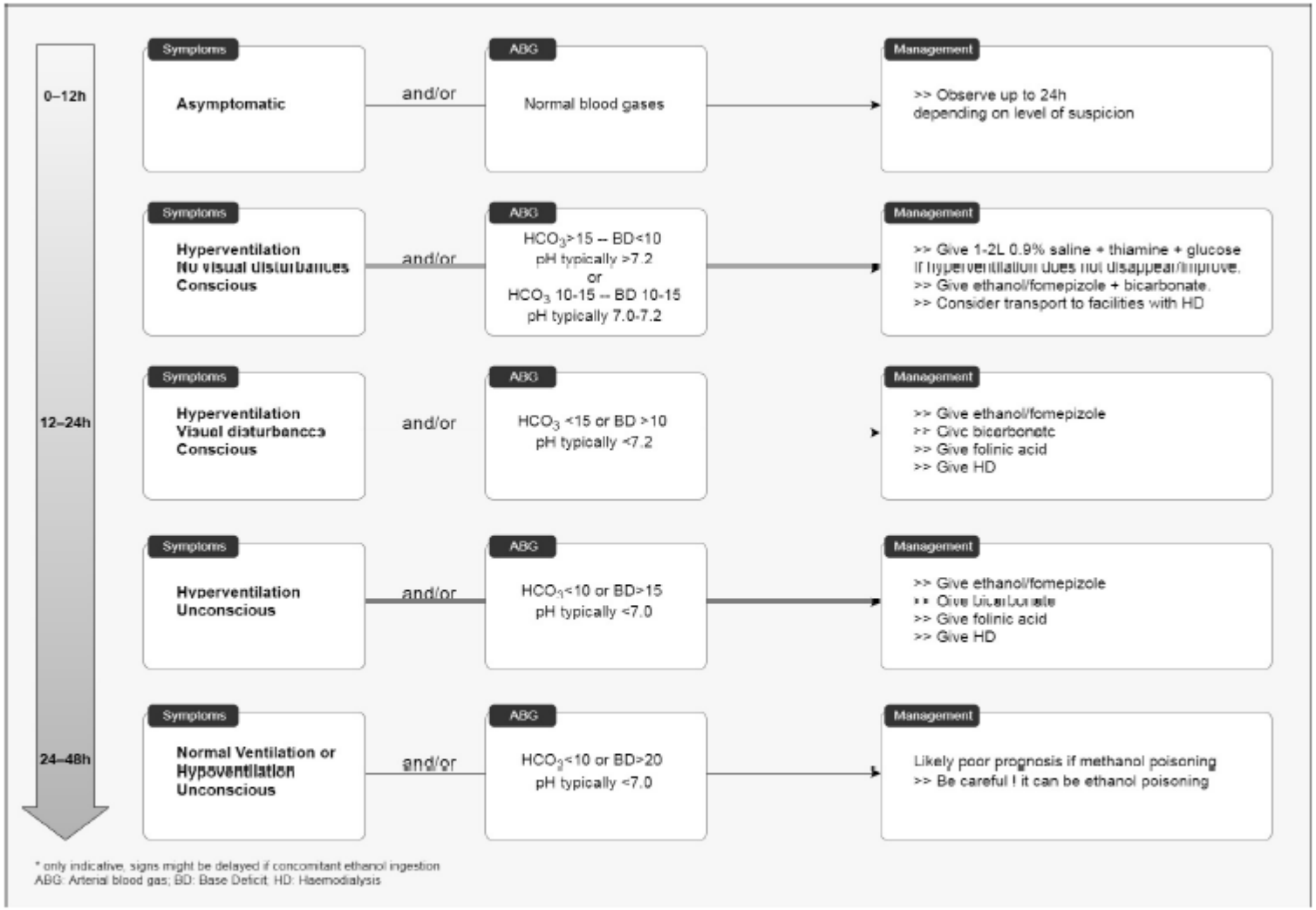
Italic values indicate statistically significant result at $p < 0.05$

OR odds ratio, *CI* confidence interval, HD modality—hemodialysis modality, arterial blood pH—arterial blood pH on admission, *GCS* Glasgow Coma Scale on admission, *S* serum, *EtOH* ethanol

Practical use of extra-renal epuration

- Is there any influence of extra-renal epuration on outcome?
  - Not on mortality, influence on toxicokinetics (methanol + formic acid)
  - Supporting evidence for correction of acidemia and visual disturbances, but effect not totally independent from the administration of antidotes
- Best timing?
  - Insufficient data to determine which patients are unlikely to benefit from extra-renal epuration on the basis of clinical and laboratory features
  - Extra-renal epuration can be implemented nonemergently when there is adequate ADH blockade and in the absence of acute clinical indications for extra-renal epuration
  - Criteria: not only based on the amount ingested by history
- Triage and economic considerations?
  - Obviously, some ethical concerns (moribund patient)
  - In case of major methanol ingestion, extra-renal epuration could reduce the costs of fomepizole therapy or reduced the duration of ethanol therapy (complexity, side effects)
- Duration?
  - 6 to 8 hours HD according to the course of metabolic acidosis, or 18 hours for CRRT

Exemple of protocol



Conclusions

- The incidence of methanol outbreaks is still increasing, with some unexpected circumstances (Covid-19)
- Even in Eastern countries, clusters of methanol poisoning could represent a critical issue for any ED and hospital facilities (lab, hemodialysis, ICU beds)
- Triage in the ED is an essential step: clinical and readily available biological criteria (gaps or formic acid for the future), exclusion of alcoholic ketoacidosis
- Correction of metabolic acidosis as supportive care
- Start antidote as early as possible: preparedness for antidote availability (even the cheapest antidote could be missing), HD decision = not urgent
  - Advantage of fomepizole in an epidemic setting: first i.v. loading dose with 12 hr efficacy, no additional blood monitoring, no need for continuous adaptation of the dosage regimen (as with ethanol), no side effects if methanol poisoning not confirmed
- In a crisis situation, use « what you have » (antidote, epuration,…)

antigif centrum centre antipoisons
070 245 245

Dr. Kurt Anseeuw

ZNA

Are Belgian ED's prepared to manage CBRN-victims?

Are Belgian ED's prepared to manage CBRN-victims ?

