Disponible en ligne sur www.sciencedirect.com
ScienceDirect
Réanimation 15 (2006) 343–353
Réanimation
http://france.elsevier.com/direct/REAURG/

Experts recommandations

ICU management of severe poisoning with medications or Illicit substances

B. Mégarbane[a,*], L. Donetti[b], T. Blanc[c], G. Chéron[d], F. Jacobs[e], panel of experts convened by the SRLF

[a] *Service de réanimation médicale et toxicologique, hôpital Lariboisière, 2, rue Ambroise-Paré, 75010, Paris cedex, France*
[b] *Service de réanimation, hôpital de Montfermeil, 10, rue du Général-Leclerc, 93370 Montfermeil cedex, France*
[c] *Unité de réanimation pédiatrique, hôpital Charles-Nicolle, 1, rue de Germont, 76031 Rouen cedex, France*
[d] *Centre d'urgences diagnostic rapide, hôpital Necker–Enfants-Malades, 49, rue de Sèvres, 75015 Paris cedex, France*
[e] *Service de réanimation médicale, hôpital Antoine-Béclère, 157, rue de la Porte-de-Trivaux, 92140 Clamart cedex, France*

Available online 26 July 2006

Steering committee

Deputy organizer: Laurence Donetti (Montfermeil); **co-organizers:** Thierry Blanc (Rouen) (pediatrics) and Frédéric Jacobs; **expert coordinator for data on adults:** Bruno Mégarbane (Paris); and **expert coordinator for data on pediatric patients:** Gérard Chéron (Paris).

Experts on the panel

Data on adults

Marc Alazia (Marseille), Frédéric Baud (Paris), Régis Bédry (Pessac), Gilles Capellier (Besançon), Patricia Compagnon (Rouen), Françoise Flesch (Strasbourg), Jean-Pierre Goule (Le Havre), Vincent Danel (Grenoble), Mohammad Hachelaf (Besançon), Philippe Hantson (Brussels), Albert Jaeger (Strasbourg), Frédéric Lapostolle (Bobigny), Philippe Lheureux (Brussels), Bruno Mégarbane (Paris), Jean-Pierre Metton (Antony), Jean-Pierre Rigaud (Dieppe), and Philippe Sauder (Strasbourg).

Data on pediatric patients

Olivier Brissaud (Bordeaux), Gérard Chéron (Paris), Laurent Chevret (Le Kremlin Bicêtre), and Isabelle Claudet (Toulouse).

SRLF committee on clinical practice guidelines

Didier Barnoud, Thierry Blanc, Thierry Boulain (Secrétaire), Alain Cariou, Laurence Donetti, Jean-Philippe Fosse, Claude Gervais, Christophe Girault, Frédéric Jacobs, Stéphane Leteurtre, Bruno Lévy, Philippe Mateu, Thierry Pottecher, Marie Thuong, Isabelle Vinartie, Michel Wolff.

1. Introduction and description of the methodology used by the experts of the French-Language Society for Intensive Care (SRLF) to develop recommendations

These recommendations were developed by a panel of 21 experts selected by the SRLF. Each expert wrote a detailed discussion of a specific section then identified the points supported by strong evidence and used them to develop recommendations. Each expert presented his or her recommendations to the panel, providing evidence to support both the content and the form. Instead of striving to establish a consensus on all the recommendations, the experts focused on identifying points of agreement – which served as the basis for recommendations – and points of disagreement or indecision – which were taken as indicating a need for further studies.

Each expert rated each recommendation as indicated in the RAND/UCLA method using a 9-point scale (where 1 indicated complete disagreement, absence of proof, or formal contraindication; and 9 complete agreement, definitive proof, or formal indication).

Three regions were defined according to the value of the median rating for the panel:

- not supported by strong evidence: panel median of 1 to 3;
- uncertain: panel median of 4 to 6;
- supported by strong evidence: panel median of 7 to 9.

The level of agreement was determined according to the dispersion of the ratings. Full agreement was defined as all

* Corresponding author.
E-mail address: bruno-megarbane@wanadoo.fr (B. Mégarbane).

doi:10.1016/j.reaurg.2006.07.005

the ratings falling within the same three-point region (1–3, 4–6, or 7–9) and poor agreement as most ratings falling within one three-point region but at least one rating equal to the upper or lower boundary of an adjacent region (e.g. ratings ranging from 1 to 4 or from 6 to 8).

The recommendations in sections 1 through 7 and in section 9 are relevant to both adults and children. Section 8 reports recommendations that are specific of children. Ethanol poisoning is not included in these recommendations, whose scope is limited to severe poisoning with medications and illicit substances.

