Société
de Réanimation
de Langue Française

EPURATION EXTRA RENALE EN TOXICOLOGIE

Nozha BRAHMI
Service de Réanimation Médicale et de Toxicologie-
CAMU - Tunis

ASSOCIATION TUNISIENNE DE REANIMATION
ATR
الجمعية التونسية لطب الإنعاش

INTRODUCTION

- La question du traitement optimal au cours des intoxications aiguës reste posée, en termes d'efficacité, malgré les progrès thérapeutiques durant les 20 dernières années.

- Tendances actuelles :

  - Réaffirmer le traitement symptomatique précoce,

  - Favoriser les antidotes

  - Réévaluer l'efficacité des méthodes d'épuration, digestive, rénales et extrarénale

INTRODUCTION

Développement des techniques d'épuration sanguine

1955 ***Schreiner*** ***Hémodialyse***

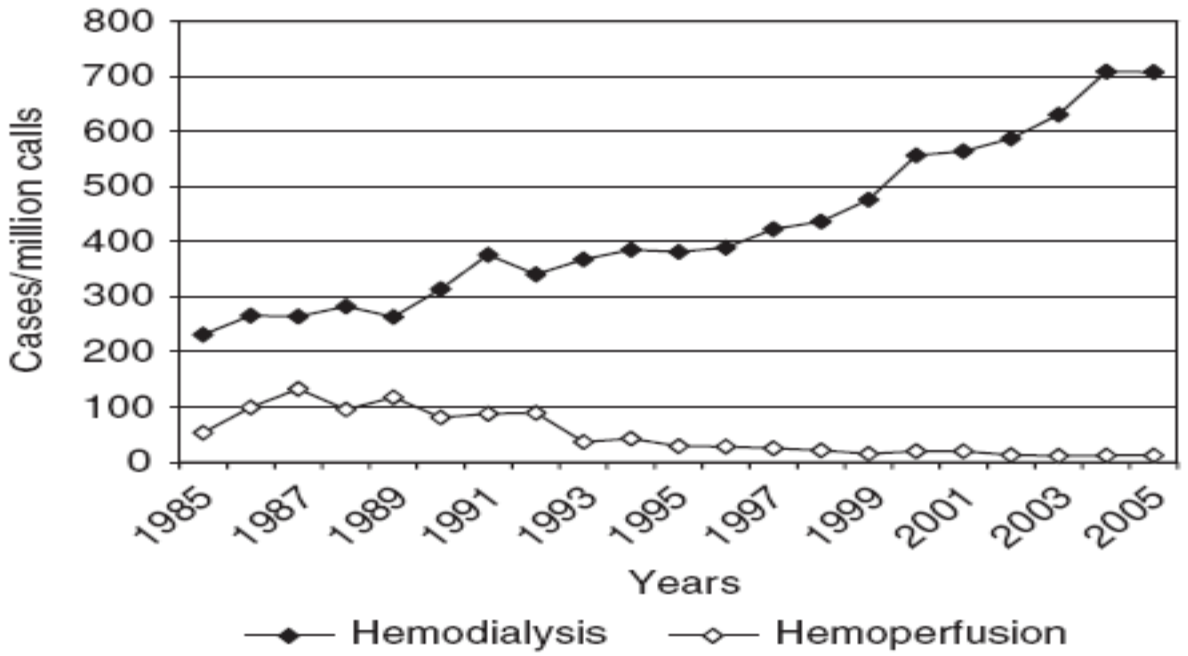
(intoxication salicylée)

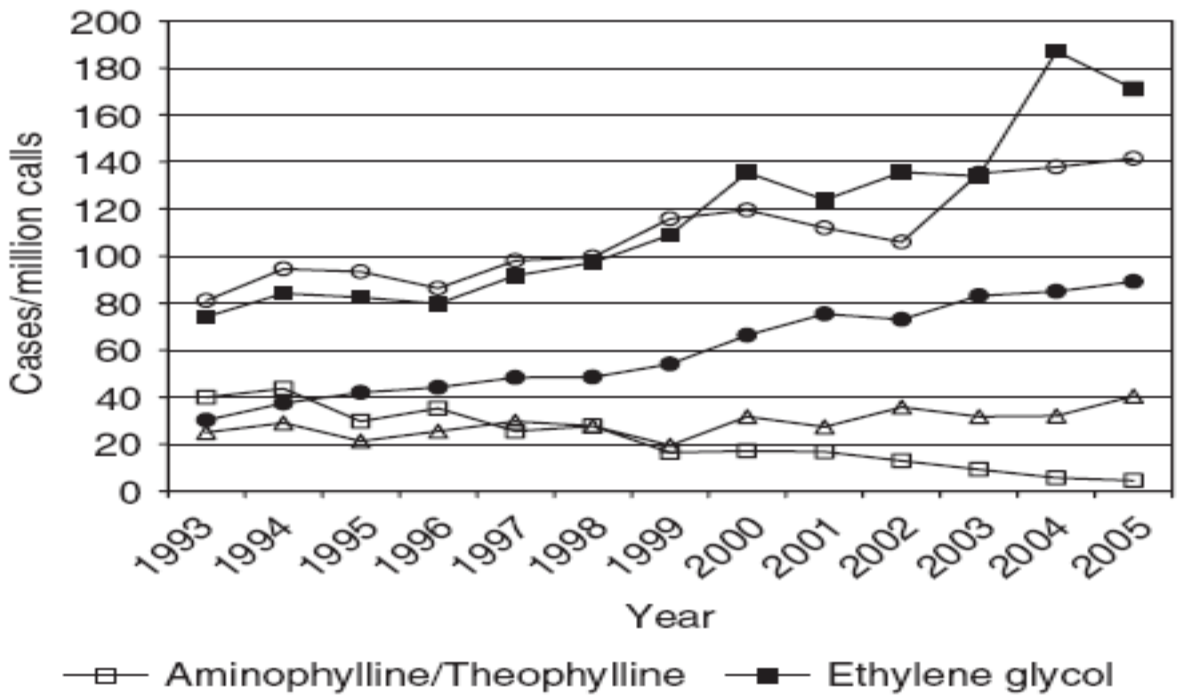
Enthousiasme

2000 ***Strange*** ***Molecular Adsorbent Recirculating System (MARS)***

(Intoxication par la théophylline)

EER ET INTOXICATIONS: EPIDEMIOLOGIE





1985–1990	1991–1995	1996–2000	2001–2005
Lithium (397)	Lithium (714)	Lithium (1178)	Lithium (2583)
Ethylene glycol (290)	Ethylene glycol (649)	Ethylene glycol (1138)	Ethylene glycol (2077)
Methanol (236)	Salicylates (358)	Salicylates (580)	Salicylates (1490)
Salicylates (233)	Aminophylline (284)	Methanol (289)	Valproic acid (516)
Aminophylline (229)	Methanol (240)	Aminophylline (240)	Acetaminophen (474)
Phenothiazine (73)	Acetaminophen (135)	Acetaminophen (192)	Methanol (463)
Ethanol (73)	Ethanol (84)	Valproic acid (170)	Ethanol (297)
Acetaminophen (71)	Phenothiazine (65)	Ethanol (111)	Benzodiazepine (281)
Isopropanol (49)	Isopropanol (59)	Other (90)	Other (274)

Holubeck, KI 2008

CRITERES A REMPLIR

- **L'EER d'un toxique doit être significativement plus efficace que son élimination spontanée.**