Kurt Anseeuw, MD, MSc

Department of Emergency Medicine
Ziekenhuis Netwerk Antwerpen (ZNA)

znа
wij zorgen voor u

Conflict of interest

- None

Conflict of interest - CBRN

Chemical – nuclear - radiological threats

Tokyo (1995) - Lessons learned

- No plan
  - No chemical incident plan
  - No hospital disaster plan
  - No multidisciplinary coordination and communication

- No preparedness
  - Majority self-presenters
    - 12 dead + 5500 wounded
    - 700 by EMS
  - No awareness
    - After 2 hours “acetonitrile” (FD)
    - After 3 hours “Sarin” (Police) – no interagency sharing

Acad Emerg Med 1998, 5(6): 613-7 Acad Emerg Med 1998, 5(6): 618-24 Crit Care 2005, 9:397-400
Acad Emerg Med 1998, 5(6): 625-8 Resuscitation 2006, 68:193-202 Toxicol Appl Pharmacol 2005, 207(2):471-6

Tokyo (1995) - Lessons learned

- No safety
  - No decontamination
    - On site
    - In hospitals
  - No PPE
    - Hospital
    - EMS
- Secondary contamination
  - Medical 20% staff
  - Police & Fire 10% staff
  - Extent of secondary exposure ≈ duration and degree of physical contact

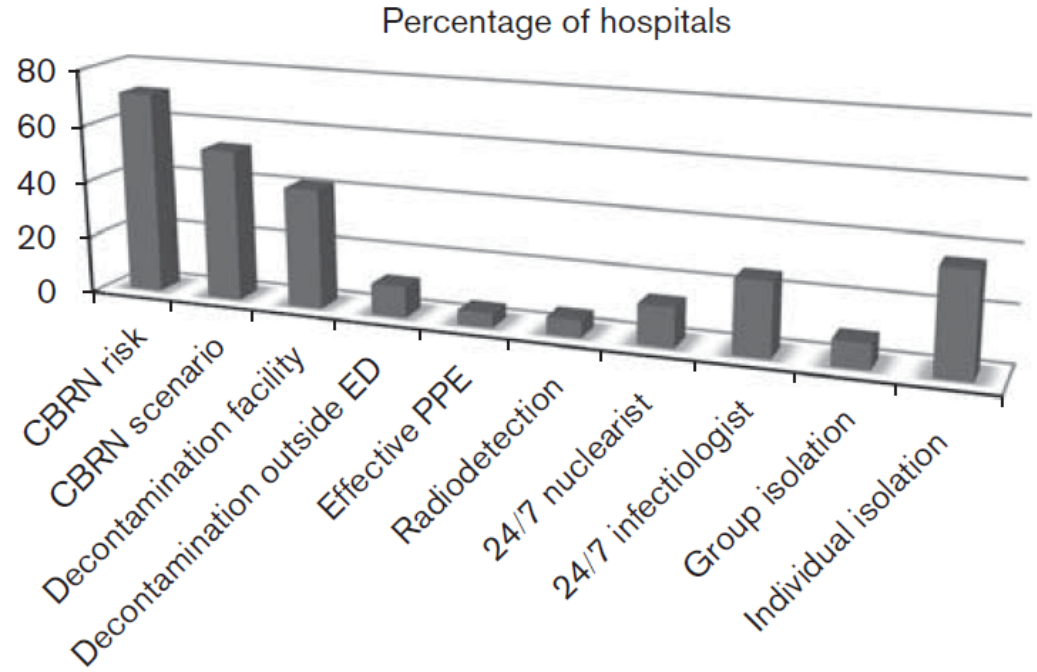
Acad Emerg Med 1998, 5(6): 613-7 Acad Emerg Med 1998, 5(6): 618-24 Crit Care 2005, 9:397-400
Acad Emerg Med 1998, 5(6): 625-8 Resuscitation 2006, 68:193-202 Toxicol Appl Pharmacol 2005, 207(2):471-6

Are Belgian ED's prepared ?

Preparedness of Belgian civil hospit
biological, radiation, and nuclear inc

Luc J.M. Mortelmans[a,c], Sam Van Boxstael[b], H
Marc B. Sabbe[b,c] and A Belgian Society of Er
Disaster Medicine (BeSEDiM) study

Fig. 3



Major data on preparedness expressed in terms of percentage of hospitals possessing the indicated aspect of preparedness.

- 138 Belgian ED's
- Serious gaps in the CBRN preparedness (limited and mass casualties)

Are Dutch Hospitals Prepared for Chemical, Biological, or Radionuclear Incidents? A Survey Study

Luc J.M. Mortelmans, MD;[1,2] Menno I. Gaakeer, MD;[3] Greet Dieltiens, MD;[1] Kurt Anseeuw, MD;[1] Marc B. Sabbe, MD, PhD[2,4]

Prehosp Disaster Med. 2017;32(5):1-9.

- 40% decontamination facility
- Mean capacity/hour
  - 3 ambulatory
  - 1 supine
- 56% PPE available
  - 18% level A or B

ORIGINAL RESEARCH

Hospital Disaster Preparedness in Switzerland Over a Decade: A National Survey

Simone Dell'Era; Olivier Hugli, MD, MPH; Fabrice Dami, MD, MBA

https://doi.org/10.1017/dmp.2018.59

TABLE 2

Features of Disaster Plans in 2016

Type of Disaster	N = 83 (%)	**Activation of the Plan Within the Last 3 Years**	N = 80
Mass casualty incident	76 (92)	Hospitals with plan activated in the last 3 years	18 (23)
Hospital accident (fire, black-out, security or communication problem)	76 (92)	**Plan Tested in Last 3 Years**	N = 80 (%)
Infectious problem (eg, Ebola, SARS)	65 (79)	HICS activation only	38 (48)
NRBC + B + T Risks	N = 80 (%)	Simulated patients	33 (41)
Nuclear/radiological	14 (18)	Descriptive cards	27 (34)
Biological	25 (31)	Plan tested ≥ 1 time/year	42 (52)
Chemical	27 (34)	Plan tested ≥ 1 time/3 years	80 (100)
Burned	15 (19)	**Presence of a HICS**	N = 80 (%)
Polytraumatized	46 (58)	HICS present	70 (88)
Plan Designed for Specific Populations of Patients	N = 80 (%)	**Leader of HICS**	N = 68 (%)
Children	19 (24)	Hospital's board member	38 (56)
Geriatric patients	12 (15)	ED medical officer	14 (21)
Migrants	10 (13)	Surgery medical officer	4 (6)
Reception of relatives	33 (41)	Anesthesia medical officer	1 (2)
Care Team for Victims' Relatives	N = 80 (%)	Specialist according to the type of accident	3 (5)
Staff from emergency department	37 (46)	Other	8 (11)
Staff from psychiatry department	11 (14)	**Time Needed for HICS to be Operational**	N = 68 (%)
Staff from other departments	31 (39)	< 20 minutes	7 (10)
Other	30 (38)	20-40 minutes	38 (56)
Patients' Flow Management	N = 80 (%)	≥ 40 minutes	23 (34)
The flow of daily patients is separate from disaster's flow	Yes 41 (51)	**Type of Risk Treated**	N = 78 (%)
Flow Management Tool in a *Daily Situation*	N = 83 (%)	Chemical	47 (60)
		Biological	32 (41)
Digital support	67 (81)	Nuclear/radiological	25 (32)
Paper	20 (24)	No decontamination zone	30 (39)
Other	3 (4)	**Readiness of Decontamination Zone**	N = 48 (%)
None	4 (5)	Time necessary to be operational (min)	Average Median
Flow Management Tool in a *Disaster Situation*	N = 78 (%)		40.3 30.0
Digital support	52 (67)	**Decontamination Manager**	N = 48 (%)
Paper	56 (72)	Hospital care staff	26 (54)
Other	6 (8)	Hospital technical staff	23 (48)
None	5 (6)	Professional firefighters	19 (40)
Hospital Access Control Manager	N = 80 (%)	Civil protection (FEMA in USA)	1 (2)
Private security	29 (36)	Army	1 (2)
Police	24 (30)	Other	10 (21)
Other (technical staff)	34 (43)	**Personal Protective Equipment (PPE)**	N = 48 (%)
None	13 (16)	Simple masks and disposable gloves	44 (92)
Recall of Additional Staff	N = 80 (%)	Light chemical protective seal (PPE)	38 (79)
ED staff	74 (93)	Other	7 (15)
Staff from other departments	71 (89)	None	2 (4)
Administrative staff	64 (80)		

