

TOXIC ALCOHOLS

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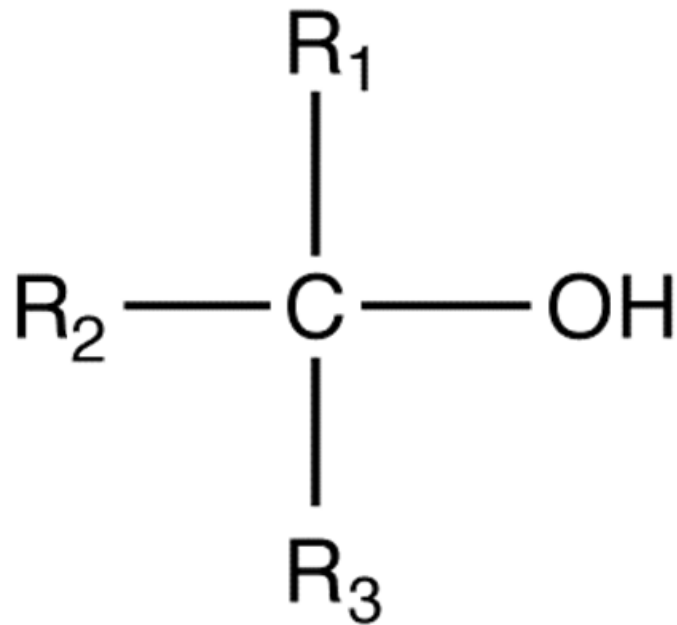
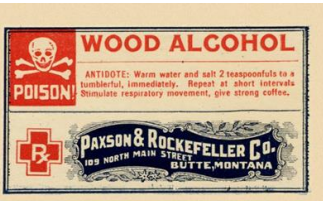
CONFLICTS OF INTERESTS

- None

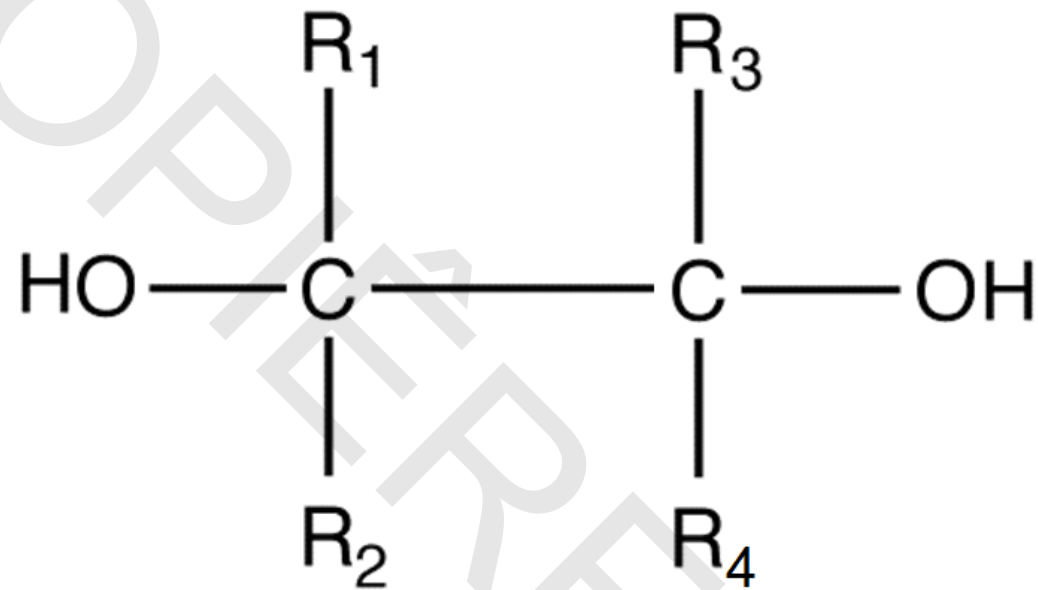
OBJECTIVES

- Assess the risk associated with toxic alcohol exposures
- Understanding the value of diagnostic tests, esp osmol + anion gaps
- Review the value of gastric decontamination, adjuvant treatments, ADH inhibitors, RRT