- **Apport bénéfice réel par rapport aux thérapeutiques existantes (symptomatiques, antidotes +++),**

- **Doit répondre à trois objectifs:**

CRITERES A REMPLIR

OBJECTIFS

- **Correction des troubles métaboliques liés à sa dégradation ainsi que le traitement de l'insuffisance rénale aiguë d'origine toxique.**

- **Elimination du toxique de manière significative d'un point de vue toxicocinétique.**

- **Raccourcissement de la durée d'évolution de l'intoxication ou l'amélioration de son pronostic, d'un point de vue toxicodynamique.**

EFFICACITÉ TOXICOCINÉTIQUE

Paramètres influençant l'augmentation de l'élimination du toxique:

- **Volume de distribution et concentration plasmatique**
- **Clairance corporelle totale (élimination spontanée)**

  Cl Tot (ml/mn)= Vd (ml)x log.2/t(1/2)plasm (min)

- **Clairance d'épuration (caractéristiques du toxique et de la technique)**
- **Quantité épurée (durée d'épuration, [C] à l'entrée du circuit)**

EFFICACITÉ TOXICODYNAMIQUE

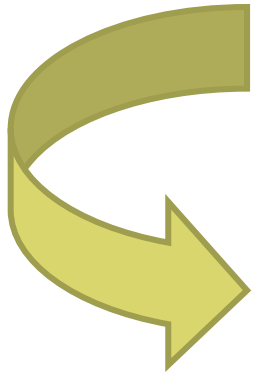
La notion d'impact toxicodynamique est capitale; elle sous-entend clairement qu'il doit exister:

- **Corrélation nécessaire entre gravité / [C]. plasmatique / [C]. organes cibles**
- **Raccourcissement de la durée de la symptomatologie (amélioration du pronostic)**

⇨ **INTÉRÊT POUR TOXIQUES LÉSIONNELS**

DONNEES ACTUELLES?

Recommandations des différentes sociétés



- *American Academy of Clinical Toxicology,*
- *European Association of Poisons Centres and Clinical Toxicologists,*
- *Société de Réanimation en Langue Française)*

***Niveau de preuve de l'utilité de l'EER est assez faible*.**

Peu de toxiques peuvent bénéficier

d'EER +++

CRITERES DES TOXIQUES DIALYSABLES

- Faible volume de distribution < 1l/kg
- Faible poids moléculaire
- Faible liaison aux protéines plasmatiques (< 60 %).
- Clairance endogène < 4 ml/Kg/min.
- Clairance d'élimination obtenue par la technique au moins égale ou supérieure à la clairance spontanée, ou une demi vie diminuant de moitié.

Jaeger in intoxications aiguës, Paris 1999, 162-178

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | guidelines for hemodialysis in toxicology | Search

RSS | Save search | Advanced | Help

Show additional filters

Text availability
Abstract available
Full text available

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Article types
Practice Guideline
Review
Systematic Reviews
more ...

Languages
English
more ...

Clear all

Show additional filters

Display Settings: Summary, 20 per page, Sorted by Recently Added

Send to:

Filters: Manage Filters

Results: 6

1. The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: **guideline** methodology.
Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, Kielstein JT, Mactier R, Maclaren R, Mowry JB, Bunchman TE, Juurlink D, Megarbane B, Anseeuw K, Winchester JF, Dargan PI, Liu KD, Hoegberg LC, Li Y, Calello DP, Burdmann EA, Yates C, Laliberté M, Decker BS, Mello-Da-Silva CA, Lavonas E, Ghannoum M.
Clin Toxicol (Phila). 2012 Jun;50(5):403-13.
PMID: 22578059 [PubMed - Indexed for MEDLINE]
Related citations

2. Availability of decontamination, elimination enhancement, and stabilization resources for the management of acute toxic exposures and poisonings in emergency departments in Malaysia.
Awang R, Al-Sohaim SI, Zyoud SH, Khan HR, Hashim S.
Intern Emerg Med. 2011 Oct;6(5):441-8. Epub 2011 Jul 13.
PMID: 21750875 [PubMed - Indexed for MEDLINE]
Related citations

3. An overview of pediatric poisonings.
Criddle LM.
AACN Adv Crit Care. 2007 Apr-Jun;18(2):109-18. Review. No abstract available.
PMID: 17473538 [PubMed - Indexed for MEDLINE]
Related citations

4. Position Paper on urine alkalinization.
Proudfoot AT, Krenzelok EP, Vale JA.
J Toxicol Clin Toxicol. 2004;42(1):1-26. Review.
PMID: 15083932 [PubMed - Indexed for MEDLINE]
Related citations

5. American Academy of Clinical **Toxicology** practice **guidelines** on the treatment of methanol poisoning.
Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA; American Academy of Clinical **Toxicology** Ad Hoc Committee on the Treatment **Guidelines** for Methanol Poisoning.
J Toxicol Clin Toxicol. 2002;40(4):415-46. Review.
PMID: 12216995 [PubMed - Indexed for MEDLINE]
Related citations

6. A cancer risk assessment of di(2-ethylhexyl)phthalate: application of the new U.S. EPA Risk Assessment **Guidelines**.
Doull J, Cattley R, Elcombe C, Lake BG, Swenberg J, Wilkinson C, Williams G, van Gemert M.

Find related data
Database: Select
Find items

Search details
("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields]) AND ("haemodialysis"[All Fields]

Search

See more...

Recent activity
Turn Off | Clear

- guidelines for hemodialysis in toxicology (6) PubMed
- Dialysis and hemoperfusion in poisoning. PubMed
- The role of hemoperfusion and hemodialysis in toxicology PubMed
- hemodialysis and toxicology (330) PubMed
- Have advances in extracorporeal removal techniques changed the indications for PubMed

See more...

HEMODIALYSE & INTOXICATIONS

INDICATIONS CERTAINES

- Alcools toxiques
  - **Méthanol**
  - **Ethylène glycol**

- Lithium

HEMODIALYSE & METHANOL

- **Méthanol : Profil toxicocinetique stable**

- PM 32 Da
- Vd 0,7 l/kg
- Pas de liaison protéique
- Cl HD 95-280 ml/mn>1-30 ml/mn par rein
- T ½ 2,2-3,8 h Vs 8-20 h

HD: 3 objectifs potentiels

- ↘ [Met], ↘ [formates]
- Correction de l'acidose métabolique

Intensive Care Med (2005) 31:189–195 *Nephron Clin Pract 2010;115:c1–c6*

Intensive Care Med (2005) 31:189–195
DOI 10.1007/s00134-004-2521-0

REVIEW

Bruno Mégarbane
Stephen W. Borron
Frédéric J. Baud

Current recommendations for treatment of severe toxic alcohol poisonings

HEMODIALYSE & METHANOL

Methanol poisoning:
Initial arterial pH <7.10[9] or 7.25–7.30 [16]
Drop in arterial pH >0.05 resulting in a pH outside the normal range despite bicarbonate infusion
Inability to maintain arterial pH >7.3 despite bicarbonate therapy
Decrease in bicarbonate concentration >5 mmol/l, despite bicarbonate therapy
Visual impairment
Renal failure
Deteriorating vital signs despite intensive supportive care
Initial plasma methanol concentration ≥ 0.5 g/l (15.6 mmol/l)[a]
Rate of methanol decline <0.1 g/l (3.1 mmol/l) per 24 h