European Review for Medical and Pharmacological Sciences 2019; 23: 1239-1247

Preparedness for chemical crisis situations: experiences from European medical response exercises

R.K. DAVIDSON[1,6], S. MAGALINI[2], K. BRATTEKÅS[1], C. BERTRAND[3], R. BRANCALEONI[2], C. RAFALOWSKI[4], E. ROSTRUP NAKSTAD[5]

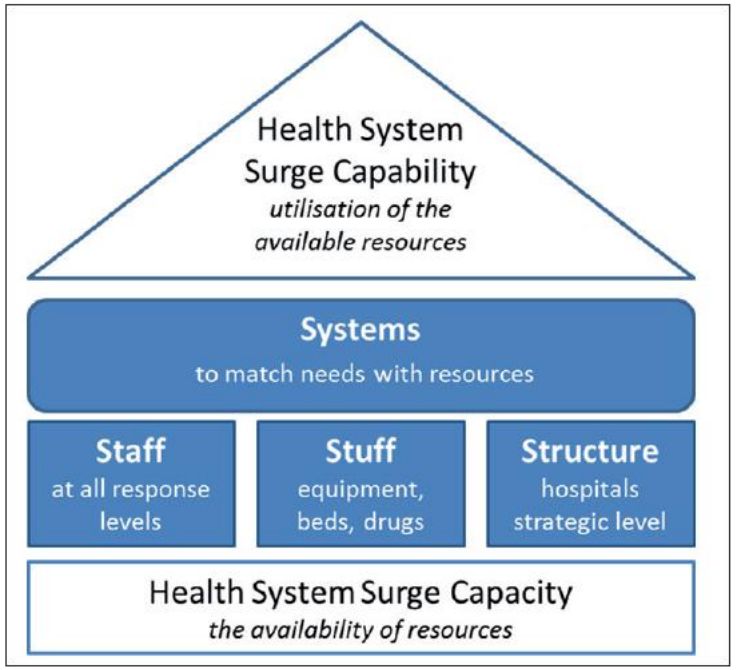
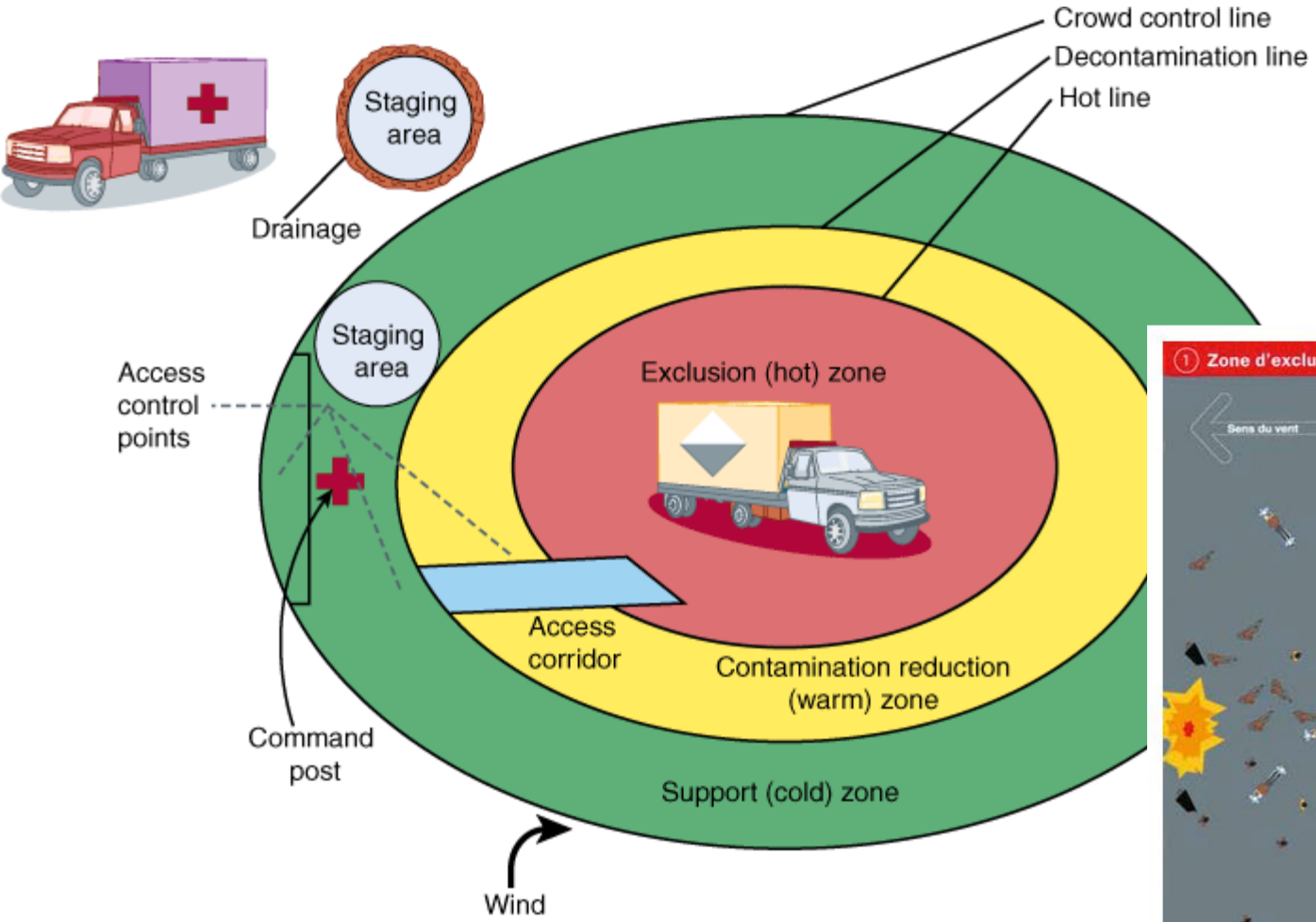