ALCOOLS ET GLYCOLS



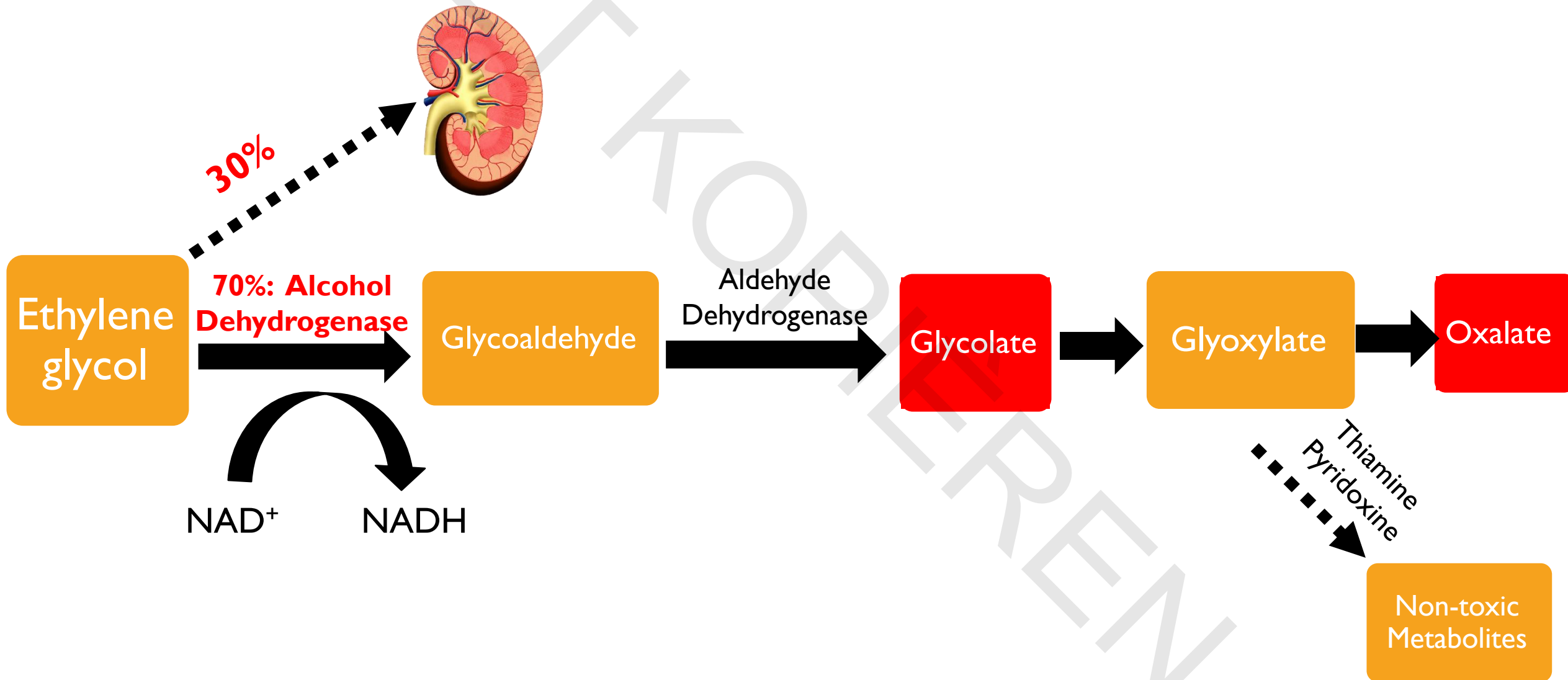
ALCOOL



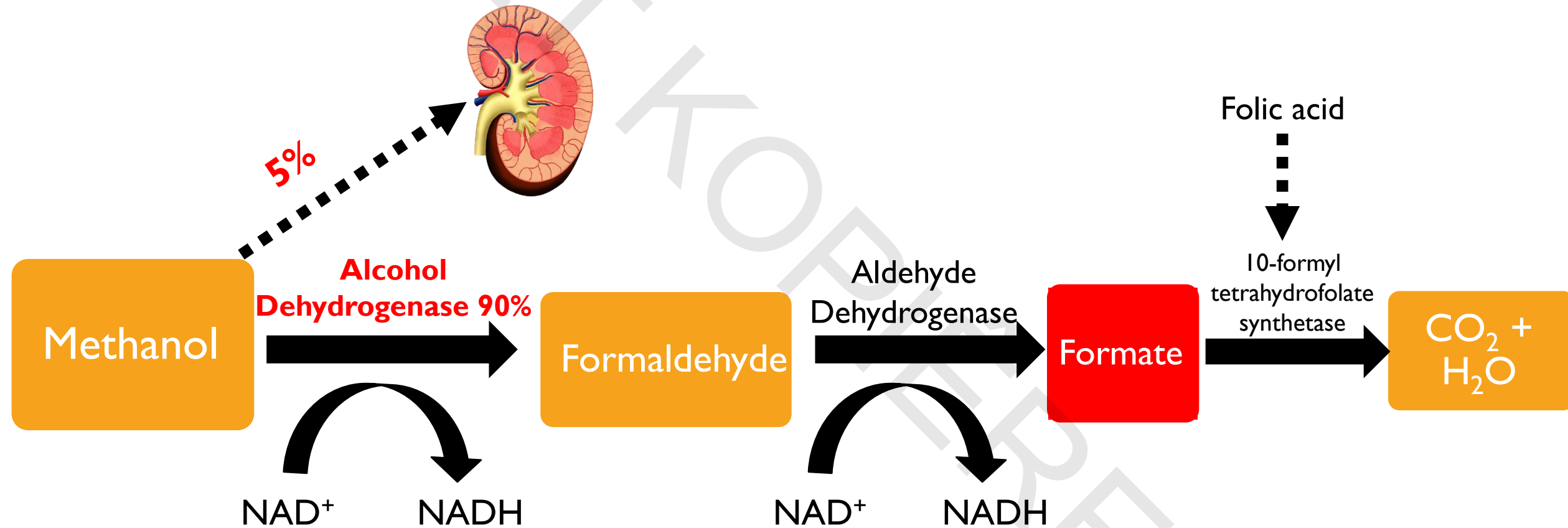
GLYCOL



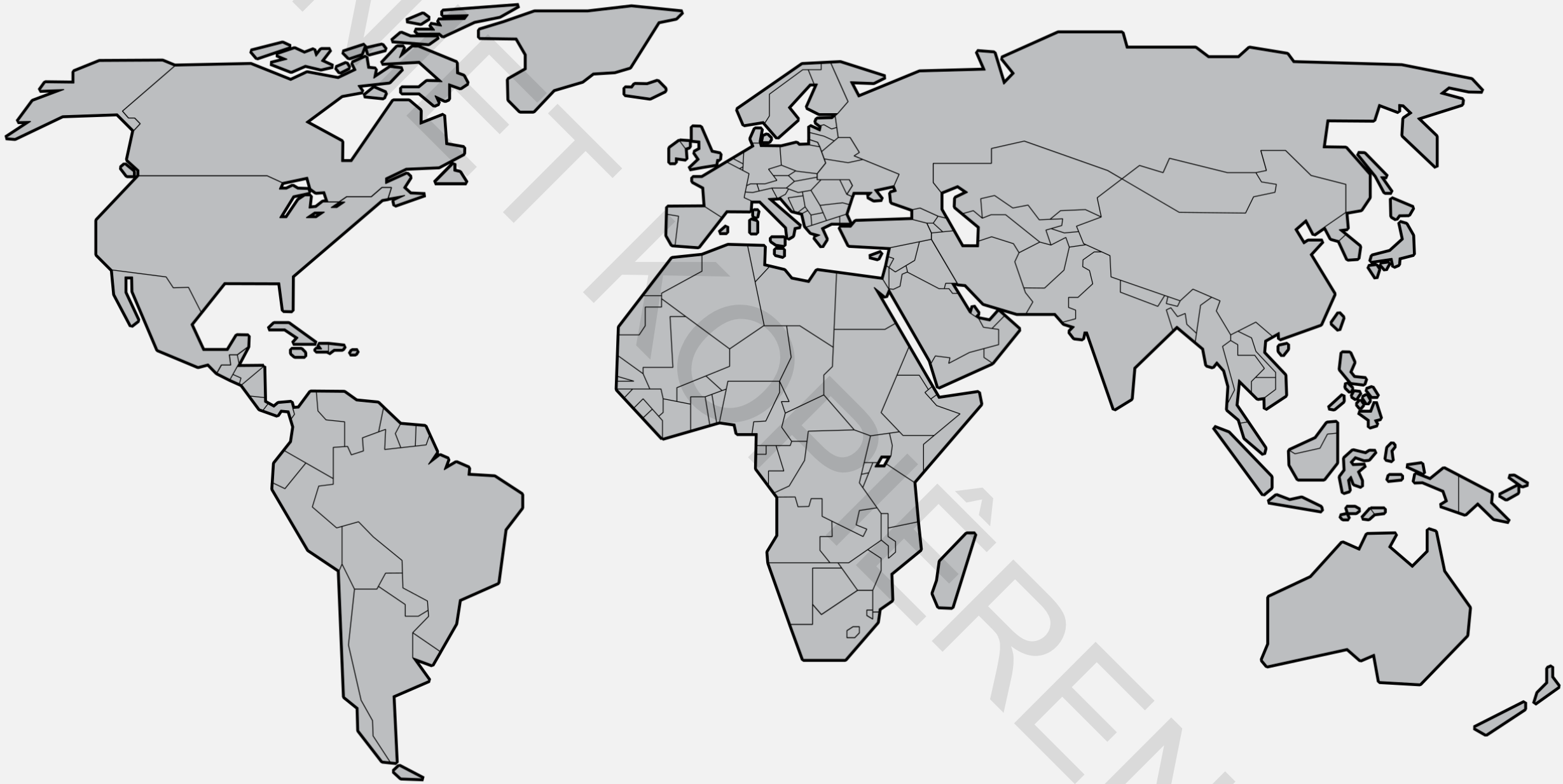
ETHYLENE GLYCOL: METABOLISM + ELIMINATION



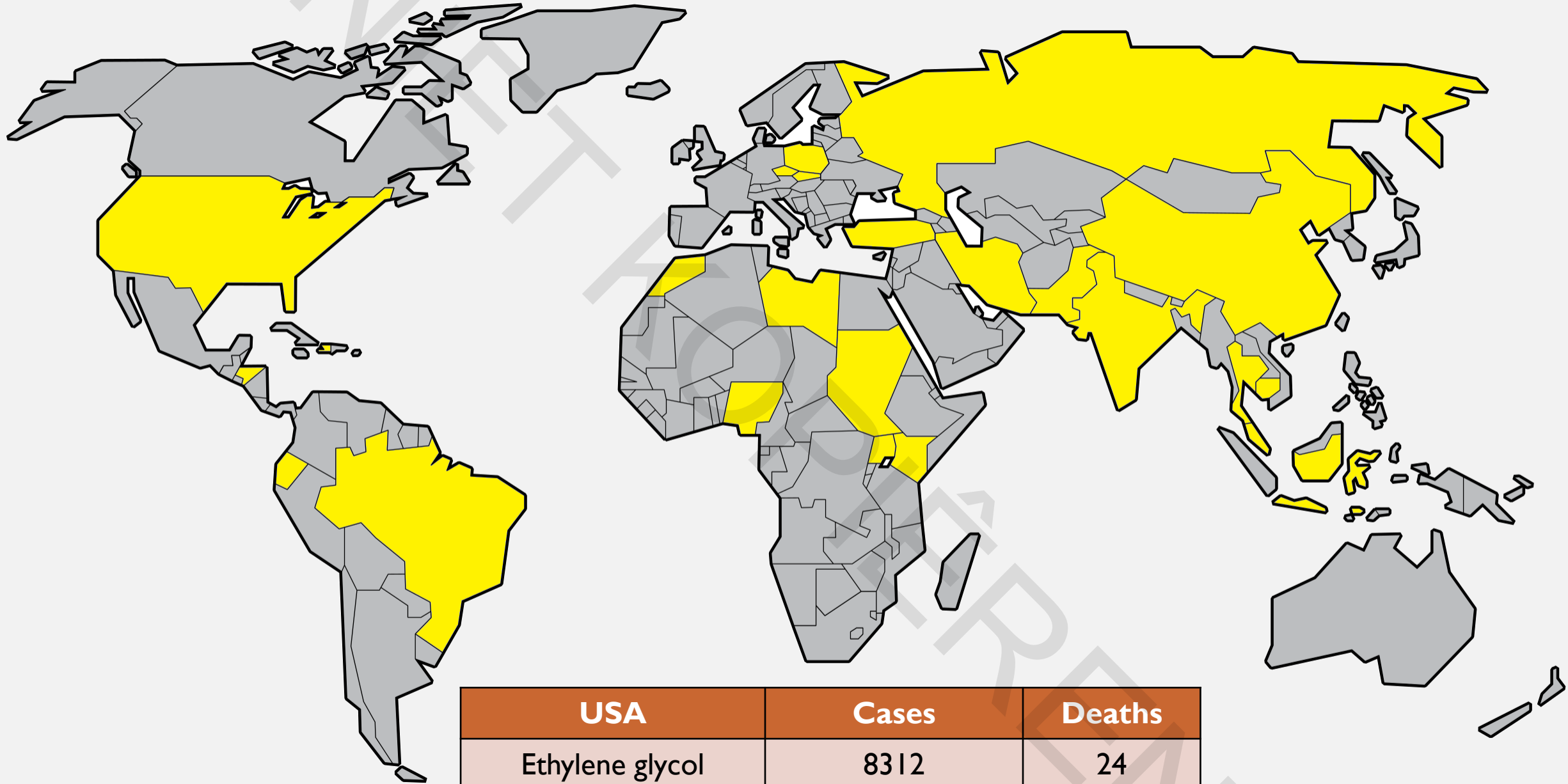
METHANOL: METABOLISM + ELIMINATION



METHANOL OUTBREAKS, 2011-2021, > 50 PATIENTS



METHANOL OUTBREAKS, 2011-2021, > 50 PATIENTS



USA	Cases	Deaths
Ethylene glycol	8312	24
Methanol	2676	16

TOXICITY

	Ethylene glycol	Methanol
Similarities	Early: inebriation	
	↑ AG, metabolic acidosis	
	↑ Osmol gap	
	Late: coma, seizures	

METHANOL: VISUAL MANIFESTATIONS



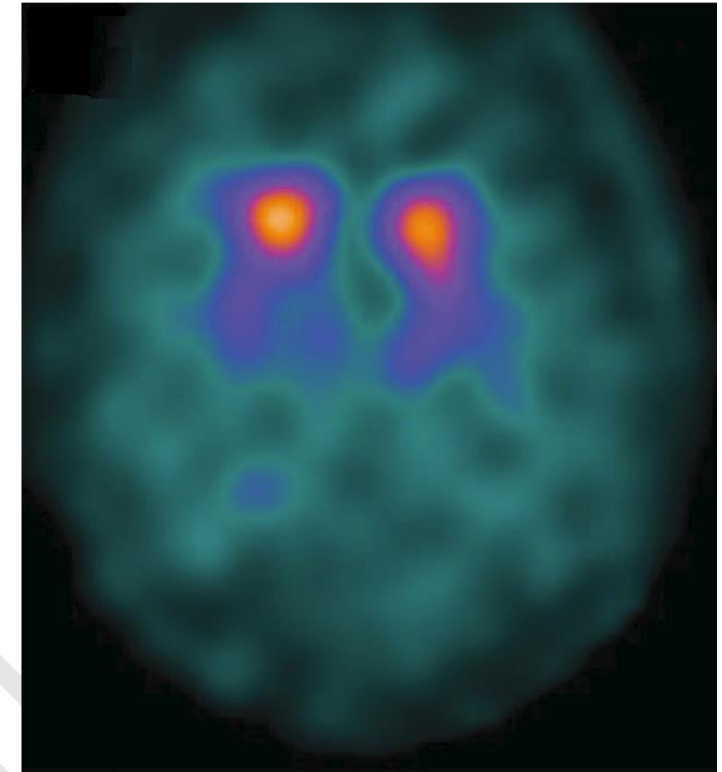
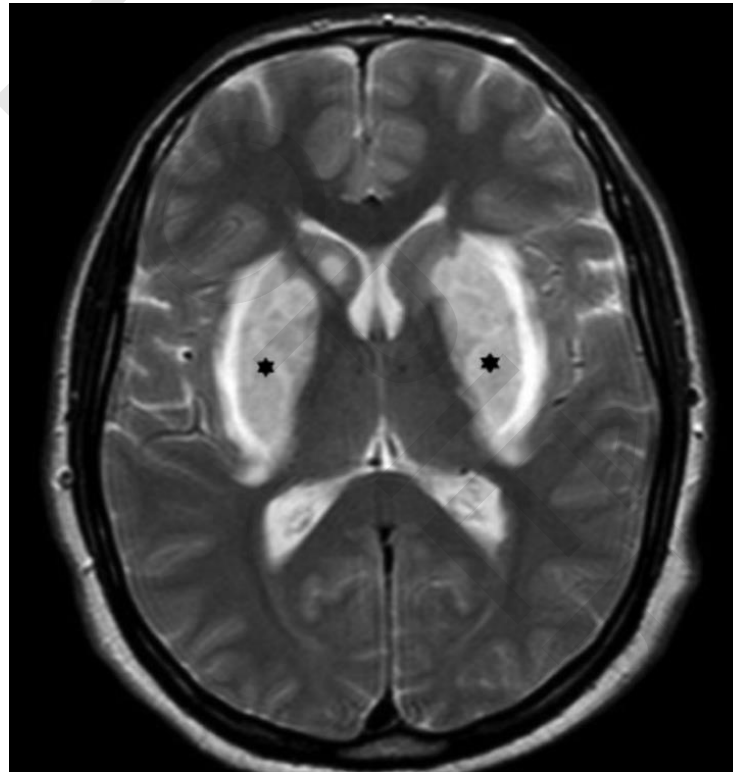
On follow-up: 40% of patients have sequelae, 10% have blindness

Galvez-Ruiz, A., et al. (2015). "Cupping of the optic disk after methanol poisoning." *Br J Ophthalmol* **99**(9): 1220-1223

Zakharov, S., et al. (2015). "Long-term visual damage after acute methanol poisonings: Longitudinal cross-sectional study in 50 patients." *Clin Toxicol (Phila)* **53**(9): 884-892.