Hémodialyse > 8 heures

→ **Correction Acidose/ annulation [Meth]**

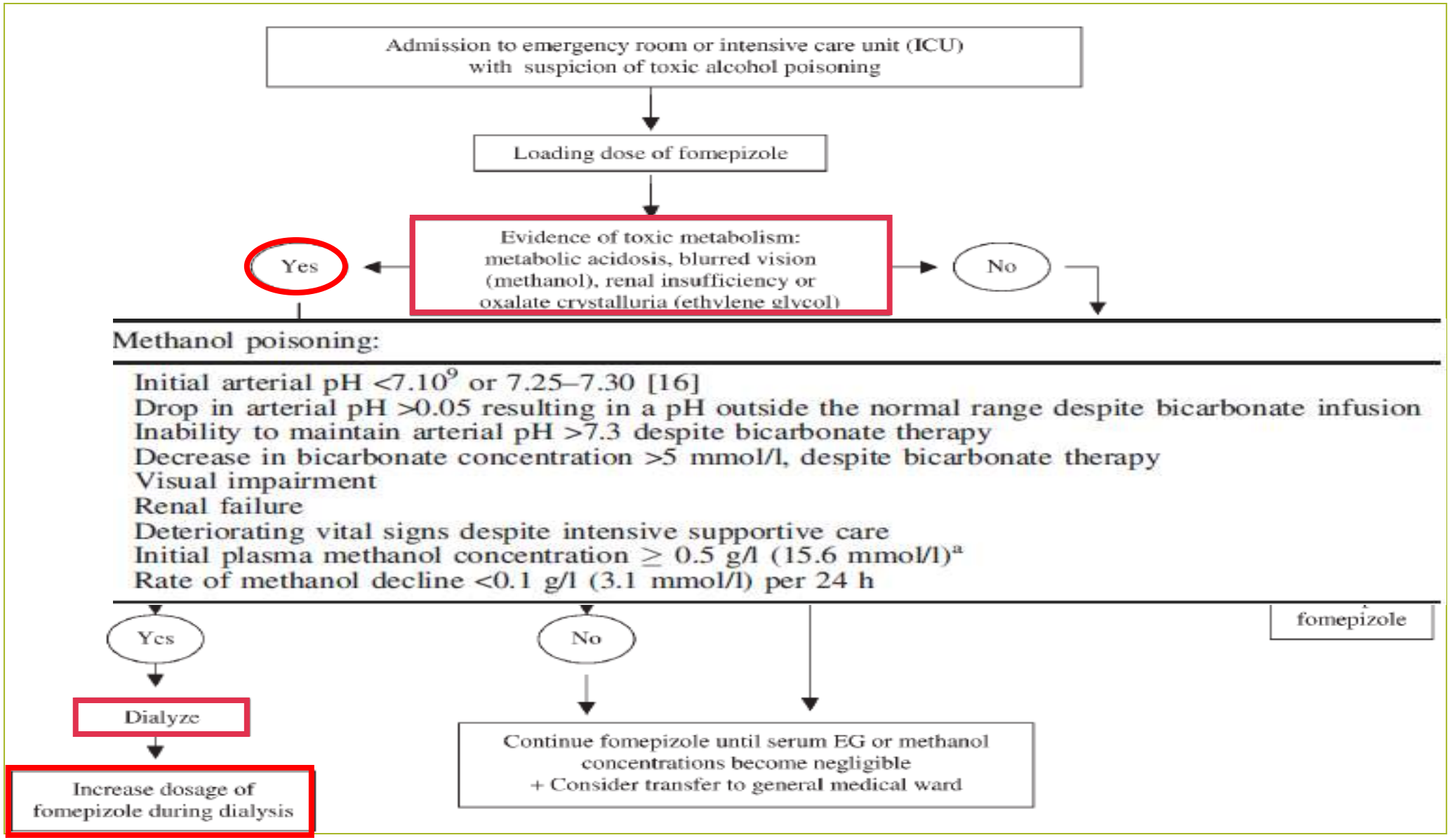
la plus précoce possible

Intensive Care Med (2005) 31:189–195
DOI 10.1007/s00134-004-2521-0

REVIEW

Bruno Mégarbane
Stephen W. Borron
Frédéric J. Baud

Current recommendations for treatment of severe toxic alcohol poisonings



Clinical Toxicology (2012), **Early Online:** 1–9

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2012.728224

informa
healthcare

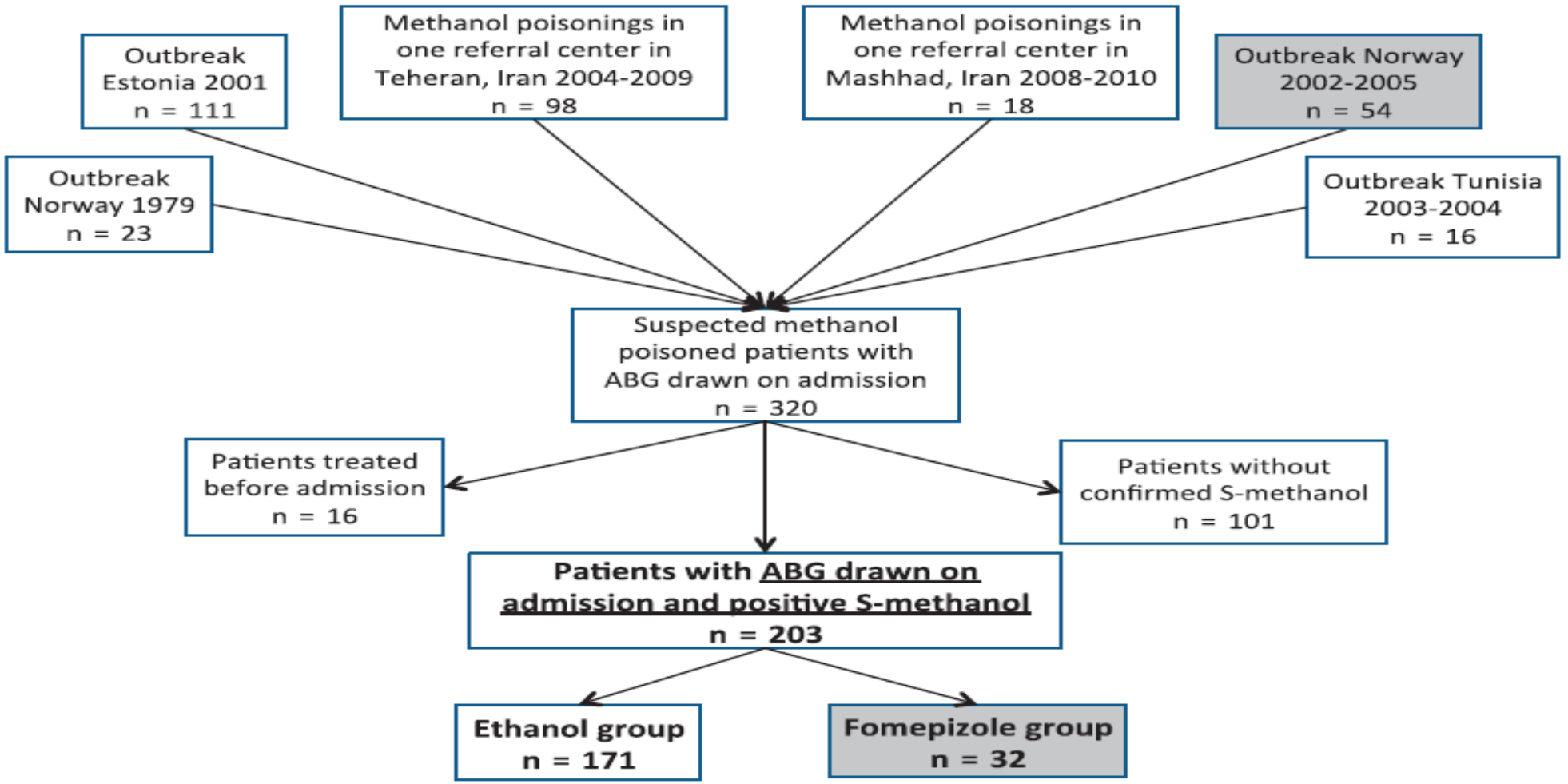


Fig. 1. Overview of the patients in the study. The patients treated with fomepizole and their origin is shaded.