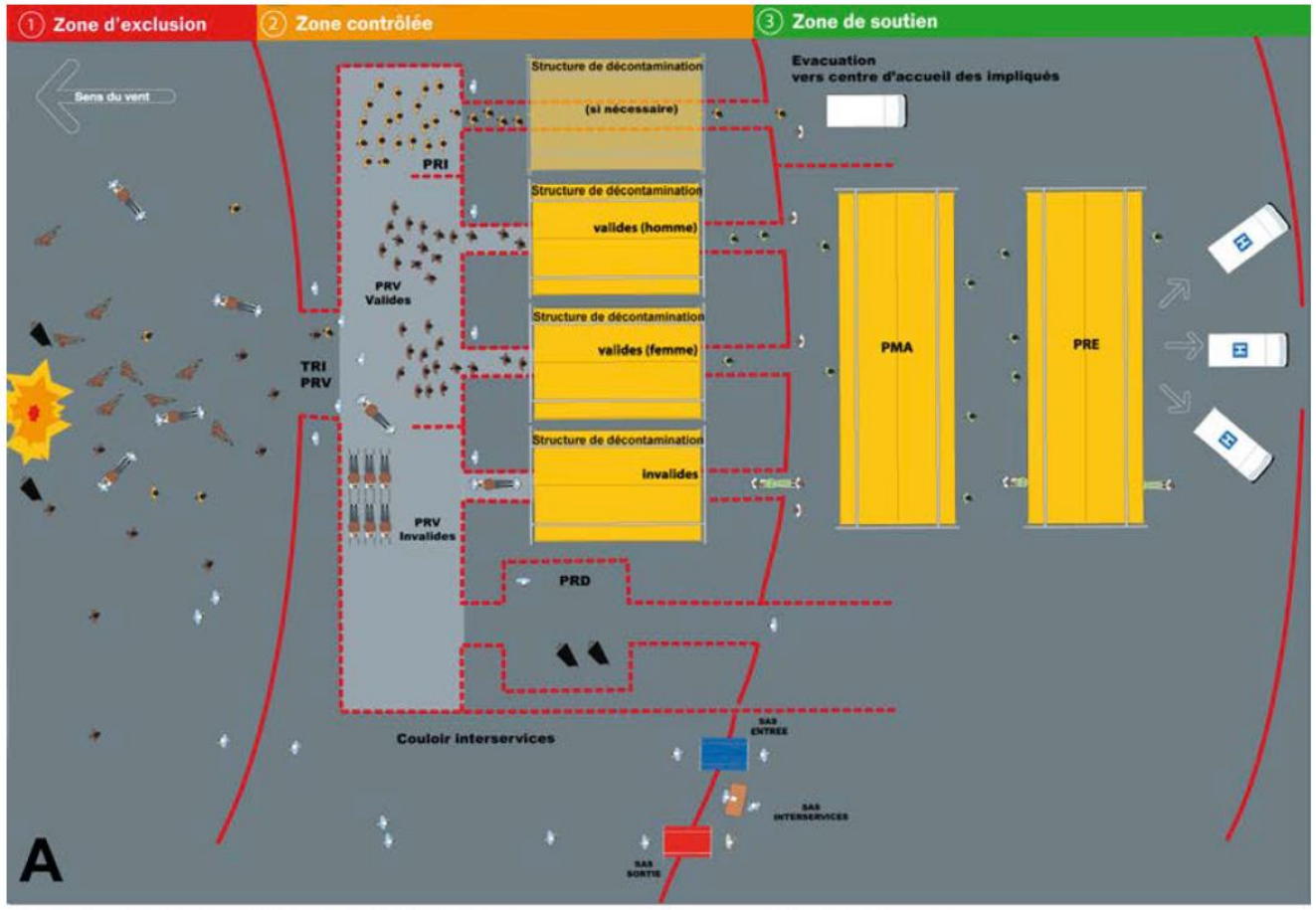
Figure 1. The four Ss of health system surge capacity that can lead to surge capability: staff, stuff, structure and systems.

- Plan
- Preparedness
  - Knowledge
  - Training
- Safety
  - PPE
  - Decontamination
- Stuff
  - Antidotes
  - Detection equipment