METHANOL: BRAIN LESIONS

50% Incidence on MRI
2/3rds are hemorrhagic
Basal ganglia / subcortical white matter



ETHYLENE GLYCOL: AKI

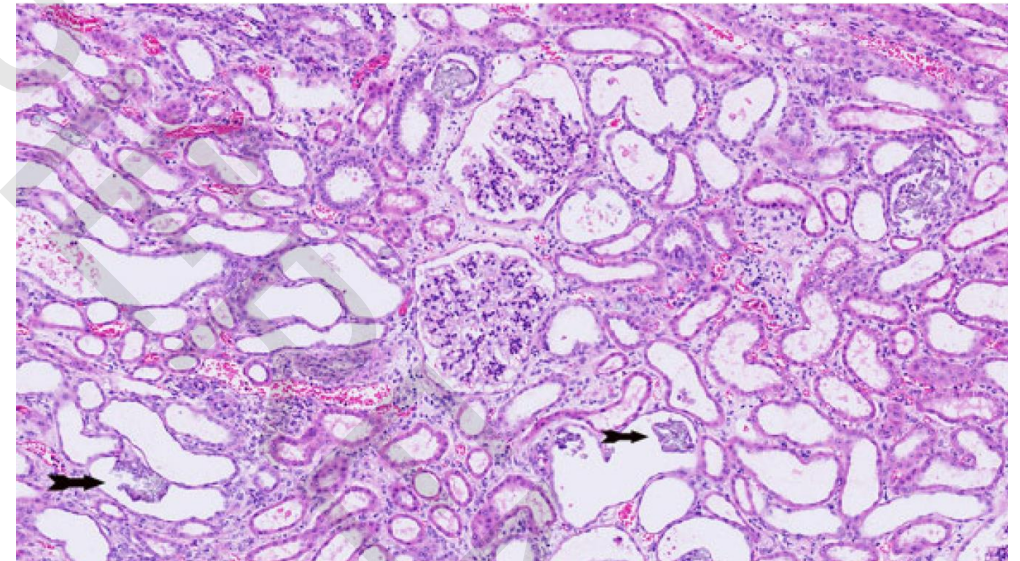
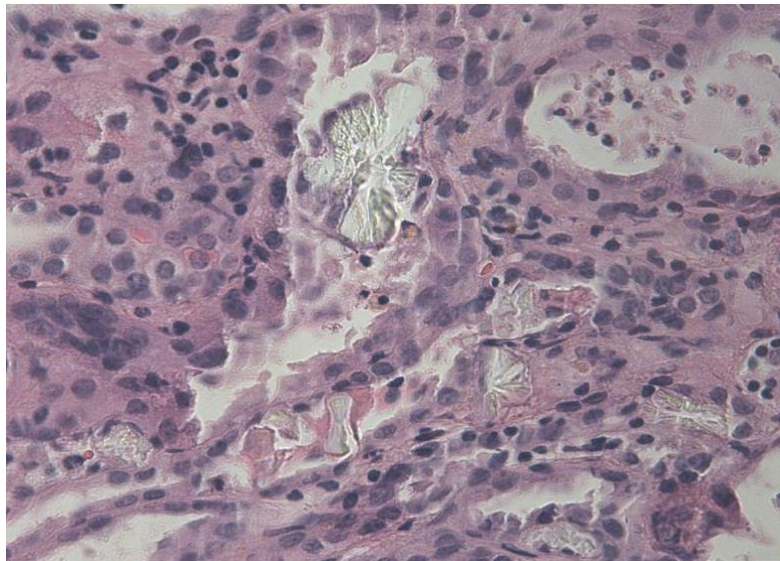
Incidence $\approx$ 60%

Median time of RRT = 7 days

Median time to creatinine normalization = 21 days

Return to baseline in most patients

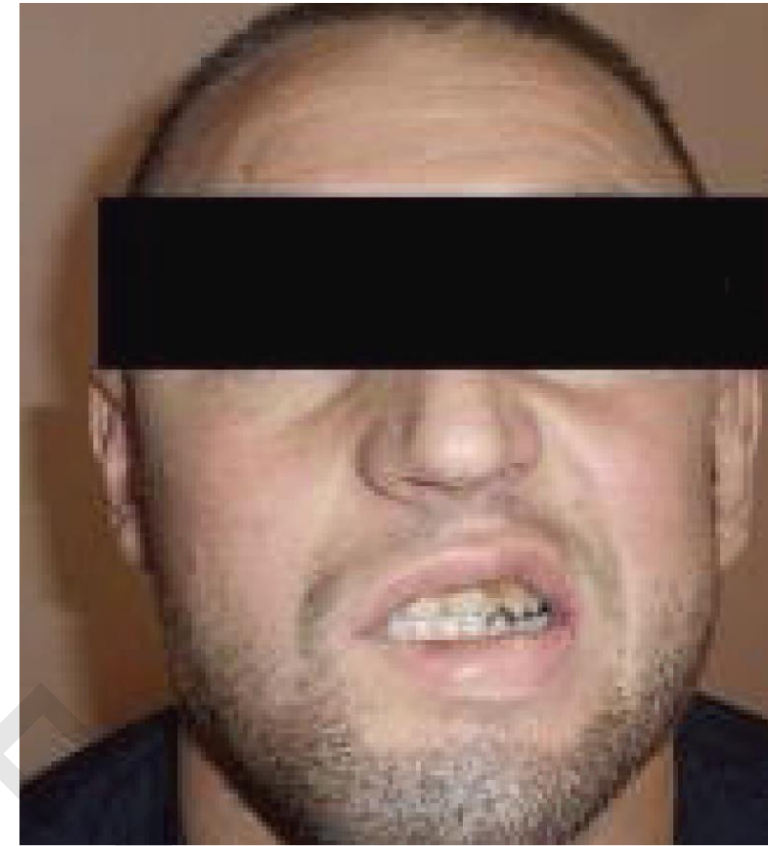
<1% of patients remained dialysis-dependent at 6 weeks



ETHYLENE GLYCOL: CRANIAL NERVE PALSY



Rare
Can occur after 2 weeks
Despite dialysis
Usually resolves spontaneously

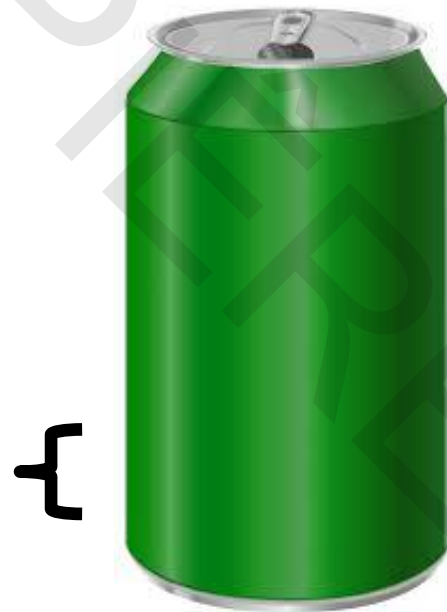


PROGNOSIS

- Mortality
 - up to 70% if untreated
 - 10-30% in outbreaks
 - 5-10% if access to antidotes + dialysis

HOW MUCH IS TOXIC?

- Assuming:
 - 70kg, Untreated $LC_{50} = 12\text{mmol/L}$ (74mg/dL), $V_D = 0.6\text{ L/kg}$, Full absorption
- Lethal dose (untreated) = 30 mL



PROTECTIVE FACTOR: ETHANOL CO-INGESTION

- ETHYLENE GLYCOL: 3-4x less likely of dying or developing AKI

Przegląd Lekarski 1996/53/4

Ethylene Glycol Acute Poisoning Treatment Results in Kraków in the Years 1990-1994

Tomasz STOMPÓR, Agnieszka SZYMCHAKIEWICZ-MULTANOWSKA

Analiza wyników leczenia ostrych zatrueć glikolem etylenowym w Krakowie w latach 1990-1994

Clinical Toxicology, 39(6), 607-615 (2001)

Ethylene Glycol Toxicity: The Role of Serum Glycolic Acid in Hemodialysis

William H. Porter,^{1,*} Philip W. Rutter,¹ Barbara A. Bush,¹ Alex A. Pappas,² and James E. Dunnington³

¹University of Kentucky Medical Center, Lexington, Kentucky

²University of Arkansas for Medical Sciences, Little Rock, Arkansas

³Samaritan Hospital, Lexington, Kentucky

- METHANOL: 5-10x less likely of dying or developing visual symptoms
 - + ethanol level on admission: 0/42 died, 4/42 had sequelae
 - - ethanol level on admission: 21/58 died, 26/58 had sequelae

Zakharov, S., et al. (2016). "Use of Out-of-Hospital Ethanol Administration to Improve Outcome in Mass Methanol Outbreaks." *Ann Emerg Med* **68**(1): 52-61.

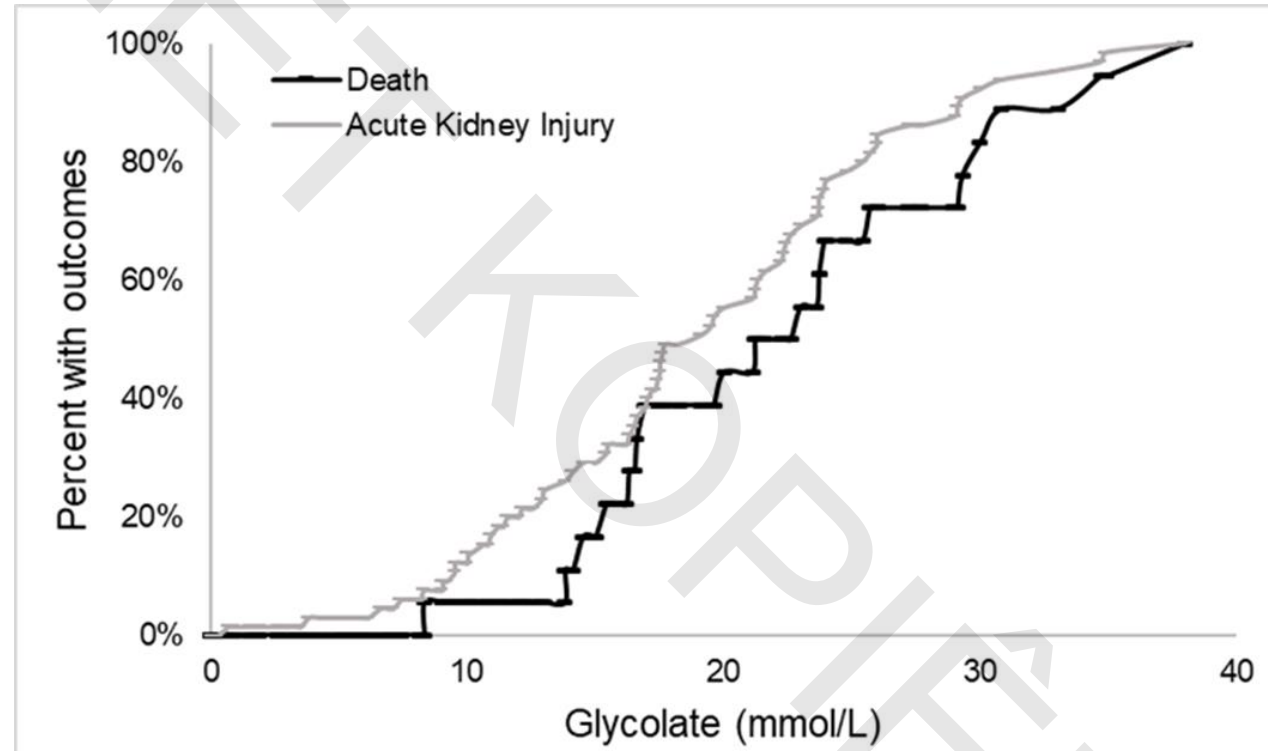
Stompór, T., et al. (1996). "Ethylene glycol acute poisoning treatment results in Krakow in the years 1990-1994." *Przegląd lekarski* **53**(4): 360-364.

Porter, W. H., et al. (2001). "Ethylene glycol toxicity: the role of serum glycolic acid in hemodialysis." *J Toxicol Clin Toxicol* **39**(6): 607-615.

Zakharov, S., et al. (2015). "Long-term visual damage after acute methanol poisonings: Longitudinal cross-sectional study in 50 patients." *Clin Toxicol (Phila)* **53**(9): 884-892.