Table 1. The different outcome groups among the patients as related to different admission parameters.

	Group I* (n = 121)	Group II* (n = 34)	Group III* (n = 48)	Overall (n = 203)	Overall p (ANOVA)	Significance between groups (p-values)** I–II	I–III	II-III
Gender (♂:♀)	99:22	27:7	34:14	160:43	–	–	–	–
Age (years) Median (range)	44 (3–77)	42 (17–65)	42 (15–65)	44 (3–77)	–	ns	ns	ns
Coma (GCS <8) on admission n (%)***	8 (6.6%)	11 (32.4%)	41 (85.4%)	60 (30.0%)	–	<0.001	<0.001	<0.001
Serum-methanol (mmol/L)**** Median (range)	31 (1–179)	65 (18–158)	59 (8–199)	45 (1–199)	–	–	–	–
pH Median (range)	7.24 (6.52–7.57)	7.15 (6.60–7.46)	6.73 (6.34–7.29)	7.16 (6.34–7.57)	p < 0.001	<0.001	<0.001	<0.001
pCO_2 (kPa) Median (range)	3.2 (1.0–7.5)	2.9 (1.2–6.8)	4.3 (1.3–15.9)	3.4 (1.0–15.9)	p < 0.001	ns	<0.001	0.002
HCO_3^- (mmol/L) Median (range)	10 (2.0–37.8)	7 (1.0–26.0)	4.2 (1.0–11.0)	6.2 (1.0–37.8)	p < 0.001	0.03	<0.001	0.04
Base deficit (mmol/L) Median (range)	17 (−3–30)	23 (−2–41)	29 (18–42)	21 (−3–42)	p < 0.001	0.04	<0.001	0.001
Serum-K (mmol/L) Median (range)	4.3 (2.6–7.7)	4.2 (3.7–8.1)	5.8 (3.0–8.1)	4.6 (2.6–8.1)	p < 0.001	ns	<0.001	0.02
Serum-creatinine (µmol/L) Median (range)	79 (35							
Antidote (F = fomepizole E = ethanol)	F: 22 (E: 99 (							

Table 3. Factors associated with mortality.

Prognostic marker	Threshold	Odds ratio (95% CI)
Coma*	yes/no	48.2 (18.1–128.7)
pH*	7.00	35.4 (14.1–88.8)
Creatinine (mol/L)	106	15.0 (3.9–58.2)
BD (mmol/L)	25	13.1 (5.1–33.8)
HCO_3^- (mmol/L)	5	6.6 (3.1–14.1)
pCO_2** (kPa)	3.1	5.0 (1.2–4.7)
Serum-K (mmol/L)	5.1	3.0 (0.97–9.3)

Clinical Toxicology (2012), **Early Online:** 1–9

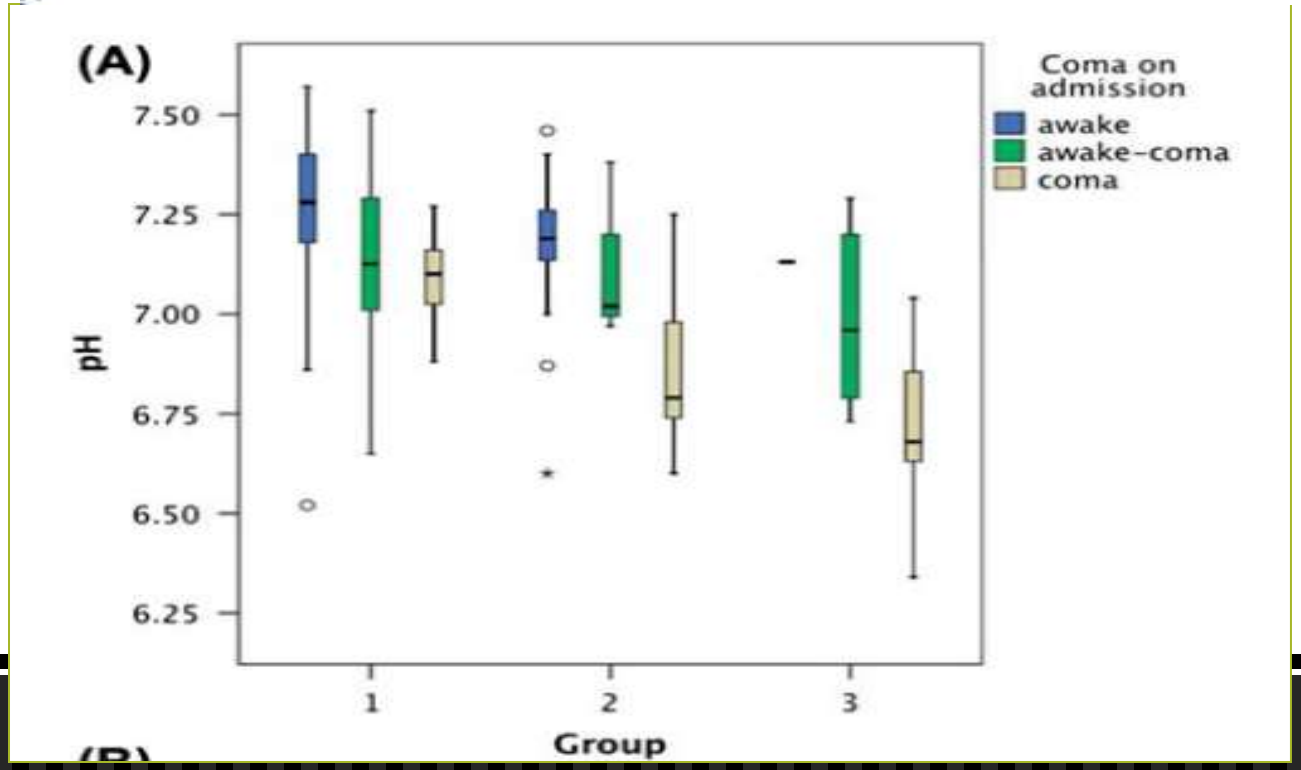
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2012.728224