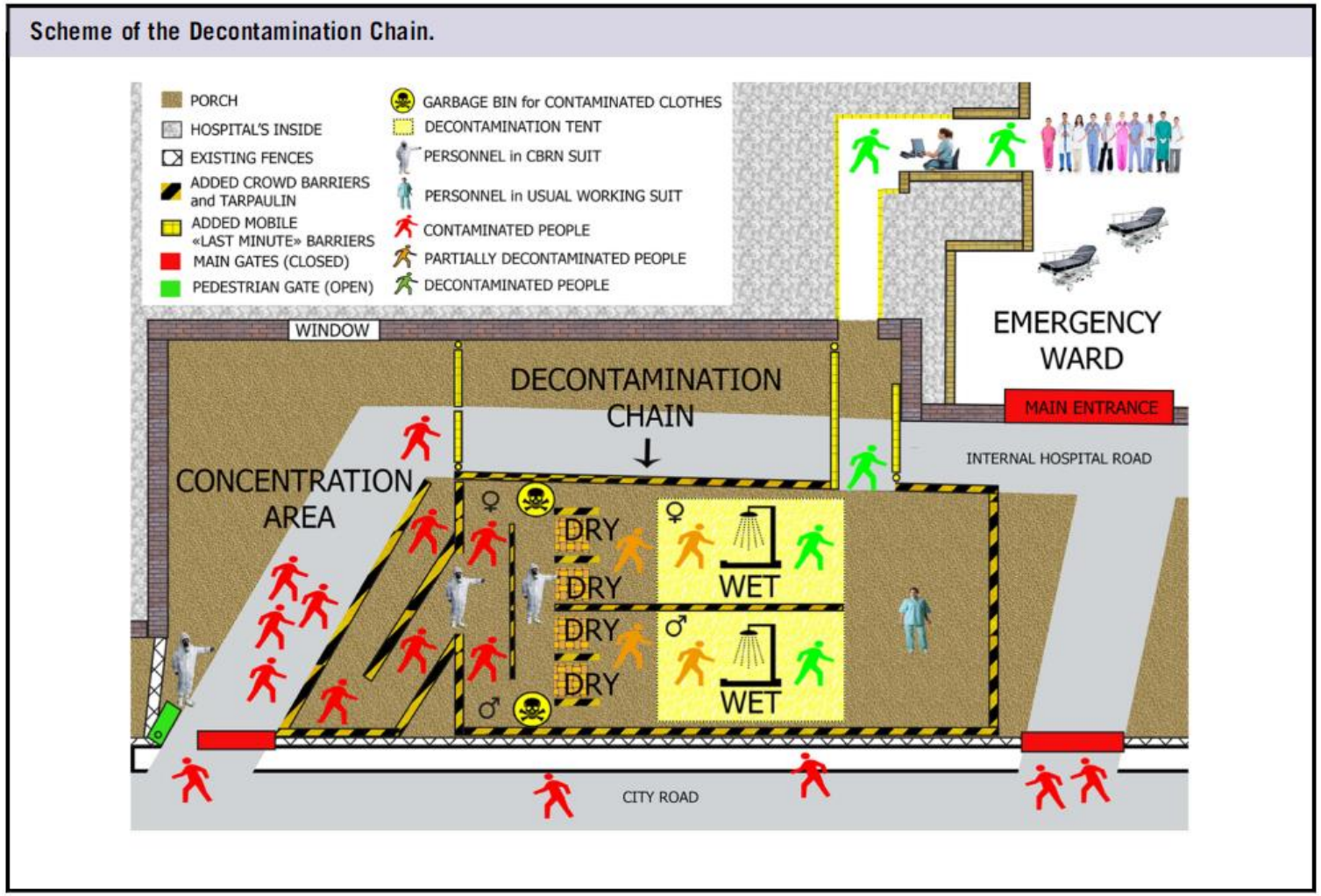
Hazmat incident preparedness



Source: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE: *Goldfrank's Toxicologic Emergencies, 9th Edition*: http://www.accessemergencymedicine.com



Hospital preparedness

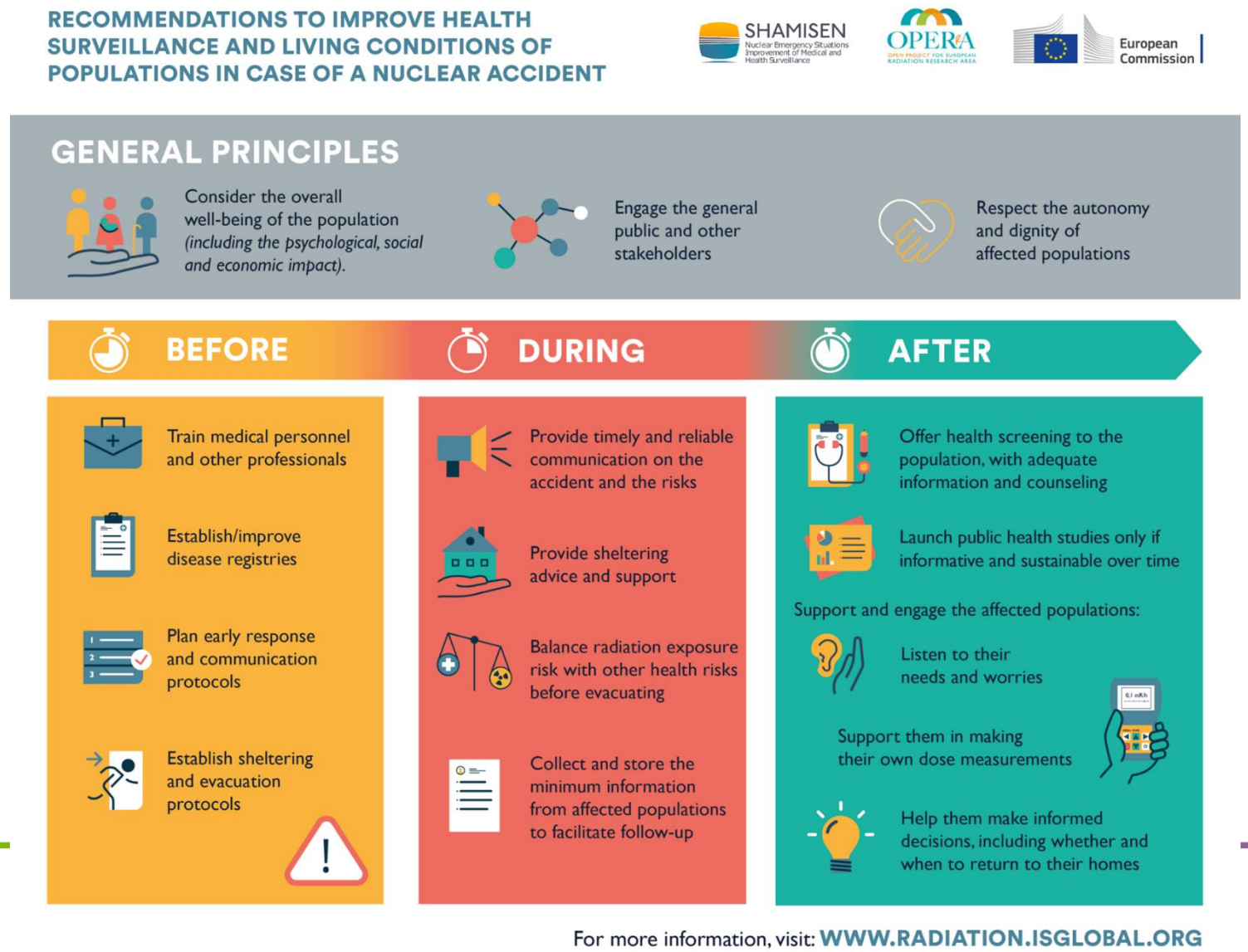


Personal Protective Equipment

- Level A - D
  - More expensive
  - More troublesome
  - More training

- PPE
  - (Hot zone = level A)
  - Warm zone = level B or C

Nuclear incident preparedness



Current situation

Personal opinion on ED preparedness

- Plan
- Preparedness
  - Knowledge
  - Training
- Safety
  - PPE
  - Decontamination
- Antidotes

Personal opinion on ED preparedness

- Plan
- Preparedness
  - Knowledge
  - Training
- Safety
  - PPE
  - Decontamination
- Antidotes

Ziekenhuisnoodplan (ZNP)

Deel V
Leidraad CBRN

Plan d'urgence hospitalier (PUH)

Partie V
Guide CBRN

2018

Personal opinion on ED preparedness

- Plan
- Preparedness
  - Knowledge
  - Training
- Safety
  - PPE
  - Decontamination
- Antidotes

Table 2 Teaching methods and duration of each topic in the competency-based training program for hospital staff in respect of medical response to CBRN emergencies

			Hospital			First responders
Domain (topic)	Teaching method	Duration (h)	Medical staff at ED, OR and ICU	Supportive staff	Administrative staff	EMS staff
Threat identification and risk analysis	e-Learning	2	√	–	√	√
	Traditional: exercise	2				
Health effects of CBRN agents	e-Learning	3	√	√	–	√
	Video lecture	1				
Planning and organization	e-Learning	3	√	–	√	√
	Video lecture	1				
	Traditional: exercise	1				
Hospital incident command system	e-Learning	2	√	–	√	–
Communication and information management	e-Learning	1	√	–	√	√
Safety, personal protective equipment, and decontamination	Traditional: lecture	2	√	√	–	√
	Traditional: exercise	4				