Zakharov, S., et al. (2015). "Fomepizole versus ethanol in the treatment of acute methanol poisoning: Comparison of clinical effectiveness in a mass outbreak." *Clin Toxicol* **53**(8): 797-806.

PROGNOSTIC VALUE OF METABOLITES



	Symptoms	Sequelae / Mortality
Glycolate (EG)	> 8mmol/L (AKI)	> 12mmol/L
Formate (MeOH)	> 4mmol/L (Visual)	> 12mmol/L

DIAGNOSIS

IF WE HAD RAPID TOXIC ALCOHOL + METABOLITE ASSAYS...

- It would be soooooo easy:
- Toxic alcohol >0  Block ADH
- Metabolite >0  Remove it with dialysis

UNFORTUNATELY..

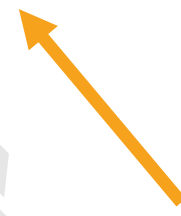
- Parent alcohol assays
 - 2.6% in Irish hospitals
 - 30% in US teaching hospitals
 - 40% of cases never have ANY assay identification in the US and UK
 - Turn-around time $\approx$ 8-12h in the Netherlands
- Metabolite assays
 - Even rarer
- **SO WHAT DO WE DO????**

HOW BEST TO ESTIMATE THE TOXIC ALCOHOL CONCENTRATION???

THE OSMOL GAP

$$= \text{Osmolality} - \text{Osmolarity}$$

- 
- 1) Measured
 - 2) Units: mOsm/KgH₂O
 - 3) Serum osmolality represents the sum of ALL particles in plasma

- 
- 1) Calculation
 - 2) Units: mmol/L
 - 3) Represents the impact of major E⁺, urea, glucose

PROBLEM 1: MANY WAYS TO ESTIMATE OSMOLARITY

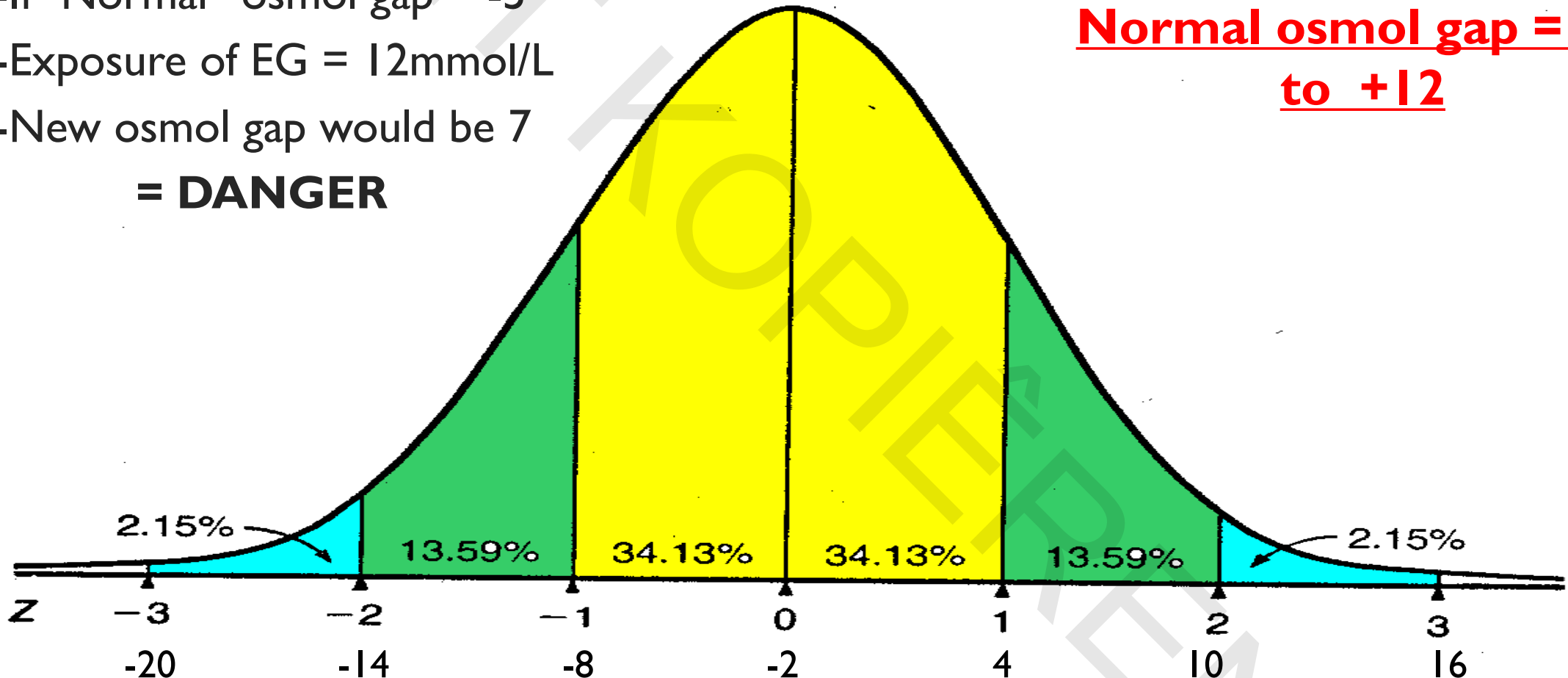
Formula	Reference
$2 \times \text{Na} + \text{Urea} + \text{Glucose} + \text{Ethanol}$	Gennari, 1984
$2 \times (\text{Na} + \text{K}) + \text{Urea} + \text{Glucose} + 1.2 \times \text{Ethanol}$	?
$(1.86 \times \text{Na} + \text{Urea} + \text{Glucose} + \text{Ethanol}) / 0.93$	Aabakken, 1994
$2 \times \text{Na} + \text{Urea} + 1.15 \times \text{Glucose} + 1.2 \times \text{Ethanol}$	Khajuria, 2005
$2 \times \text{Na} + 1.2 \times \text{Urea} + 1.4 \times \text{Glucose} + 1.2 \times \text{Ethanol}$	Lepeytre, 2017

PROBLEM 2: WHAT IS A NORMAL OG?



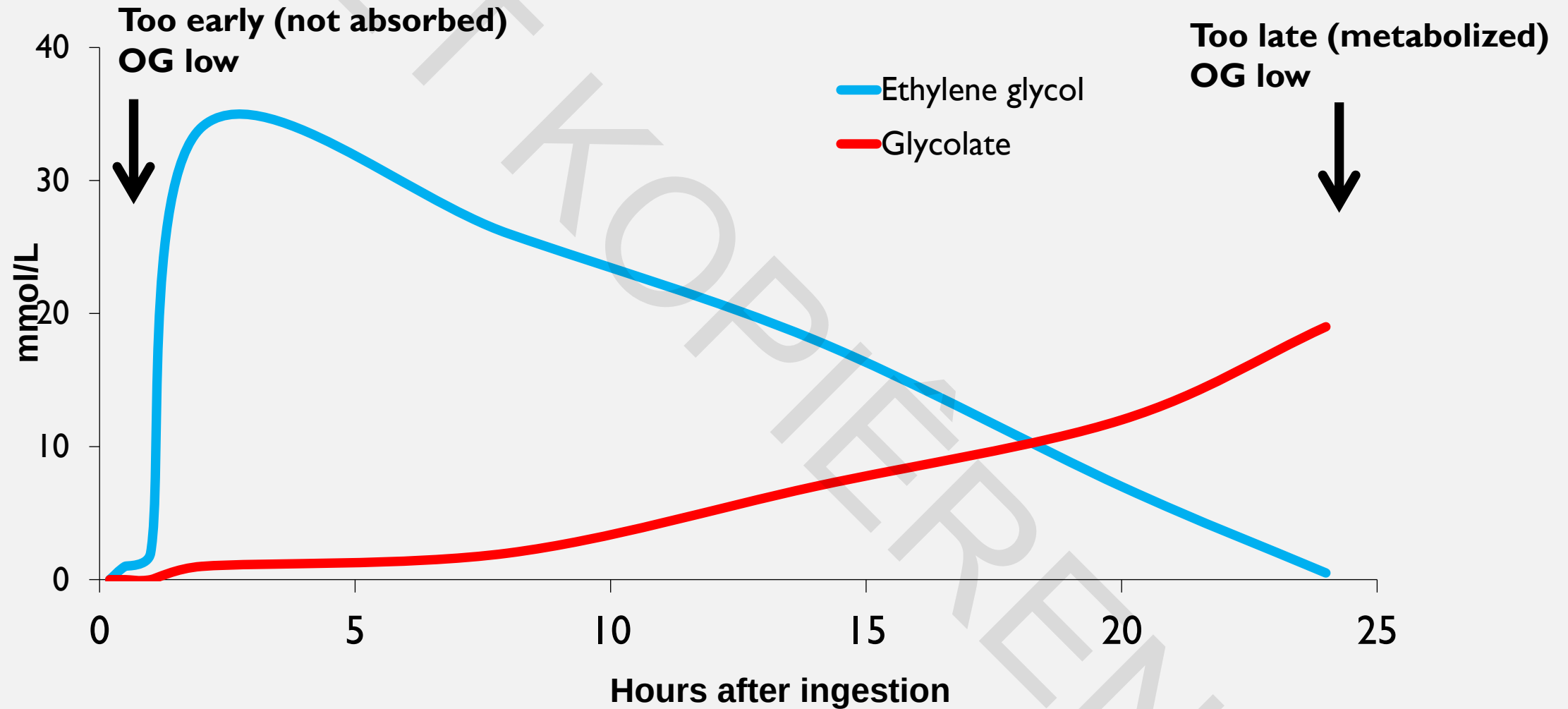
- -If “Normal” osmol gap = -5
- -Exposure of EG = 12mmol/L
- -New osmol gap would be 7
- **= DANGER**