2. Severe poisoning: epidemiology, definition, intensive care unit (ICU) admission criteria

2.1. What is severe poisoning?

Poisoning with medications or illicit substances is considered severe when close monitoring is required because the patient was exposed to large amounts of toxic agents (full agreement), exhibits severe symptoms (coma, seizures, respiratory distress, alveolar hypoventilation, hemodynamic instability, or heart rhythm or conduction disturbances) (full agreement), or has risk factors (severe co-morbidities, advanced age or infant) (poor agreement). Patients with severe poisoning by medications or illicit substances should be admitted to the ICU (full agreement).

2.2. Evaluating poisoning severity

Severity may result from the specific effects of the toxic agents or from nonspecific complications of poisoning (full agreement).

When predicting the prognosis of poisoning, the following should be considered: characteristics of the substance(s), estimated amount ingested, formulation (sustained-release), characteristics of the patient (age and co-morbidities), time from ingestion to management, delayed symptom development (activating metabolism), and occurrence of complications (full agreement).

Severe poisoning may be present in a patient who is asymptomatic when first found or first examined (poor agreement).

When evaluating severity, the co-ingestants should be considered, since additive or synergistic effects may occur (full agreement). The depth of a coma thought to be caused by a toxic substance is not directly related to the outcome in ICU patients (full agreement).

Currently available all-purpose severity scores (SAPSII, APACHE, Edinburgh scale, Reaction Level Scale) are not reliable for outcome prediction in the individual patient or as a guide to treatment decisions in patients with poisoning. Scores that are more specific (Toxscore and Poisoning Severity Score [PPS]) have been developed but have not yet been thoroughly validated in the field of toxicology (full agreement).

2.3. Criteria for ICU admission according to the substance

In patients exposed to an overdose of psychotropic agents, indications for admission to the ICU or continuous monitoring unit include:

- exposure to benzodiazepines when combined with advanced age or respiratory failure (poor agreement);
- exposure to barbiturates, given the prolonged risk of coma and respiratory arrest, which may occur suddenly (fast-acting barbiturates) (full agreement);
- exposure to neuroleptics, given the risk of repolarization or conduction disorders (full agreement);
- exposure to meprobamate, given the risk of shock related to vasoplegia or heart failure (full agreement);
- and exposure to lithium in patients previously on lithium or having received an overdose (full agreement);

Cardiotropic agents, most notably those with membrane-stabilizing effects, result in excess mortality. Routine ICU admission is in order in patients exposed to excessive amounts of cardiotropic agents (full agreement).

Acute poisoning with polycyclic antidepressants is potentially severe, as seizures, ventricular rhythm disturbances, and myocardial failure may occur. QRS widening is the main prognostic factor (full agreement).

In asymptomatic patients, the potential severity of poisoning with a single dose of acetaminophen (paracetamol) should be evaluated by measuring the serum acetaminophen (paracetamol) level at least 4 hours after ingestion, and the Rumack and Matthew nomogram should be used to interpret the result according to the time from ingestion (full agreement).

Criteria used to evaluate the prognosis of salicylate poisoning in pediatric patients and adults include neurological disorders, severity of acidosis, and serum salicylate level > 500 mg/L (full agreement).

2.4. Role for poison centers

Poison centers should serve as information resources and toxic exposure surveillance systems (a) to identify high-risk situations and situations that may impact public health (full agreement); (b) to identify new or previously unknown toxic agents, with the corresponding symptoms, which may serve as orientation for toxicologic screening (poor agreement); and (c) to evaluate the effects of preventive steps (e.g. restrictions placed on drug prescription or retail) (poor agreement).

3. Toxidromes

3.1. What is a toxidrome?

Toxidromes are clinical syndromes caused by toxic agents. Each toxidrome is a constellation of signs and symptoms, laboratory test abnormalities, and/or electrocardiographic abnormalities that suggests a specific class of poisons. The

components of the toxidrome stem directly from the toxicodynamic effects of the xenobiotic. A toxidrome is a pattern that is typical for a specific class of toxic agents; it is not specific for poisoning. Poisoning with multiple agents or the development of nonspecific complications may modify the clinical picture. A single drug class or agent may induce one or more toxidromes (full agreement).

Knowledge of the main toxidromes is essential to recognize poisoning as a possible diagnosis that needs to be confirmed by tests, to identify a mechanism of action, and to suggest the appropriateness of specific antidotes (full agreement). Differentials should be considered in patients with polymorphic manifestations occurring in a setting and with a history that does not conclusively indicate poisoning (poor agreement).

The clinical approach should focus on detecting toxidromes. A structured and thorough physical examination should be performed on several occasions, and the results should be recorded in writing. An electrocardiogram should be obtained routinely in patients admitted to the ICU for severe poisoning (full agreement).