Menu

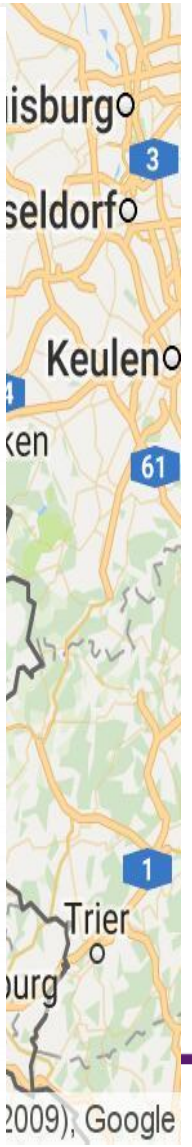
MELODY

The main objective of the MELODY project is to define, develop and deploy a harmonised CBRN training curriculum for first responders and medical staff, including ambulance drivers, paramedics and emergency room (ER) personnel. The target group includes members of agencies that are responsible for dealing with emergencies, being unintentional or intentional releases of CBRN, which require immediate action. The training curriculum should provide a clear picture of the possible consequences and effects and how to act together in a safe and effective and efficient way.

Eur J Emerg Med 2017; 24(4):371-376

Personal opinion on ED preparedness

- Plan
- Preparedness
  - Knowledge
  - Training
- Safety
  - PPE
  - Decontamination
- Antidotes



Personal opinion on ED preparedness

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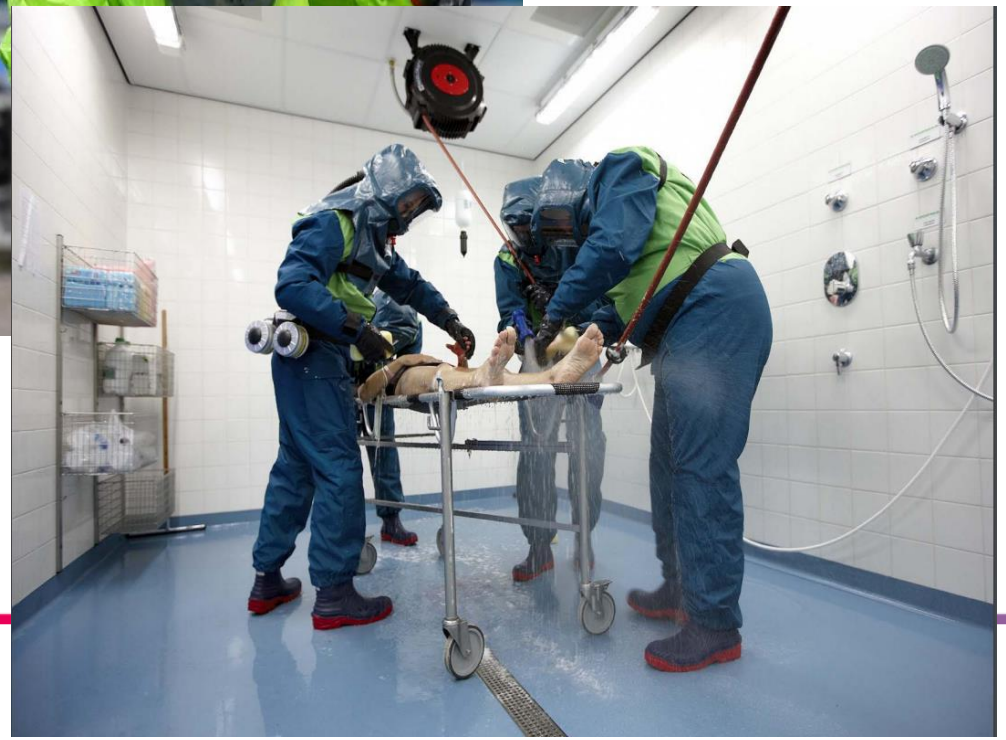


Personal opinion on ED preparedness

- Plan
- Preparedness
  - Knowledge
  - Training
- Safety
  - PPE
  - Decontamination
- Antidotes

Table 1 Antidotes and availability

Antidote	Hospitals possessing the antidote (%)
Atropine	100
Naloxone	89
N-acetylcysteine	84
Flumazenil	83
Glucagon	81
Calcium gluconate	79
Ethanol	62

Specific and exceptional antidota

- Poison Information Center
- Military Hospital (+ CBNRe MUG/SMUR)
- ZNA Stuivenberg
- Seveso establishments

No management/policy of stocking or distribution

Eur J Emerg Med 2014; 21(4):296-300

Masterproef L. Claessens, Antidotumbeleid van uitzonderlijk gebruikte antidota in Vlaanderen, AJ 2021-2022