Normal osmol gap = -12
to +12



PROBLEM 3: TIMING

MIND THE GAP

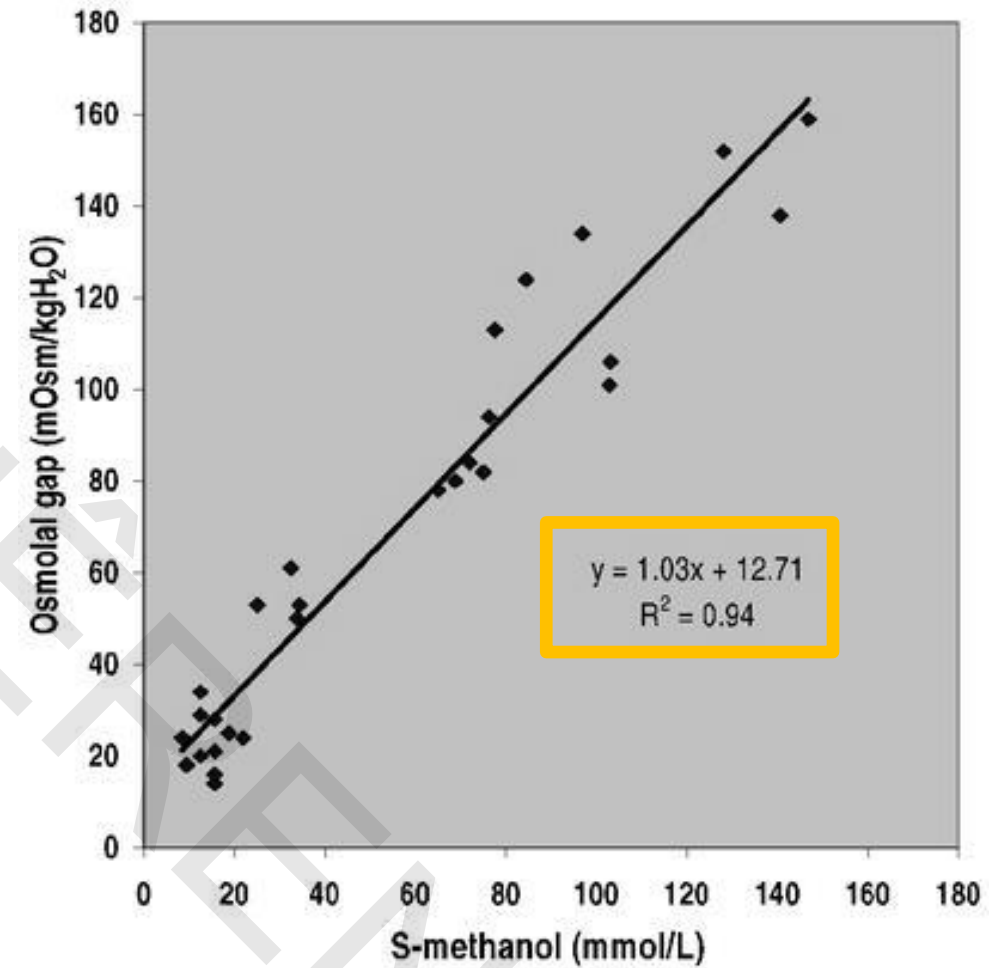
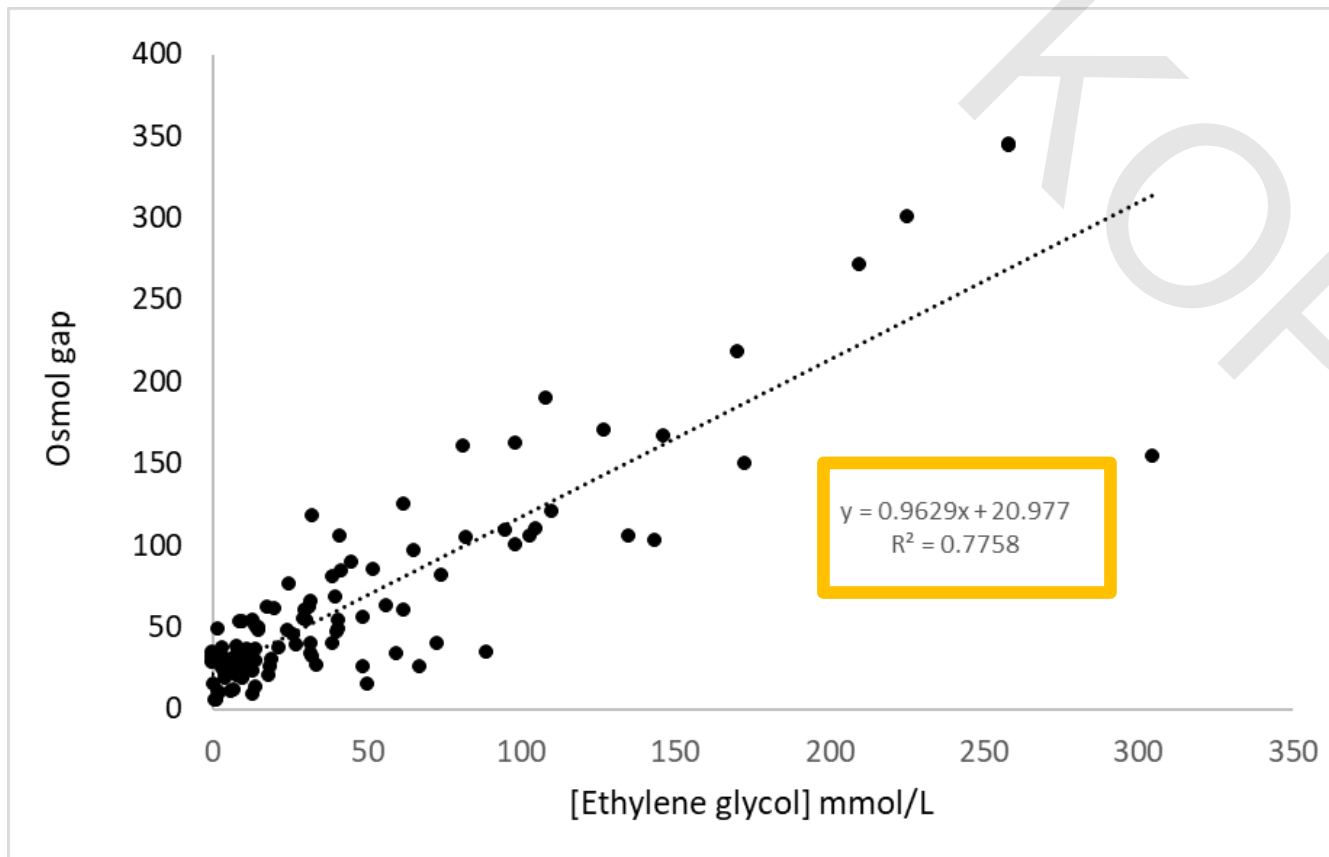


PROBLEM 4: NOT SPECIFIC, NOT SENSITIVE



- 1) A “normal” OG does not exclude toxic alcohols
- 2) A “high” OG can also occur in:
 - AKI/ ESKD
 - Septic shock
 - Diabetic ketoacidosis
 - Alcohol ketoacidosis
 - Mannitol / other alcohols

OG $\approx$ TOXIC ALCOHOL CONCENTRATION

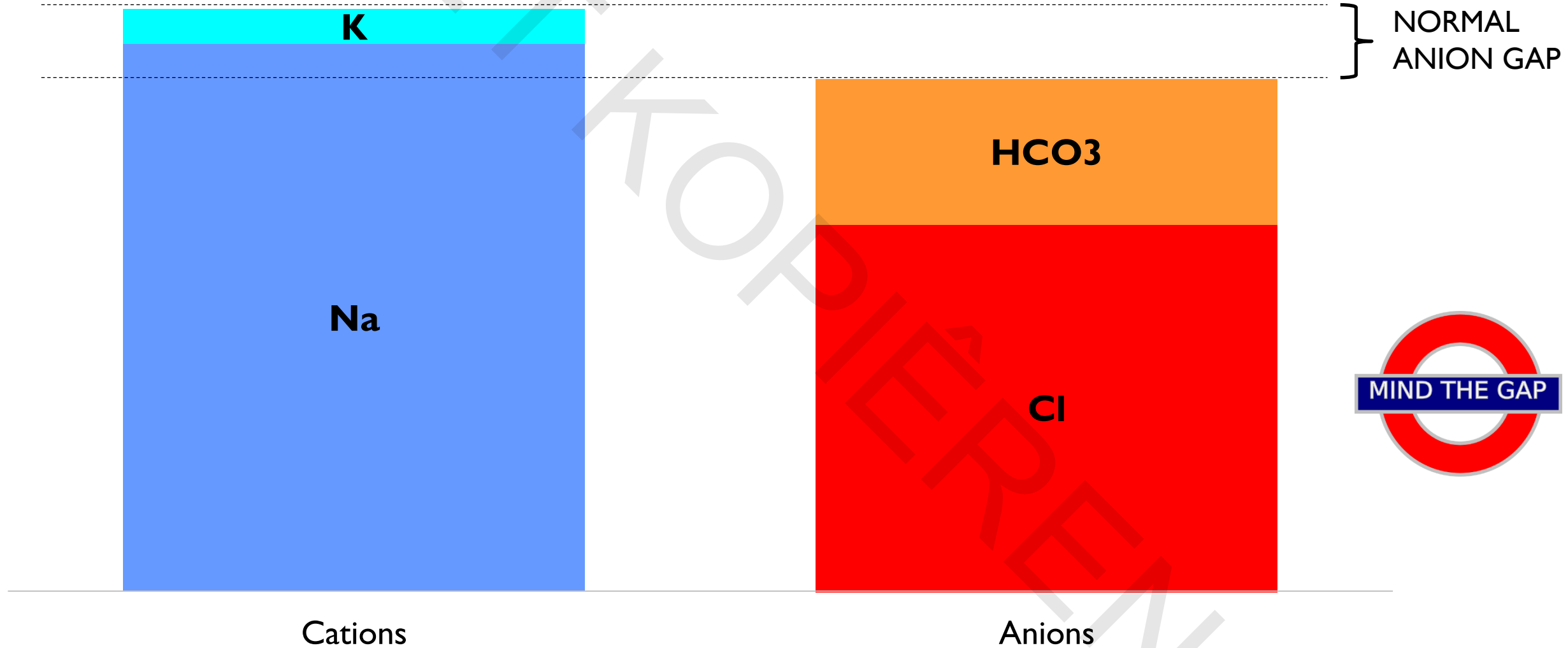


HOW BEST TO ESTIMATE THE METABOLITE CONCENTRATION???