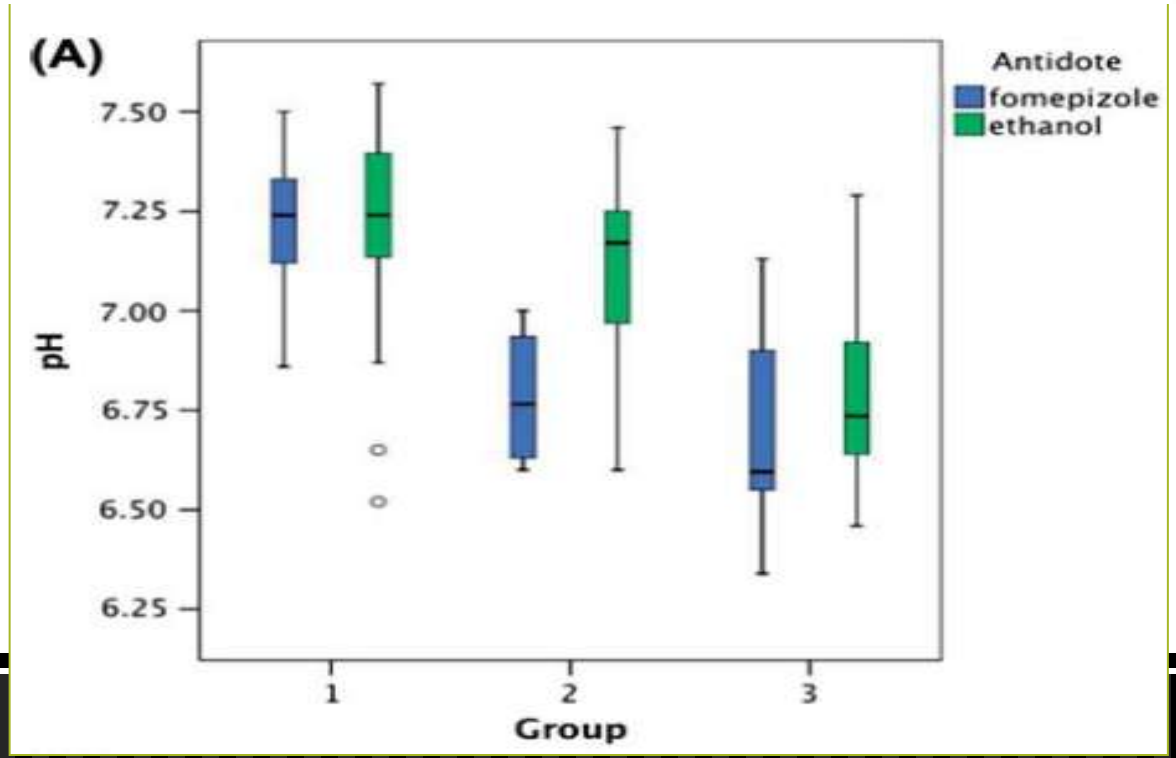
informa
healthcare

RESEARCH ARTICLE

Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes – a multicenter study

RAIDO PAASMA,[1] KNUT ERIK HOVDA,[2] HOSSEIN HASSANIAN-MOGHADDAM,[3] NOZHA BRAHMI,[4] REZA AFSHARI,[5] LEIV SANDVIK[6,7] and DAG JACOBSEN[8]





HEMODIALYSE & ETHYLENE GLYCOL

- **Ethylène glycol**

  - **PM 62 Da**
  - **Vd 0,7 l/kg**

Ethylene glycol poisoning:

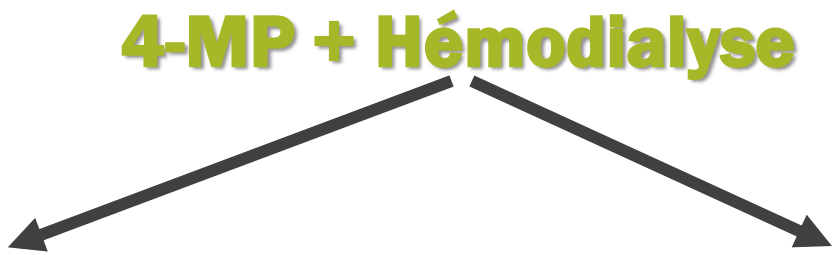
Arterial pH <7.10[9] or 7.25–7.30 [16]
Drop in arterial pH >0.05 resulting in a pH outside the normal range despite bicarbonate infusion
Inability to maintain arterial pH >7.3 despite bicarbonate therapy
Decrease in bicarbonate concentration >5 mmol/l, despite bicarbonate therapy
Renal failure (serum creatinine concentration >265 µmol/l or rise in the serum creatinine by >90 µmol/l [10])
Deteriorating vital signs despite intensive supportive care
Initial plasma e.g., concentration ≥ 0.5 g/l (8.1 mmol/l) unless fomepizole is administered in the absence of both renal dysfunction and significant acidosis[a]