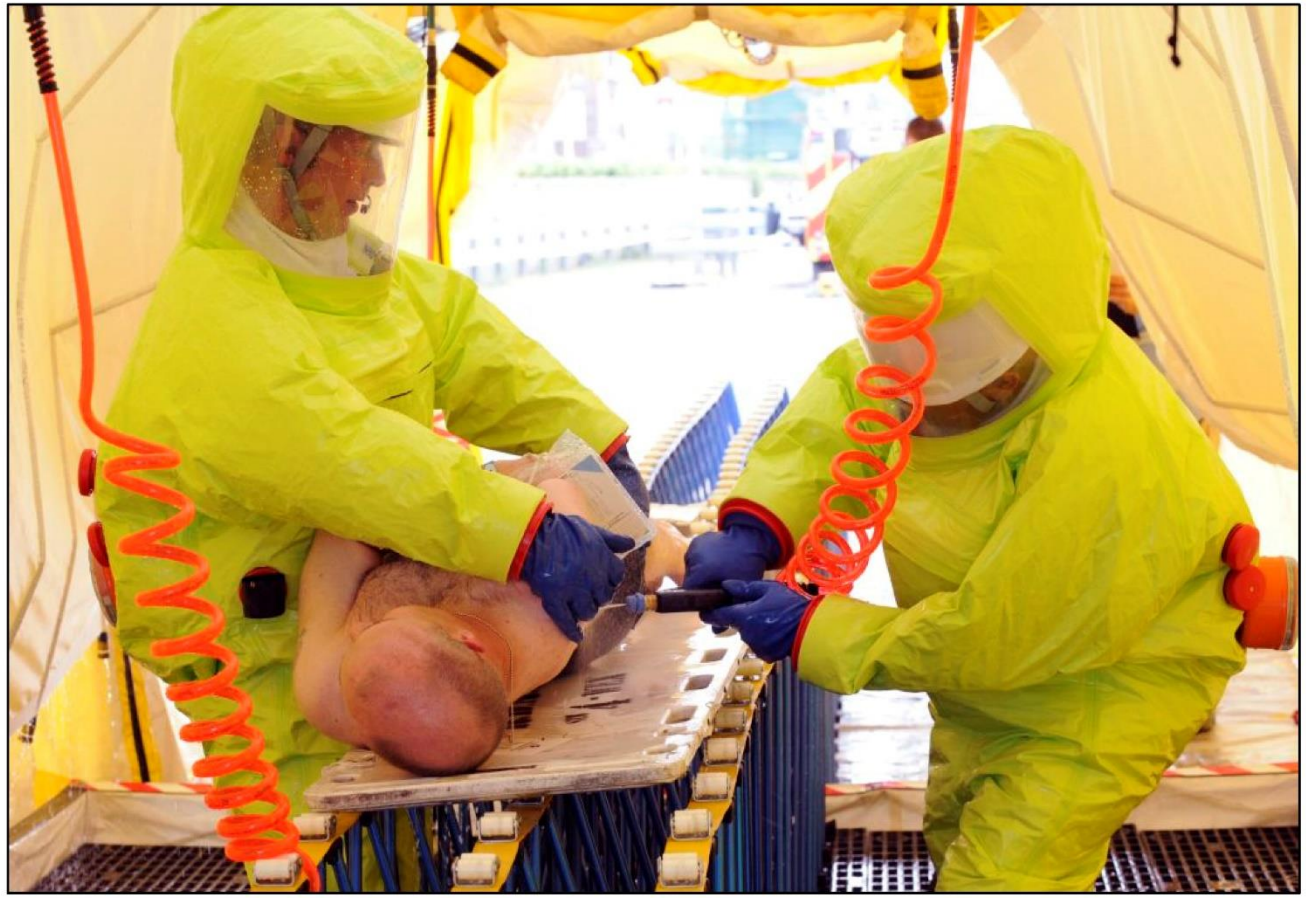
Conclusion

- Fundaments in place

- Need
  - More education and training
  - Multidisciplinary communication and coordination (PIC / Clin tox)
  - More resources
    - AHLS teams
    - PPE and decontamination capacity
  - Antidote policy and management

- Funding / resources

Thank you for your attention



antigif centrum centre antipoisons
070 245 245

Prof. dr. Marc Sabbe

UZ Leuven

Towards a streamlined antidote policy in Belgium

Towards a streamlined antidote policy in Belgium

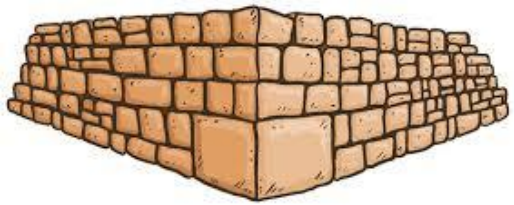
Prof Dr Marc Sabbe
Emergency Medicine UZ Leuven
Department of Public Health and Primary Care KULeuven
Interuniversity Post-Graduate Disaster Management

Poisoning

- Individual case
- Several cases
- Incident/disaster
  - Risks?
  - Exposure?
  - Number of victims?

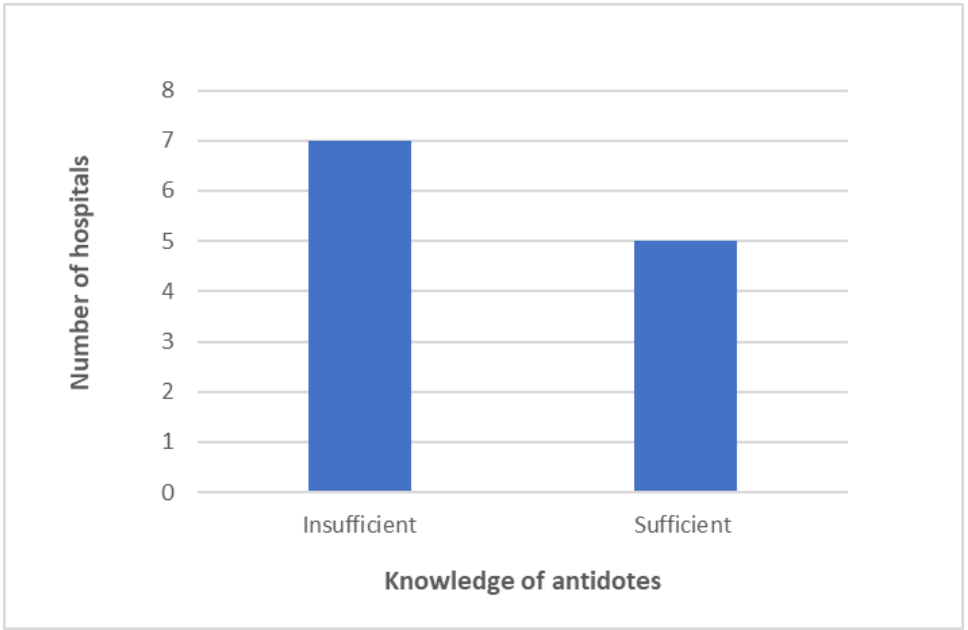
Therapeutic cornerstones

- **Supportive therapy**
- **Limit absorption**
- **Enhance elimination**
- **Antidotes (including lipid resuscitation)**
- **Psychosocial therapy**