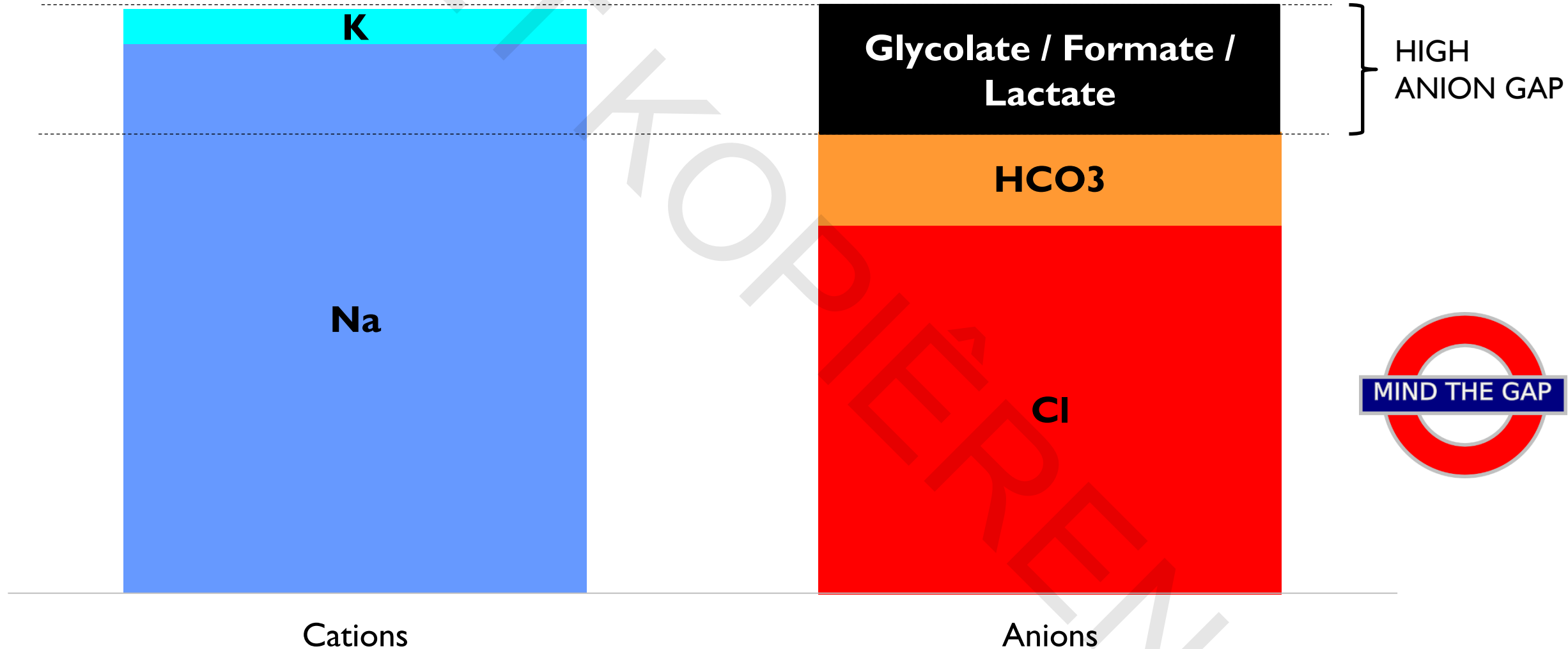
THE ANION GAP

$$= (\text{Na} + \text{K}) - (\text{HCO}_3 + \text{Cl})$$

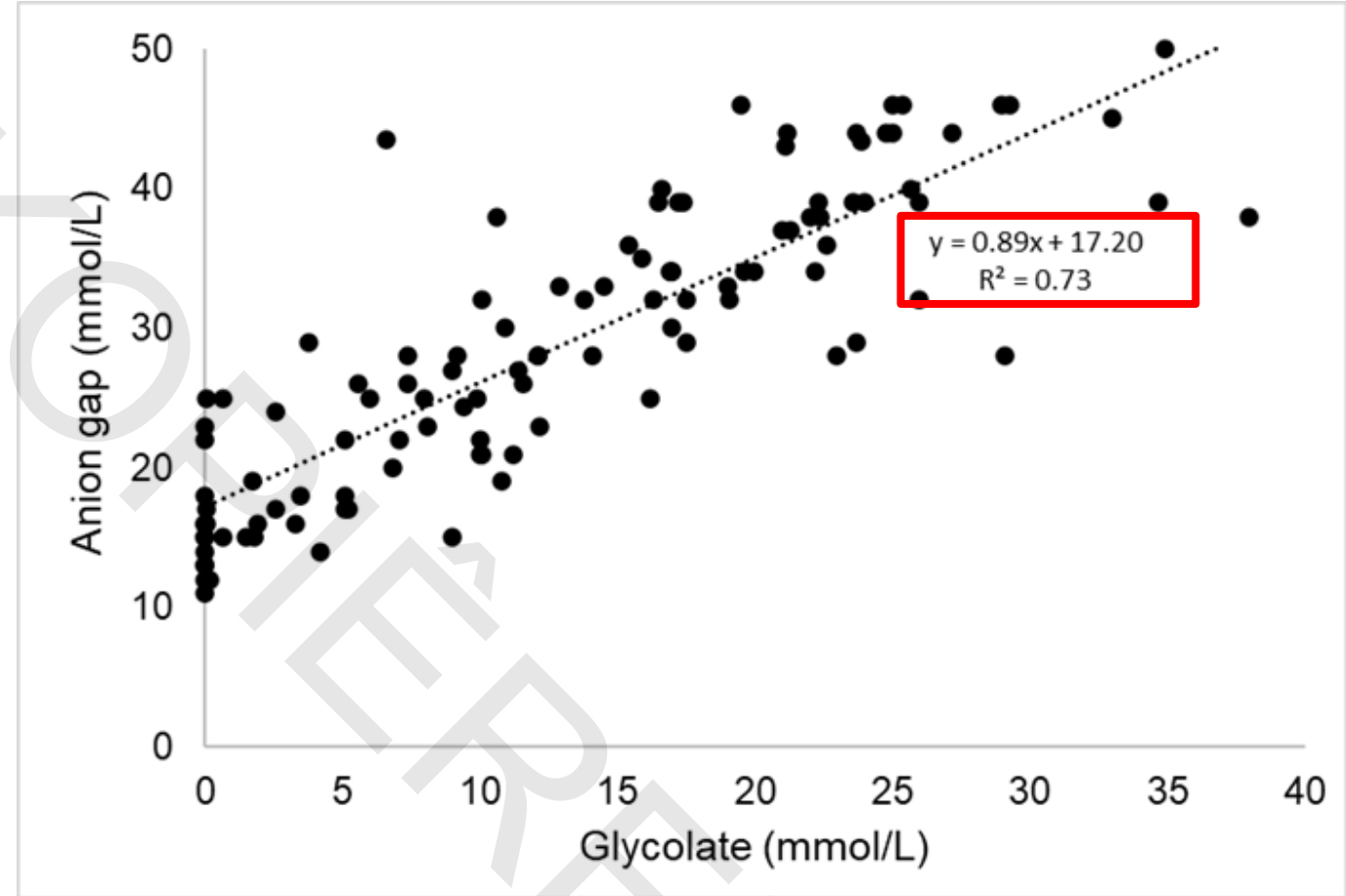
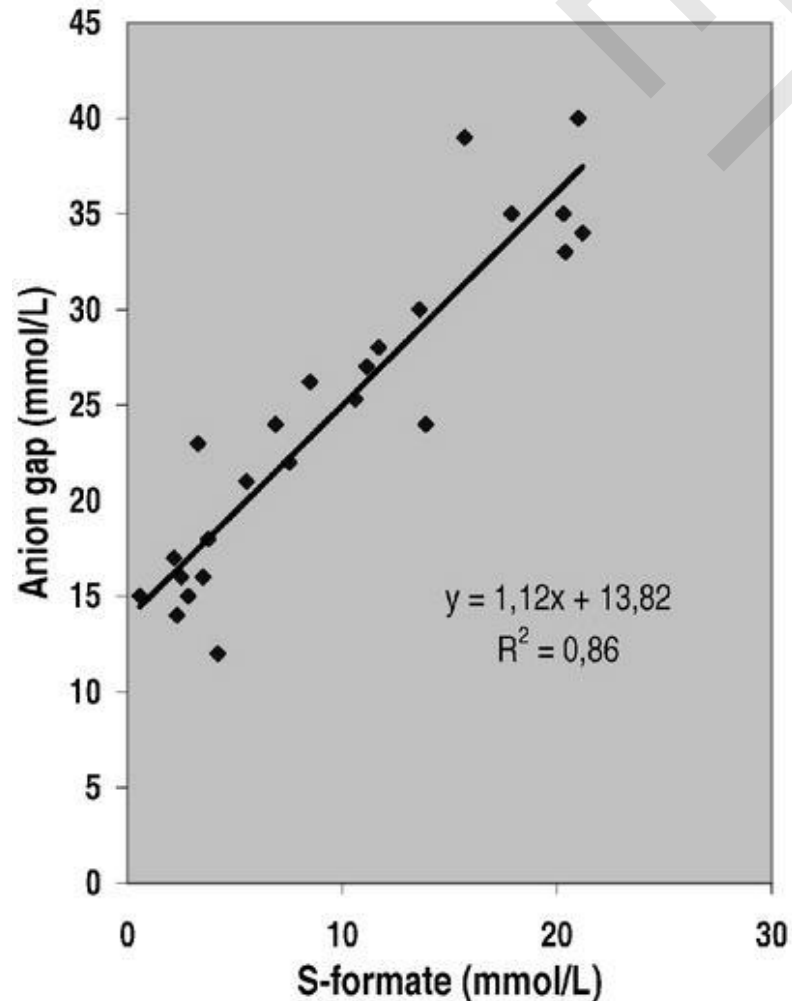
ANION GAP



ANION GAP



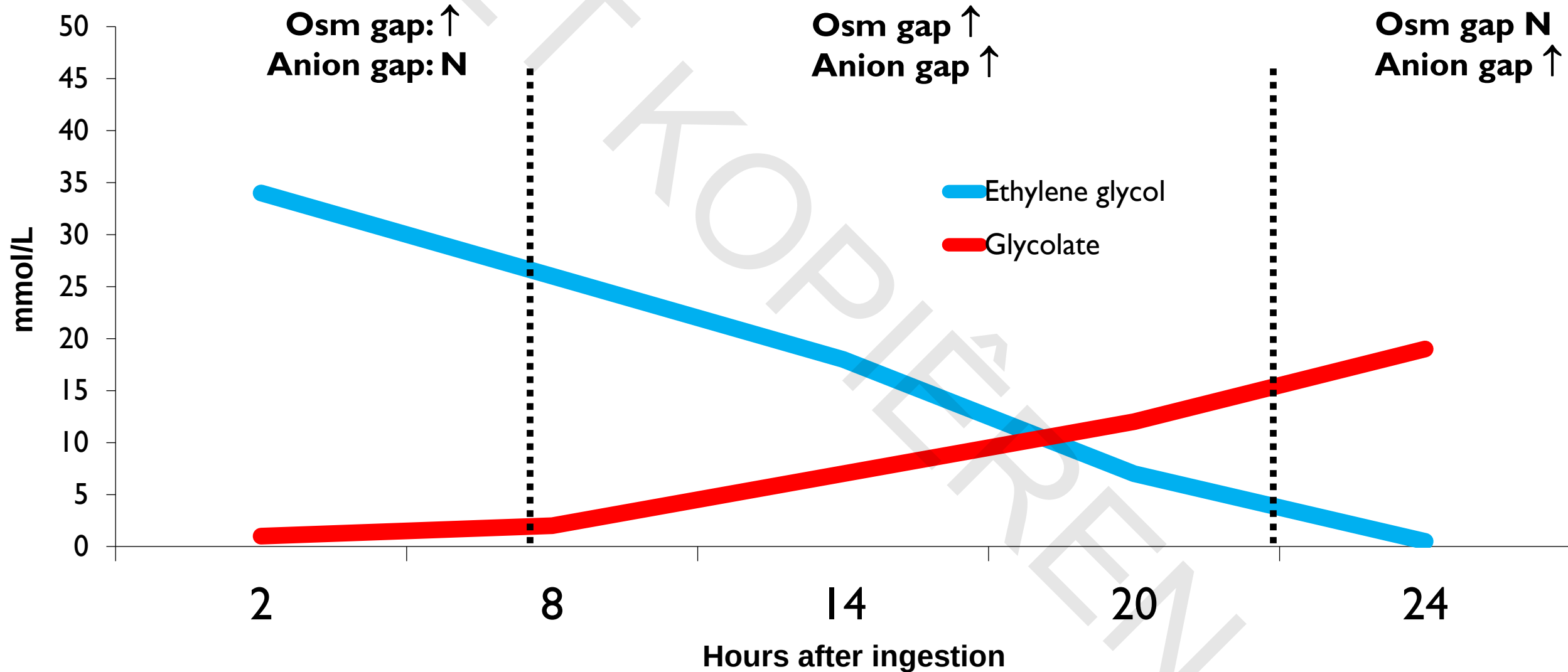
THE ANION GAP CORRELATES WITH METABOLITE CONCENTRATION



Hovda, K. E., et al. (2004). "Anion and osmolal gaps in the diagnosis of methanol poisoning: Clinical study in 28 patients." *Intensive Care Medicine* **30**(9): 1842-1846.

Roberts, D. M., et al. (2022). "The serum glycolate concentration: its prognostic value and its correlation to surrogate markers in ethylene glycol exposures." *Clin Toxicol (Phila)*: 1-10.

OSMOL GAP + ANION GAP



INVESTIGATION

- Na / K / Cl / HCO₃
- Blood gas
- Lactate
- Ethanol
- Serum osmolality
- Kidney function
- Calcium
- Urinalysis
- Toxic alcohol measurement

THE « LACTATE GAP »



POINT-OF-CARE (BLOOD GAS) ANALYZER
Spectrophotometry

Glycolate is read as lactate

Lactate = 12 mmol/L



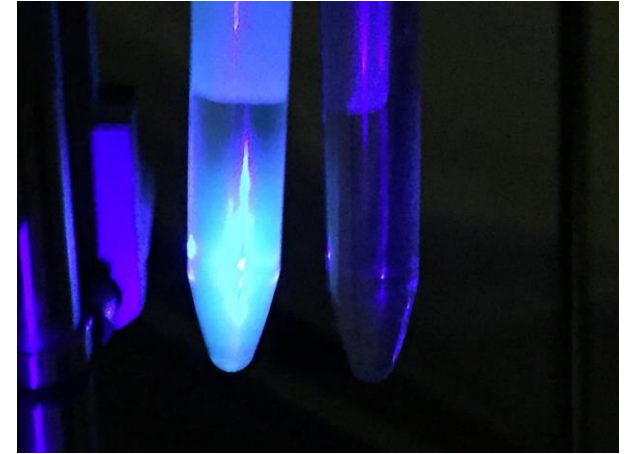
HOSPITAL LABORATORY ANALYZER
Chromatography

Lactate measured correctly

Lactate = 3 mmol/L

OTHER INDIRECT CLUES FOR EG

- Fluorescence¹
 - Fluorescein added to antifreeze (not other forms)
 - Positive test: 100% at 2h, 60% at 4h
- Calcium oxalate crystals²
 - Present in 60% of patients
 - Not specific
- Hypocalcemia³
 - No clear association



1) Casavant, M. J., et al. (2001). "Does fluorescent urine indicate antifreeze ingestion by children?" *Pediatrics* **107**(1): 113-114.