Intensive Care Med (2005) 31:189–195

HEMODIALYSE & ETHYLENE GLYCOL

Etude muticentrique prospective : META study Group

10 malades ; 4-MP/ ± Hémodialysis



½ vie: 626±474 min

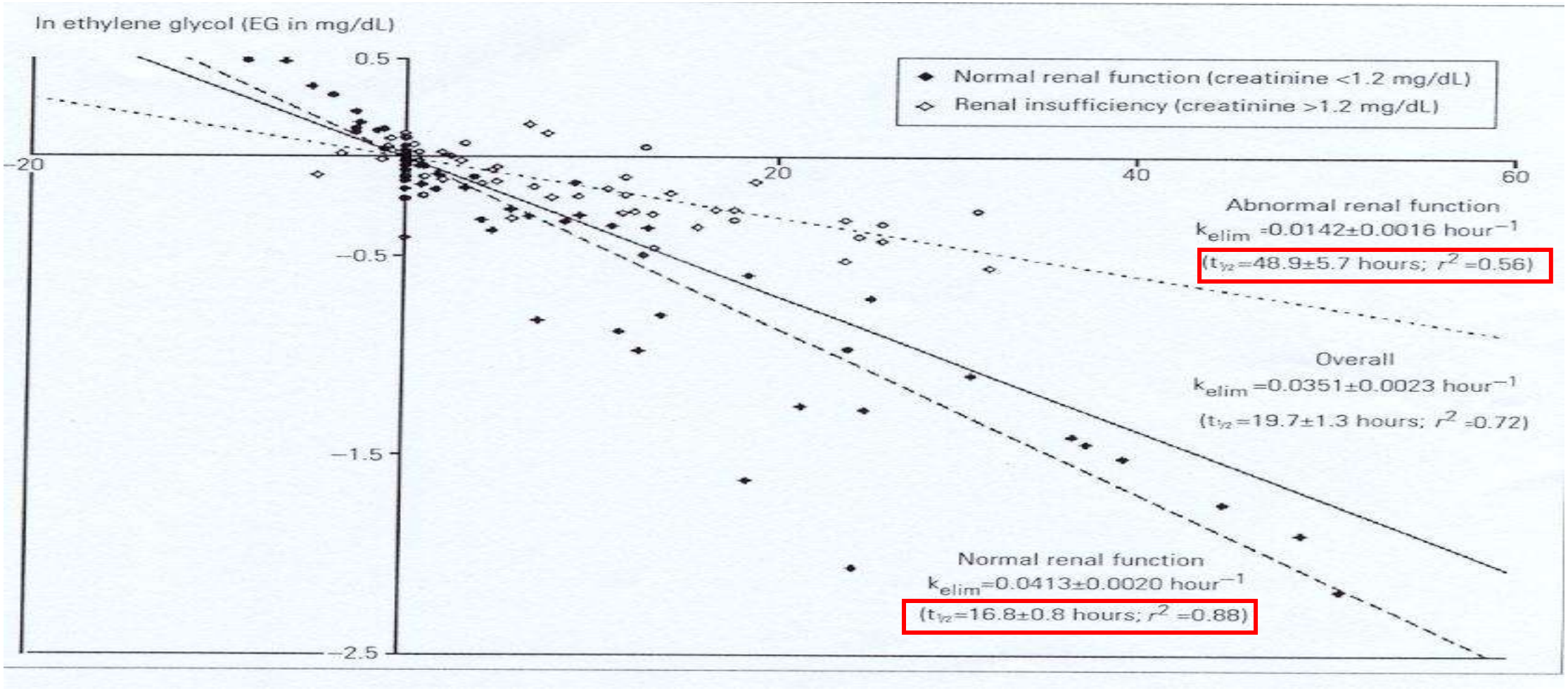
½ vie: 155± 42 min

[cl]: 170± 23 ml/min

Moreau. J Toxical Clin Toxical 1998; 36: 659-66

HEMODIALYSE et ETHYLENE GLYCOL

Etude multicentrique, University of Massachusetts



Sivilotti M.Ann Emerg Med 2000

HEMODIALYSE et ETHYLENE GLYCOL

Etude multicentrique, University of Massachusetts

Kinetic Parameter	All Subjects	Subjects With Normal Renal Function	Subjects With Renal Insufficiency	*P* Value
Fomepizole monotherapy				
k_{elim} 4-MP >10 (hour^{-1})	0.0351±0.0023	0.0413±0.0020	0.0142±0.0016	<.001
Half-life (hour)	19.7±1.3	16.8±0.8	48.9±5.7	<.001
Hemodialysis				
k_{elim}^{HD} (hour^{-1})	0.259±0.021	0.302±0.029	0.215±0.025	.028
Half-life (h)	2.68±0.22	2.29±0.22	3.23±0.38	.028
Clearance (mL/min)	209±15	226±31	177±22	NS
V_d (L/kg)	0.680±0.084	0.774±0.124	0.585±0.134	NS

NS, Not significant.

Sivilotti. Ann Emerg Med 2000, 36: 114-125

HEMODIALYSE & INTOXICATIONS

INDICATIONS CERTAINES

- Alcools toxiques
  - Méthanol
  - Ethylène glycol

- **Lithium**

HÉMODIALYSE & LITHIUM

Profil toxicocinétique

- Ion divalent (Li^{2+})
- PM 74 Da
- Vd 0,6- 0,9 L/kg
- Liaison protéique= 0
- HD Cl Li : 63-114 ml/mn

(x 5-10 ClCr)

Indications

- Anomalies SNC (confusion, coma, convulsions…)
- Détresse respiratoire
- Intoxication A°/C > intoxication A° isolée
- Lithémie ?

HÉMODIALYSE ET LITHIUM

- **Indication selon lithémie?**

- **Lithémie > 6 mmol/l (aiguë) et >4 mmol/l**

  (intoxication chronique symptomatique, plus grave)

- **Lithémie : 2,5- 4 mmol/l avec des signes neurologiques: convulsions+++, Insuffisance rénale, ou instabilité hémodynamique**

- **Pour une lithémie < 2,5 mmol/l:**

  ***insuffisance rénale terminale**

  *** cinétique à la hausse de la lithémie**

  *** lithémie > 1 mmol/l après 30 h de traitement**

Beckmann. Clin Toxicol 2001;

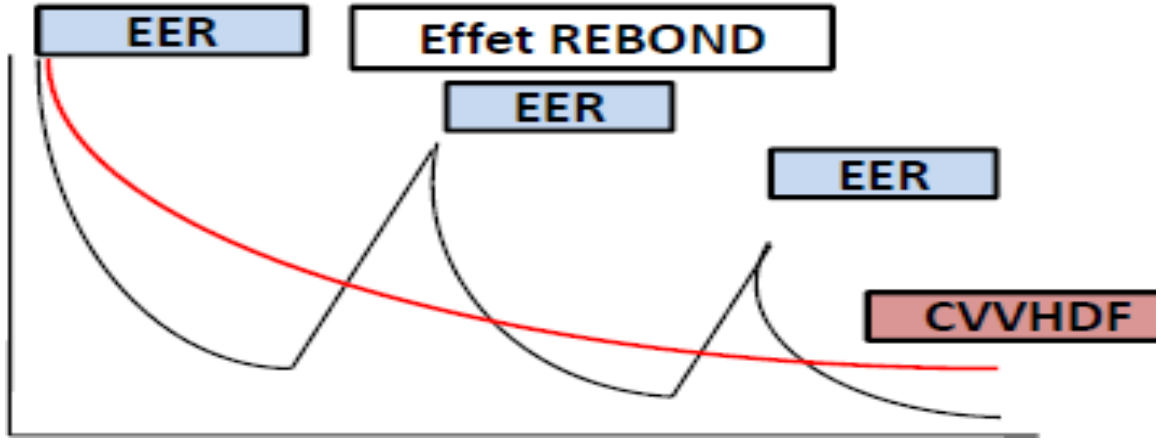
HÉMODIALYSE & LITHIUM

HD: Extraction du lithium intracellulaire est beaucoup plus lente que l'extraction du lithium plasmatique

→ **Effet rebond**

- Prolonger la séance (6- 8 h)

- HD +/- CVVHF/HDF



Elimination prolongée et plus complète du lithium intracellulaire

Intérêt: intoxications chroniques

Beckmann. Clin Toxicol 2001; 39: 393-7 *Timmer. J Am Soc Nephrol 1999; 10: 666-74*

HÉMODIALYSE & LITHIUM

HDF: Les méthodes veino-veineuses :

- **Débit d'ultrafiltration de 1000 ml/h et un flux de dialysat à base de bicarbonate de 1000 ml/h (Excrétion Li: 2 % pour l'acétate contre 60 % pour le bicarbonate).**

Clairance de lithium de 28 ml/min à 60 ml/min

- ↗ **Méthode d'EER continue de choix en cas de contre-indication ou d'impossibilité de l'HD conventionnelle.**

HÉMODIALYSE & AUTRES INTOXICATIONS

AUTRES INDICATIONS

- Les Biguanides +++
- L'Acide salicylique
- L'acide valproic
- L'Acide 2-4D dichlorophenoxy

HEMODIALYSE & BIGUANDES

Critères toxicocinétiques

Metformine

- PM 166 Da
- Vd 0,5 l/kg
- Liaison protéique= 0
- HD: Cl Big 170 ml/mn

Indications

- Acidose lactique réfractaire
- IRA
- HD: correction surtout de l'acidose lactique
- Cl Big 450 ml/mn (clairance endogène spontanée)

Metformin-associated lactic acidosis: A prognostic and therapeutic study*

Alexandre Seidowsky, MD; Saad Nseir, MD; Nicole Houdret, PhD; François Fourrier, MD, FCCM