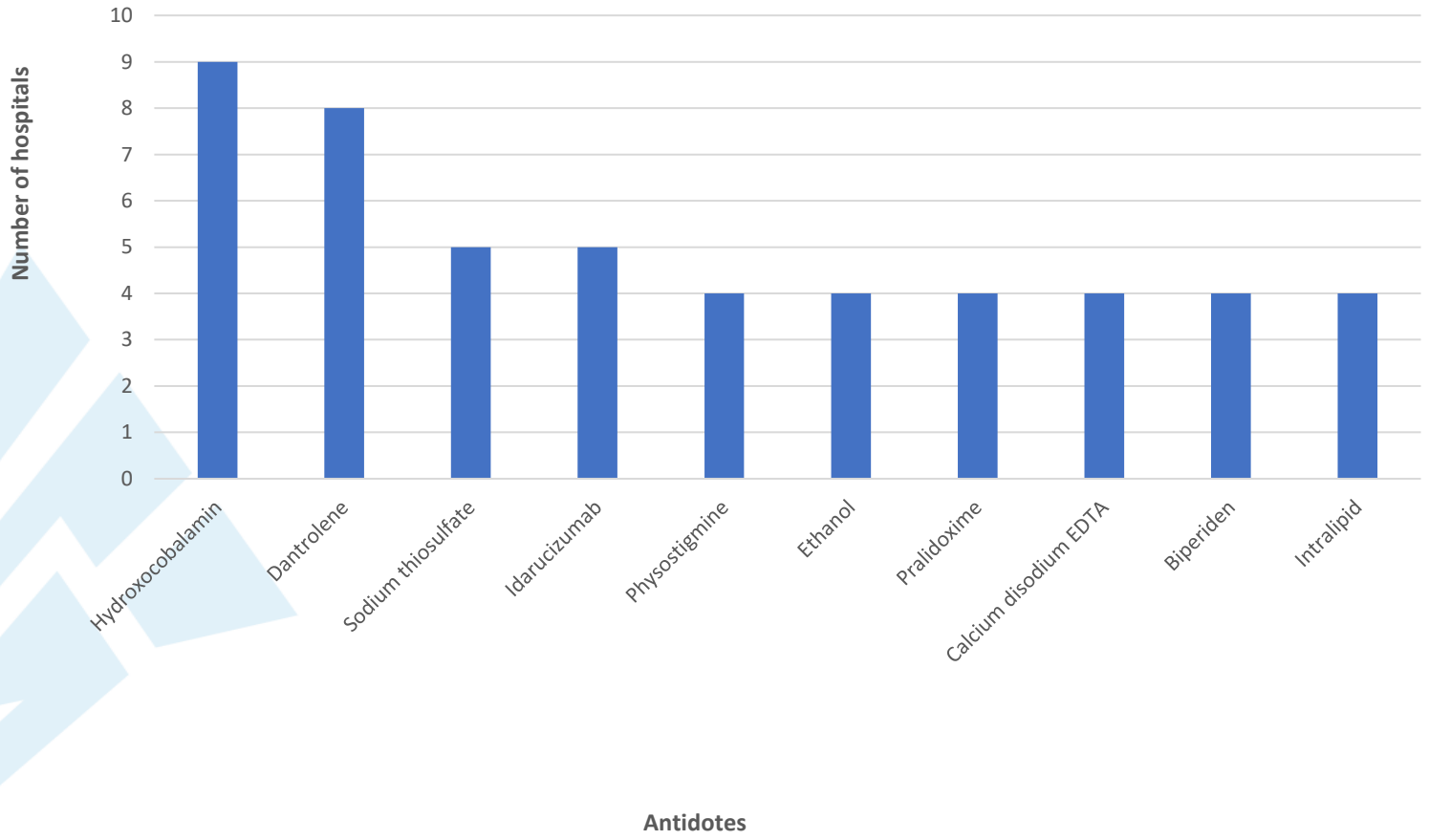


Antidotes

- Limited use
- Limited knowledge
- Expire – cost
- Storage:
  - What?
  - Where?
  - How much?



Antidote	Intoxication	Number of hospitals
Naloxone hydrochloride	Opioids	17 (100%)
Atropine sulphate	Cholinesterase inhibitors	16 (94%)
Calcium gluconate	Fluorides	16 (94%)
Ethanol	Methanol and ethylene glycol	16 (94%)
Methylene blue	Methemoglobinemia and cyanide	16 (94%)
Phytomenadione	Vitamin K antagonists	16 (94%)
Activated charcoal	General use	15 (88%)
Biperiden	Anticholinergics	15 (88%)
Hydroxocobalamin	Cyanide	15 (88%)
Idaricuzumab	Dabigatran	15 (88%)
N-acetylcysteine	Paracetamol	15 (88%)
Dantrolene	Malignant hyperthermia	14 (82%)
Glucagon hydrochloride	Beta blockers, calcium channel blockers	14 (82%)
Octreotide	Sulfonylureas	14 (82%)
Deferoxamine mesylate	Iron and aluminium	13 (76%)


Number of hospitals
10
9
8
7
6
5
4
3
2
1
0
Hydroxocobalamin
Dantrolene
Sodium thiosulfate
Idarucizumab
Physostigmine
Ethanol
Pralidoxime
Calcium disodium EDTA
Biperiden
Intralipid
Antidotes

Antidotes

- **Tiered system:**
  - **Prehospital: life saving – CBRNe medical team**
  - **ED**
  - **Hospital pharmacy**
  - **Other institution**
    - **Other hospital**
    - **Poison control center**
    - **Seveso industry**
    - **ZOO**
    - **…**

Storage: What?

- **Some national guidelines** (US, UK, Saoudi Arabia, …)
- **No Belgian consensus – guidelines**
- **Risk dependency**
- **Collaboration**
  - Hospital networks
  - Poison control center
  - Industry
  - …

Storage: What?

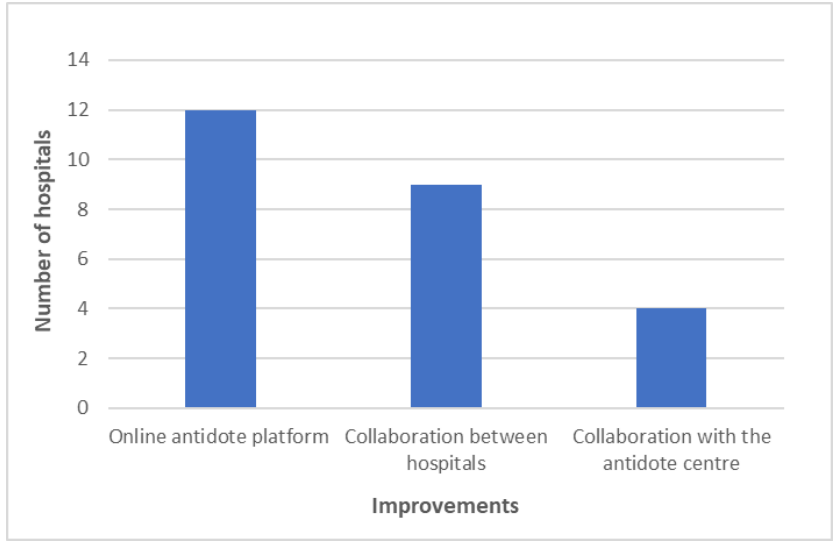
- **Belgian consensus**
  - **Who starts initiative?**
- **Collaboration**
  - **Hospital networks**
  - **Poison control center**
  - **Industry**
  - **…**

Storage: where?

- Tiered system
  - Prehospital
    - No regulation on medical supplies for medical teams
    - Only one CBRNe medical team
  - Hospitals
    - ED or pharmacy?
  - Others
    - Insufficient known

Storage: where?

- Online platform
  - Voluntary?
  - Obligation?
- Hospital collaboration
  - Networks
  - Supra-network
- Increased role PCC



Storage: How much?

Larger incident

- **Previous initiatives**
- **Risk analysis**
- **Centralised – decentralised?**
- **Start with existing number**
  - **But: N = ?**
  - **Online platform**

Conclusions

- Do we want a new face mask incident?
- Different steps are needed
  - Sensibilisation of the needs
    - Politicians
    - Professionals
  - Consensus meetings/Delphi/guidelines
  - Implementation
    - Online platform
    - Storage
- Coordinating role of PCC

Thank you for your attention.