2) Koda, R., et al. (2017). "Calcium oxalate monohydrate crystals in ethylene glycol poisoning." *Clin Exp Nephrol* **21**(4): 741-742.

3) Lim, C., et al. (2017). "Evaluating the Lo-Cal option in ethylene glycol poisoning." *Clinical Toxicology* **55**: 825-826..

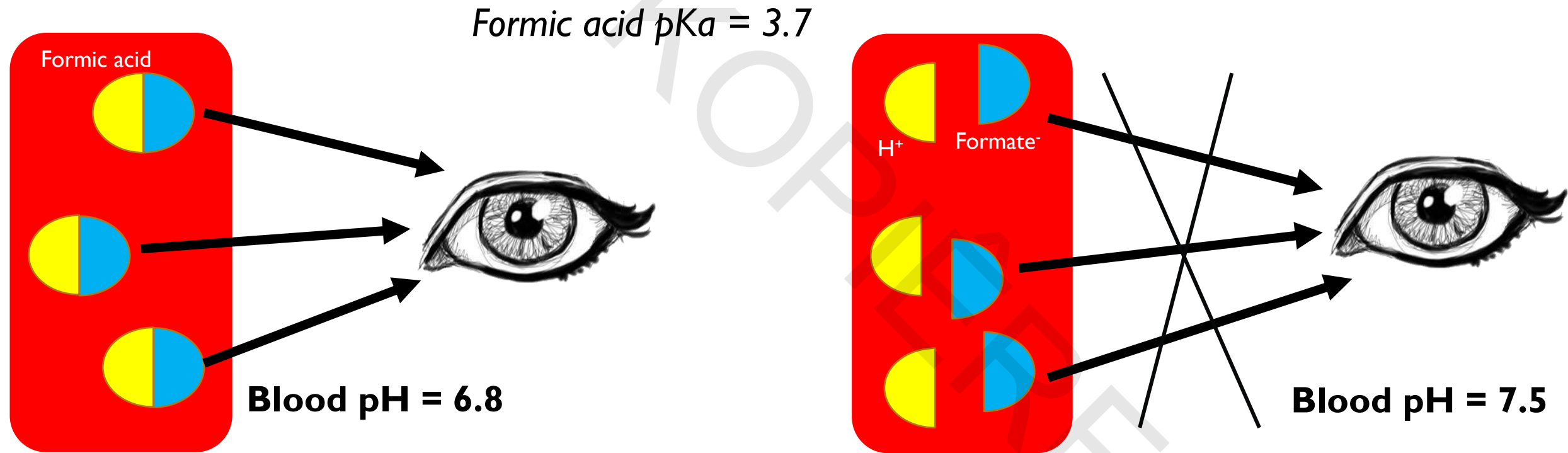
MANAGEMENT

DECONTAMINATION? NO!

- Alcohols are absorbed quickly (< 1 hour)
- Charcoal doesn't bind alcohols
- Risk of caustic injury
- Delays everything else



BICARBONATE: ↓ TOXICITY OF METHANOL



ETHANOL VS FOMEPIZOLE

- Affinity for Alcohol Dehydrogenase
 - Ethylene glycol = 1, Methanol = 1
 - Ethanol = 10
 - Fomepizole = 1000
 - Isopropanol = 5

ETHANOL VS FOMEPIZOLE EFFICACY

Meta-analysis, up to 2012, 145 articles

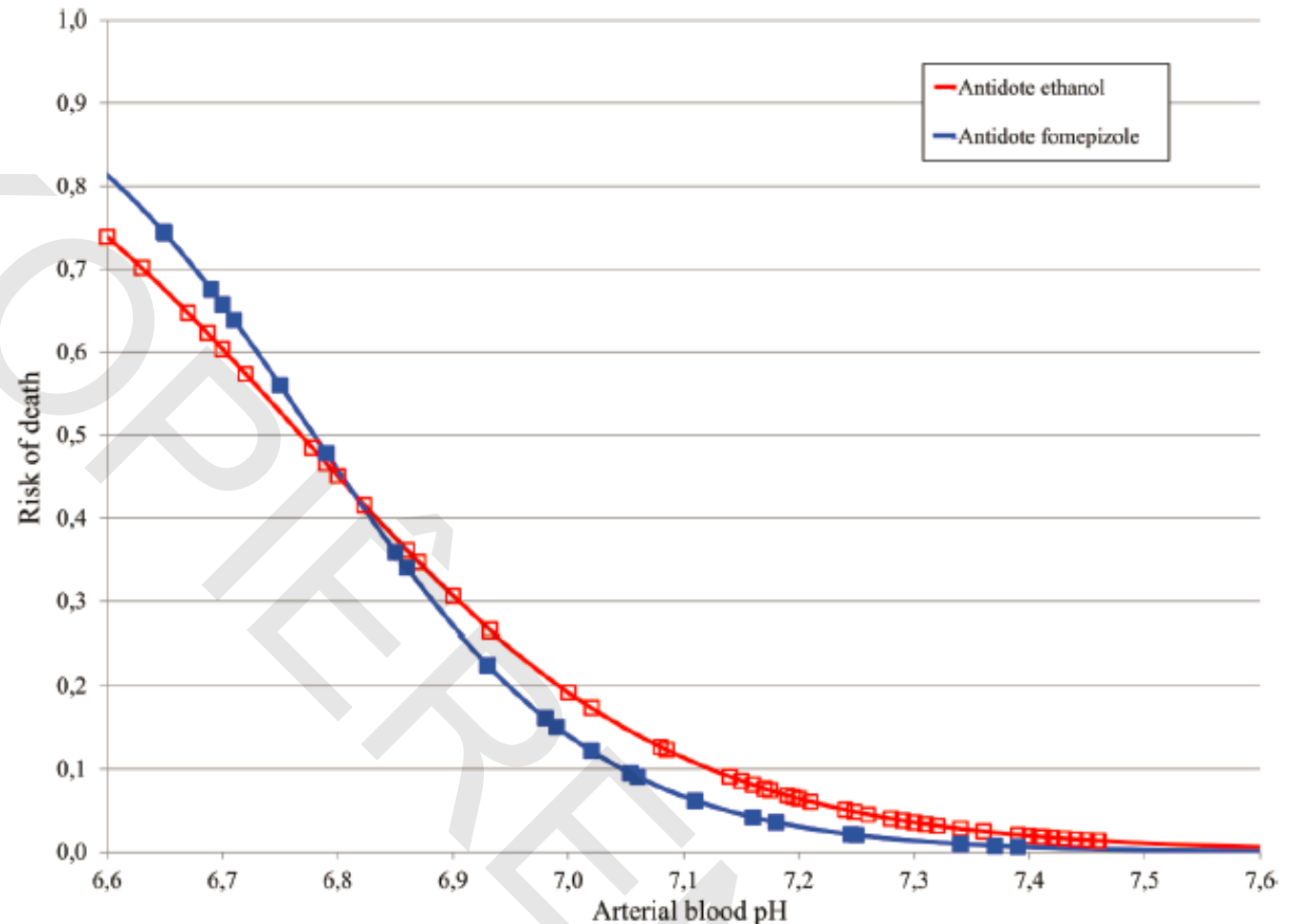
	Mortality Ethanol	Mortality Fomepizole
Ethylene glycol	18% (n=215)	4% (n=65)
Methanol	22% (n=505)	17% (n=81)

- “until further evidence on the use of ethanol and fomepizole is available, either antidote may be considered for ADH blockade.”

ETHANOL VS FOMEPIZOLE

- 25 pts fomepizole vs 68 pts ethanol
- Matched for severity
- ICU LOS
- Survival
- Sequelae
- Need for RRT

P= NS



ETHANOL VS FOMEPIZOLE ADVERSE EVENTS

	Decreased consciousness	Coma	Bradycardia / hypotension
Ethanol (n=145)	7%	6%	12%
Fomepizole (n=44)	0%	2%	2%

“Ethanol administration is associated with higher risk of medication errors and adverse reactions.”

ETHANOL VS FOMEPIZOLE ADVERSE EVENTS

	Adverse reactions	Administration errors, lack of monitoring, or inappropriate use
Ethanol	16/131	45/131
Fomezpirole	2/125	6/125
<i>P-value</i>	<i>$p < 0.001$</i>	<i>$p < 0.0001$</i>

ETHANOL VS FOMEPIZOLE CAN AVOID DIALYSIS?

- Systematic review: 115 publications
- Failure defined as death, Δ AG / HCO_3^- / BE more than 5 mmol/L, Δ creatinine more than 100 $\mu\text{mol/L}$, ECTR, neurological worsening
- 180 Ethanol monotherapy
 - 17% failed
 - 6 patients failed despite normal kidney function and modest acidosis
- 231 Fomepizole monotherapy
 - 9% failed
 - 2 patients failed despite normal kidney function and modest acidosis
 - both survived: one had a seizure, the other had a decrease in HCO_3^- from 17 to 11 mmol/L

FOMEPIZOLE VS ETHANOL COMPLEX MONITORING?

- Need to check serum ethanol q 1-2h
- Some centers have no ETOH assays (or they take long to get back)
- 22-30mmol/L: only 30% of the time
- 30% of the time the ETOH concentration was over 33mmol/L...!

ETHANOL VS FOMEPIZOLE

	Ethanol	Fomepizole
Prevents toxicity?		
Safe?		 
Easy administration?		 
Requires ICU admission?		 
May eliminate need for dialysis?		 
Easy monitoring?		 
Cost	 	   

INDICATIONS FOR FOMEPIZOLE OR ETHANOL

Clinical Toxicology, 37(5), 537–560 (1999)

American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning

Donald G. Barceloux, Edward P. Krenzelok, Kent Olson, and William Watson (*Ad Hoc* Committee on the Treatment Guidelines for Ethylene Glycol Poisoning on Behalf of the American Academy of Clinical Toxicology)

- Documented ingestion
- Methanol or EG > 20mg/dL
- High suspicion (e.g., oxalate crystals + met acidosis)
- Osmol gap, depending on pre-test probability
 - Over 30-40: most, even if no clinical suspicion
 - Over 10: if strong clinical suspicion

Akhtar, J., et al. (2007). "When to Stop Fomepizole Administration? Is 20 mg/dl too Low?" Clinical Toxicology **45**: 362.

Liu, Y. S., et al. (2020). "Outcomes After Recurrent Intentional Methanol Exposures Not Treated With Alcohol Dehydrogenase Inhibitors Or Hemodialysis." J Emerg Med **58**(6): 910-916.

Miller, H., et al. (1999). "American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee." J Toxicol Clin Toxicol **37**(5): 537-560.