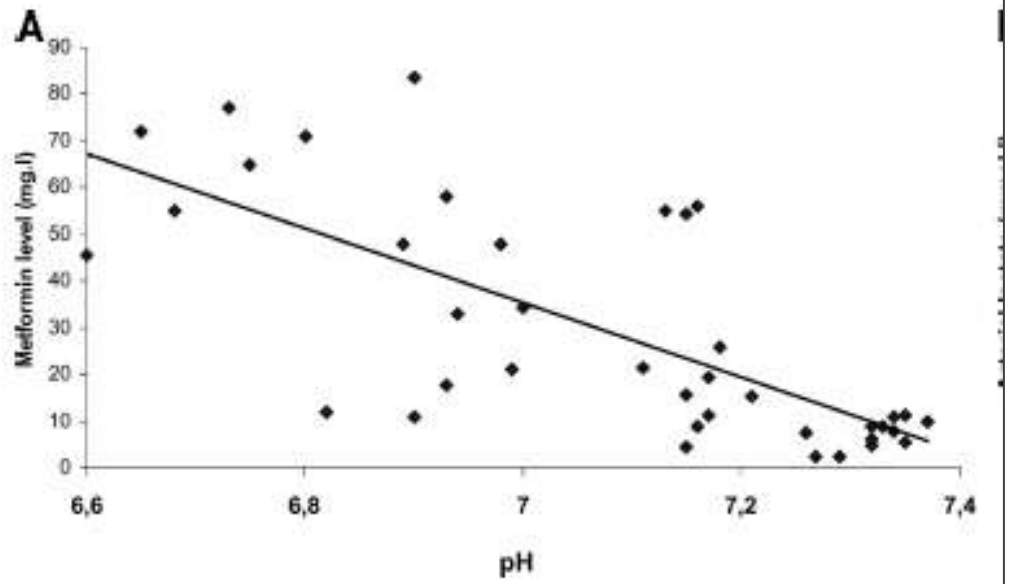
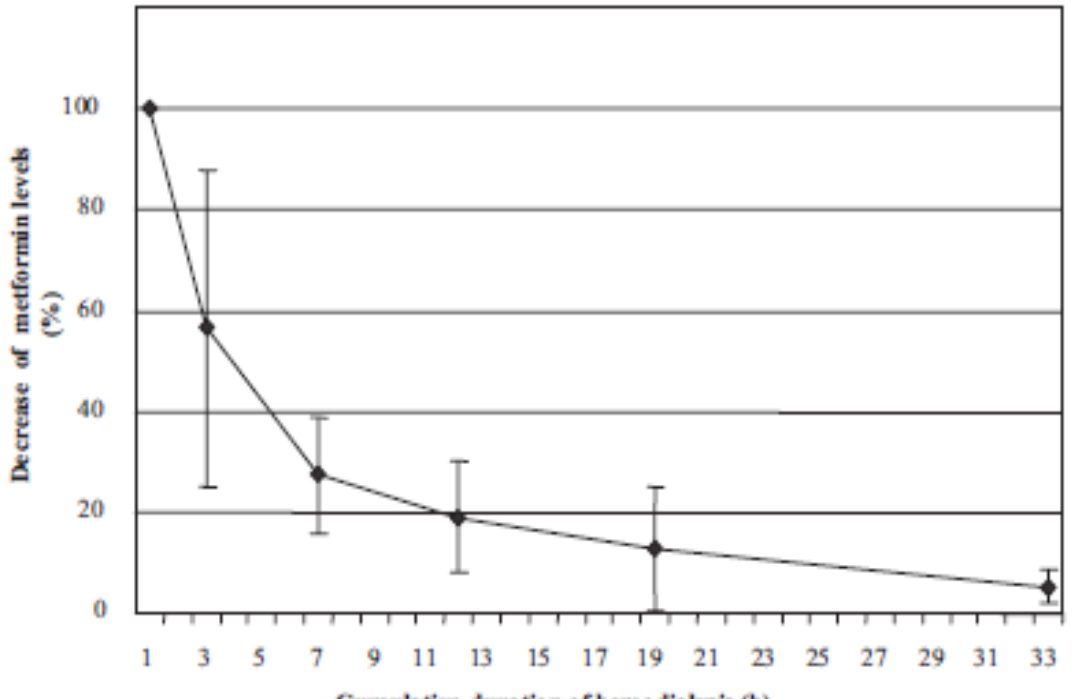
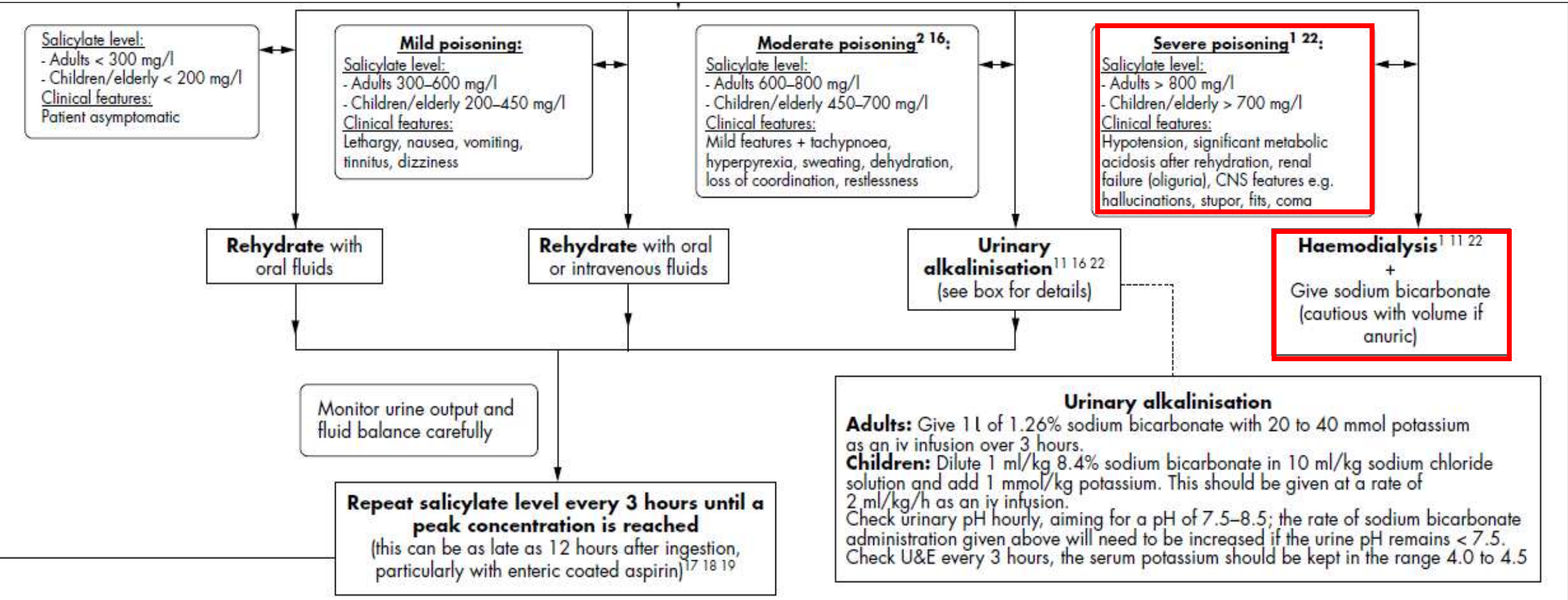


Figure 1. *A*, Correlation between arterial pH and metformin blood levels (mg/L) (%) and arterial lactate levels (mmol/L) ($r = -.568$; $p < 0.0001$).



HEMODIALYSE & ACIDE SALICYLIQUE



Emerg Med J 2002;**19**:206–209

Clinical Toxicology (2009) 47, 609–616

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650903167772

informa
healthcare

REVIEW

Extracorporeal elimination in acute valproic acid poisoning

RUBEN H.K. THANACOODY

The major reason quoted for initiation of extracorporeal elimination in most case reports was a deterioration in clinical status (mainly coma and hemodynamic instability) in association with an elevated plasma VPA concentration (generally >850 mg/L).[5–9,11,15,17–19,21,24,26–30,32,34] Other factors influencing the decision to use extracorporeal techniques included the presence of electrolyte disturbances (especially hypernatremia and hyperkalemia),[18,26,30,32,35] acid–base disturbances (metabolic acidosis)[8,11,13,24,26,30,32,34,35], and hyperammonemia.[12,17,18,24,26,32]

Clinical Toxicology (2009) 47, 609–616

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650903167772

informa
healthcare

REVIEW

Extracorporeal elimination in acute valproic acid poisoning

RUBEN H.K. THANACOODY

Conclusions

Extracorporeal techniques appear to be useful in enhancing the elimination of VPA in severe VPA poisoning. Hemodialysis is the preferred modality. Although charcoal hemoperfusion either alone or in combination with hemodialysis may also be effective, anecdotal data suggest that clearance may

INDICATIONS INUTILES OU NON PROUVÉES

- Paraquat
- Métaux lourds
- Cardiotropes

Clinical Toxicology (2012), **50**, 403–413

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2012.683436

informa
healthcare

METHODOLOGY

The EXTRIP (*EXtracorporeal TReatments In Poisoning*) workgroup: Guideline methodology

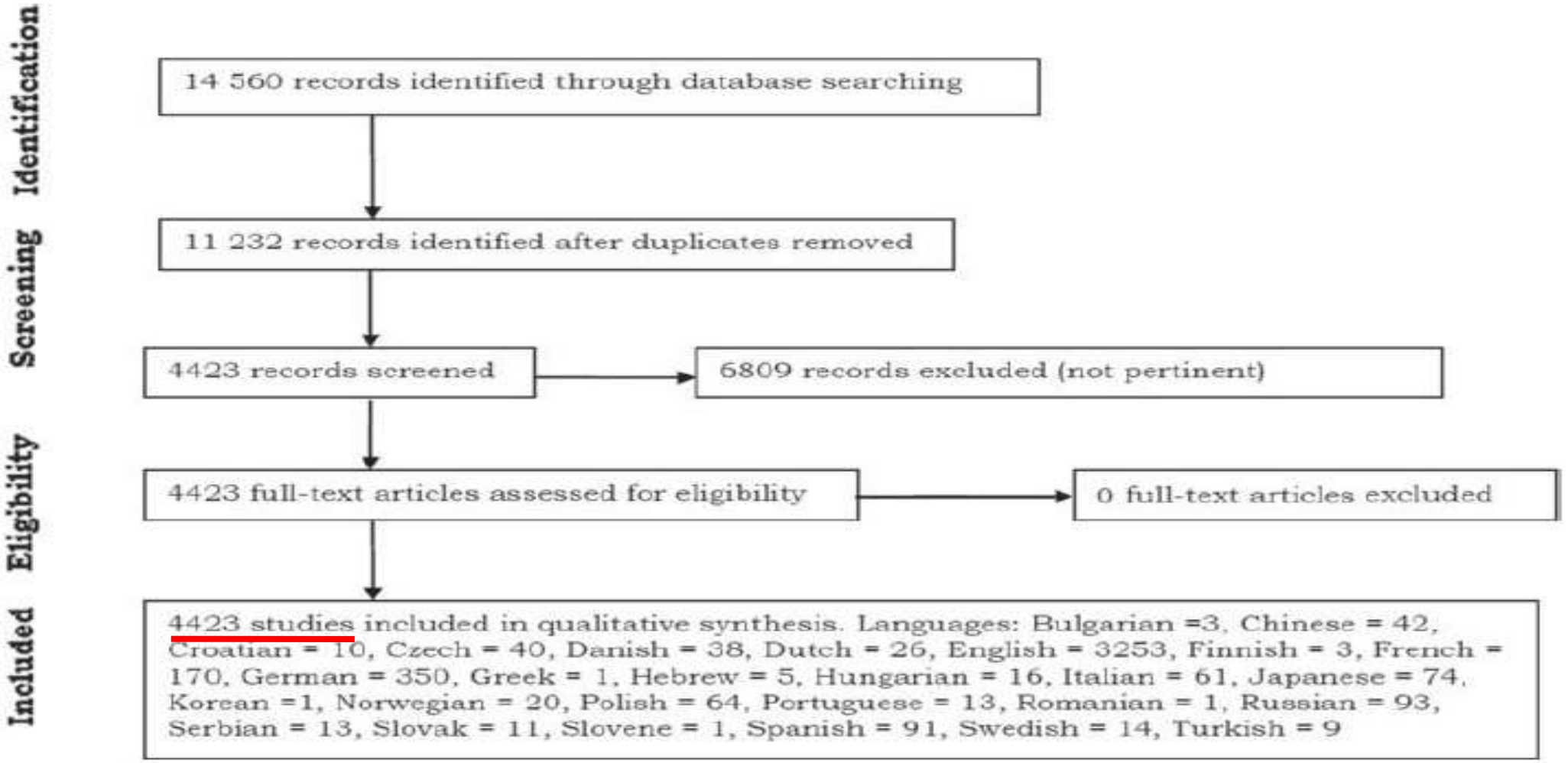


Fig. 1. Result of preliminary search (conducted October 22nd 2011).

Clinical Toxicology (2012), **50**, 403–413

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2012.683436

informa
healthcare

METHODOLOGY

The EXTRIP (*EXtracorporeal TReatments In Poisoning*) workgroup: Guideline methodology

Table 2. Poison selection.

Methanol	Paraquat/Diquat	Amanita	Fluoride
Ethylene glycol	Carbamazepine	Phenytoin	Baclofen
Lithium	Quinine/Chloroquine	Diethylene glycol	Isoniazid
Salicylates	Theophylline/methylxanthines	Organophosphates	Methotrexate
Valproic acid	Tricyclic antidepressants	Digoxin/Digitalis	Thallium
Acetaminophen	Phenobarbital/Barbiturates	Isopropanol	Metformin

EN CONCLUSION

Table 2. Treatment of selected xenobiotics

Xenobiotic	Treatment of poisoning
Carbamazepine	Multidose activated charcoal; $NaHCO_3$ possibly useful; high-flux hemodialysis for critically ill
Digoxin	Digoxin-specific Fab fragments
Lithium	Normal saline to replete extracellular fluid volume; hemodialysis for significant neurologic symptoms
Metformin	Metformin-associated lactic acidosis usually warrants hemodialysis
Paracetamol (acetaminophen)	Multidose activated charcoal; N-acetyl cysteine. Hemodialysis rarely if ever indicated, and only if very early after ingestion
Salicylates	Alkalinization of blood and urine with $NaHCO_3$ if tolerated, especially if kidney function is good; hemodialysis for impaired mental status and significant respiratory alkalosis, impaired kidney function
Theophylline	Supportive care; β-adrenergic antagonists are useful. Charcoal hemoperfusion if available is slightly more efficacious than hemodialysis, but the latter usually suffices. Hemoperfusion and hemodialysis can be used together
Toxic alcohols	Block acidosis and metabolism to toxic metabolites with fomepizole if available or ethanol. Hemodialysis often indicated for metabolic acidosis, more serious clinical manifestations, levels >50 mg/dl; pyridoxine and thiamine may be useful for ethylene glycol, folic acid for methanol
Tricyclic antidepressants	Hypertonic $NaHCO_3$ for ventricular tachycardia, dysrhythmia, hypotension; $MgSO_4$ for ventricular dysrhythmias
Valproic acid	Multidose activated charcoal and supportive care; hemodialysis indicated for rapid deterioration, liver disease, serum levels >1,000 mg/l

MERCI POUR VOTRE ATTENTION