DOSAGE OF ANTIDOTE

	43% ethanol po (scotch) [EtOH] = 20-22 mmol/L	10% IV ethanol*	Fomepizole
	1.8 mL/kg then 0.2 ml/kg/h (0.46 if alcoholic)	7.6 mL/kg then 0.8 ml/kg/h (2 if alcoholic)	15 mg/kg then 10mg/kg q12h x4 then 15mg/kg q12h
RRT	0.5 mL/kg/h 0.77 mL/kg/h (alcoholic)	2.1 mL/kg/h 3.3 mL/kg/h	10 mg/kg q4h (q8h for CKRT?)

- Thiamine 100mg/day
- Pyridoxine 100mg/day
- Folinic acid 300mg 1st dose, then folic acid 50mg q6h

TOXIC ALCOHOLS ARE IDEAL DIALYZABLE TOXINS

- Small
- Protein binding = 0%
- Small V_D (0.6 L/Kg)
- Low endogenous clearance after ADH inhibition

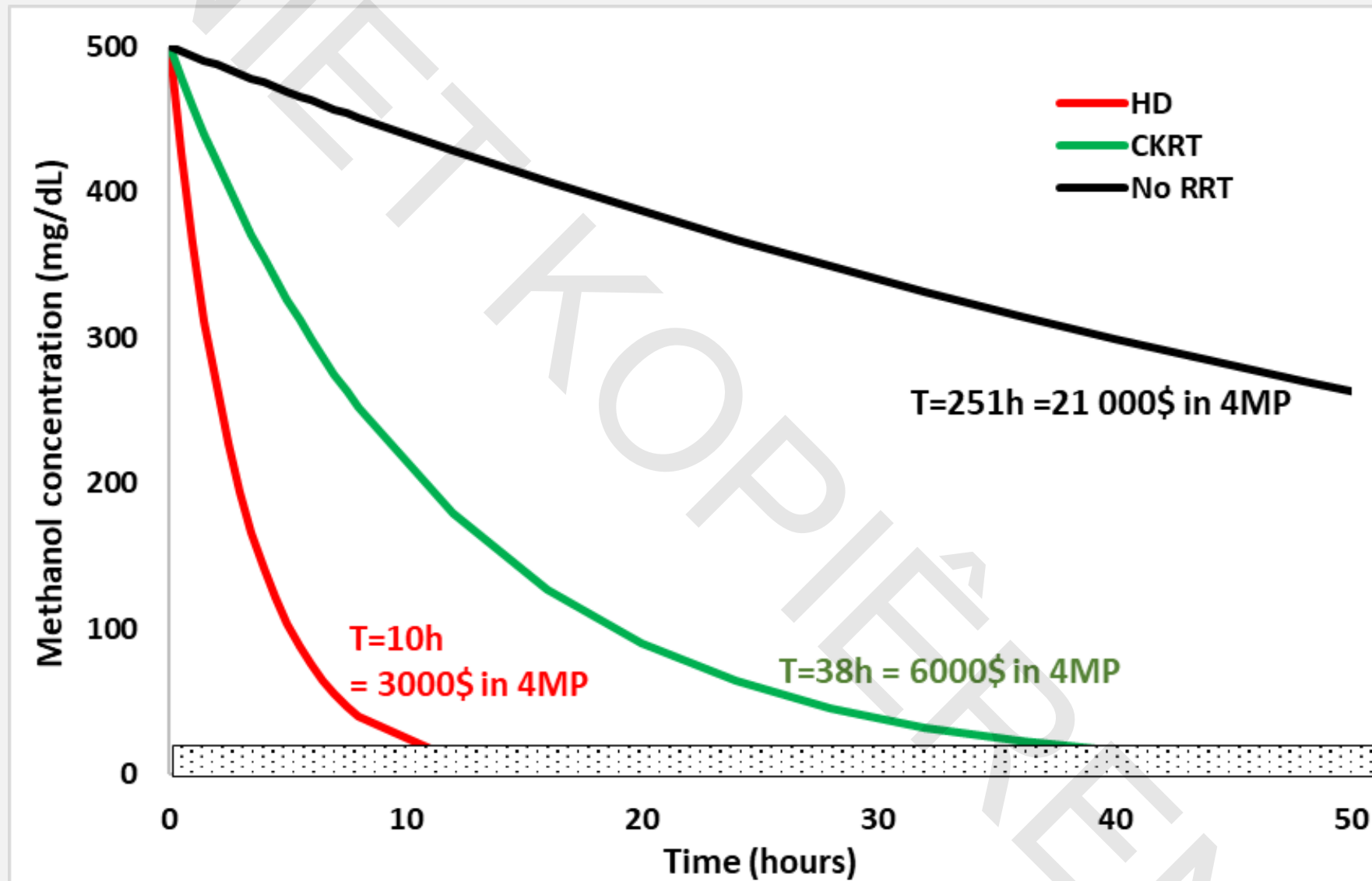
Alcohol	Molecular size (g/mol)
Ethanol	46
Methanol	32
Ethylene glycol	62
Diethylene glycol	106
Propylene glycol	76
Isopropanol	60

INDICATIONS FOR DIALYSIS

- End-organ injury
 - AKI
 - Coma, seizures
 - Visual symptoms (MeOH)
- Glycolate / Formate $>8\text{mmol/L}$ ($\approx\text{AG}$ with $\text{K} >24$)
- Question: What about a specific methanol or EG concentration??



COST: METHANOL



Roberts, D. (2019). "Cost-assessment of the use of fomepizole for the treatment of toxic alcohol poisonings in Australian practice." *Clinical Toxicology* **57**(12): 1202.

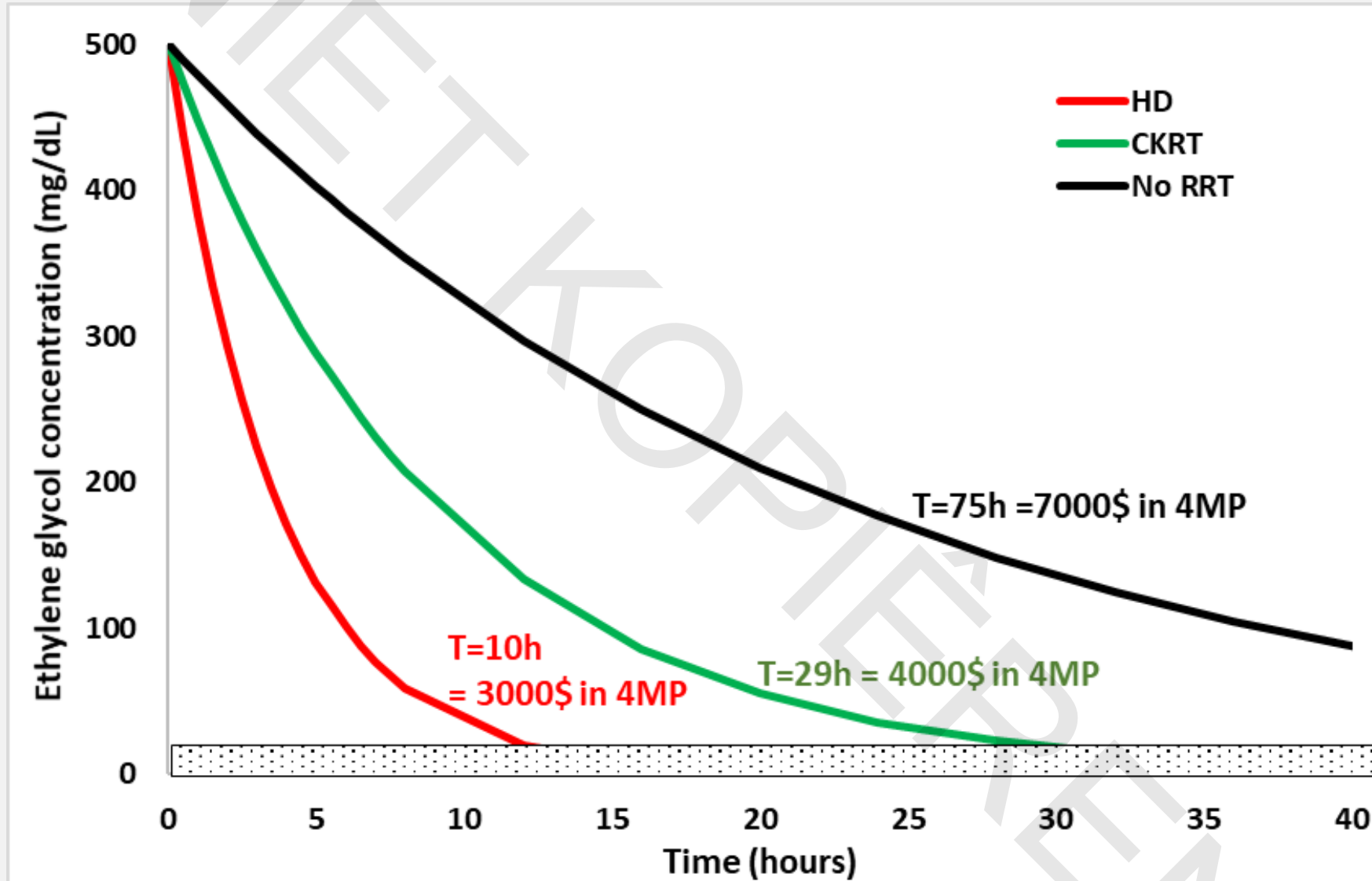
Ellsworth, H., et al. (2011). "A cost comparison of fomepizole and hemodialysis in the treatment of methanol and ethylene glycol toxicity." *Clinical Toxicology* **49**: 590-591.

Donovan, J. W., et al. (1998). "A comparison of fomepizole with hemodialysis vs fomepizole alone in therapy of severe ethylene glycol toxicity." *Clinical Toxicology* **36**(5): 451-452.

Cannarozzi, A. A. and M. E. Mullins (2010). "A cost analysis of treating patients with ethylene glycol poisoning with fomepizole alone versus hemodialysis and fomepizole." *Clinical Toxicology* **48**(3): 299-300.

Darragh, M. A., et al. (2013). "Cost of hemodialysis versus fomepizole-only for treatment of ethylene glycol intoxication." *Clin Toxicol* **51**(3): 188.

COST: ETHYLENE GLYCOL



Roberts, D. (2019). "Cost-assessment of the use of fomepizole for the treatment of toxic alcohol poisonings in Australian practice." *Clinical Toxicology* **57**(12): 1202.

Ellsworth, H., et al. (2011). "A cost comparison of fomepizole and hemodialysis in the treatment of methanol and ethylene glycol toxicity." *Clinical Toxicology* **49**: 590-591.

Donovan, J. W., et al. (1998). "A comparison of fomepizole with hemodialysis vs fomepizole alone in therapy of severe ethylene glycol toxicity." *Clinical Toxicology* **36**(5): 451-452.

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Darragh, M. A., et al. (2013). "Cost of hemodialysis versus fomepizole-only for treatment of ethylene glycol intoxication." *Clin Toxicol* **51**(3): 188.

WHEN TO STOP DIALYSIS?

- **#1: Most Important: No metabolites = Normal AG**
- #2: Disappearance of parent alcohol , $[] < 20\text{mg/dL}$



RRT PRESCRIPTION

- Phosphate / Mg replacement
- Higher fomepizole/ ethanol dose
- Anticoagulation?
 - No association between brain hemorrhages and systemic anticoagulation
- Risk of ethanol withdrawal

ISOPROPANOL: METABOLISM + ELIMINATION

Isopropanol

Alcohol
Dehydrogenase

Acetone

NAD^+

NADH



CONCLUSION

- Anion + osmol gaps are crucial for diagnosis
- Treatment
 - Parent alcohol = ADH inhibition
 - Metabolites or Symptoms (coma, AKI, seizures, visual Sx) = RRT
- Website: www.extrip-workgroup.org
- Twitter: [@extripworkgroup](https://twitter.com/extripworkgroup)