3.2. Orientation in a patient with coma

In a patient who is in a coma, poisoning should be considered when there are no focal signs (tone, reflexes, movements, pupils). A number of signs may suggest a specific medication or class of medications (full agreement):

- coma with lethargy: benzodiazepines and related agents (zolpidem, zopiclone), phenobarbital, meprobamate, sedative phenothiazines, opiates, phenytoin, sodium valproate;
- coma with agitation: polycyclic antidepressants, antihistamines, hypoglycemia-inducing substances;
- hypotonia: benzodiazepines, phenobarbital, meprobamate;
- hypertonia: polycyclic antidepressants, phenothiazines, hypoglycemia-inducing substances;
- seizures: polycyclic antidepressants, phenothiazines, antihistamines, theophylline, carbamazepine, lithium, dextropropoxyphene, cocaine, amphetamines, hypoglycemia-inducing substances;
- myoclonus: polycyclic antidepressants, lithium, selective serotonin reuptake inhibitors (SSRIs);
- pinpoint pupils: opiates;
- mydriasis (reactive): polycyclic antidepressants, atropine and derivates, cocaine, amphetamines, antiparkinson drugs, SSRIs;
- hallucinations: antihistamines, antiparkinson agents;
- hemodynamic disturbances: meprobamate, membrane-stabilizing agents, beta-blockers and calcium channel antagonists.

3.3. The main toxidromes

The anticholinergic (atropine-induced) toxidrome should be considered in a patient with confusion, sinus tachycardia, symmetrically dilated pupils, thirst, dryness of the skin and mucous membranes, urinary retention (distended bladder), absent bowel sounds, and/or fever. It may indicate intake of polycyclic antidepressants, neuroleptic agents, antihistamine agents, antiparkinson drugs, or Solanaceae (datura) (full agreement).

A combination of intraventricular conduction impairment (QRS widening) and hemodynamic disorders suggests intake of a membrane-stabilizing agent (polycyclic antidepressants, chloroquine, specific beta-blockers, class I antiarrhythmic agents, or dextropropoxyphene …) (full agreement).

The sympathomimetic (adrenergic or stimulant) toxidrome manifests as agitation, seizures, hypertension in most cases (hypotension in severe forms), tachycardia, fever, hyperglycemia, hypokalemia, and/or leukocytosis. Causes include theophylline, amphetamines, and cocaine (full agreement).

The opiate toxidrome ("overdose syndrome") consists of altered consciousness with slow breathing, sinus bradycardia, and pinpoint pupils (full agreement).

Neuroleptic malignant syndrome may occur as an adverse effect of treatment or as a result of an overdose. This diagnosis should be considered in patients with confusion, generalized hypertonia with brisk deep tendon reflexes, diaphoresis, fever, hemodynamic instability, and rhabdomyolysis (full agreement).

Serotonin syndrome occurs as an adverse effect, or after an overdose, of a serotoninergic agent (MAO inhibitors, SSRI, and selective serotonin and noradrenalin reuptake inhibitors [SSNRI] …) and should be distinguished from neuroleptic malignant syndrome. When there is no recent history of neuroleptic treatment initiation or modification, serotonin syndrome should be considered in patients exhibiting at least three of the following signs: hypomanic behavior or confusion, agitation, myoclonus, brisk reflexes, mydriasis, diaphoresis, chills, tremor, diarrhea, poor coordination, and/or fever (full agreement).

Withdrawal syndrome after discontinuation of morphine derivatives or benzodiazepines should be considered in patients with insomnia, hallucinations, agitation, diarrhea, mydriasis, fever, diaphoresis, gooseflesh, tachycardia, and/or cramps (full agreement).

A combination of sensorineural disorders (including tinnitus or hypoacusis), hyperventilation, dehydration, fever, diaphoresis, and respiratory alkalosis or metabolic acidosis should prompt a search for poisoning with aspirin or a derivate (full agreement).

Apparent death with an isoelectric electroencephalogram should suggest recent acute poisoning with barbiturates, benzodiazepines, meprobamate, or chloral derivatives, particularly when hypothermia is present (full agreement).

Generalized slate-gray cyanosis that fails to respond to oxygen therapy, with normal PaO_2 and decreased SaO_2, in the absence of a cardiovascular or respiratory cause suggests methemoglobinemia, which may be due to nitrite derivatives (poppers), dapsone, or metoclopramide in neonates (full agreement).

A cholera-like syndrome should suggest colchicine poisoning (full agreement).

4. Role for toxicological tests

4.1. Usefulness of toxicological tests

The management of poisoning relies chiefly on symptomatic treatments and a clinical approach. Biochemistry tests are always more important than toxicological tests (full agreement).

Toxicological tests aim to identify and/or quantitate the toxic substance in order to confirm or refute the diagnosis of poisoning, to evaluate the severity of poisoning, or to monitor the effectiveness of treatment (full agreement). Discussion between the physician who orders the tests and the biologist who performs them is highly desirable (poor agreement).

On an emergency basis, toxicological tests are useful only if they are specific and their results can be obtained at the same time as those of standard biochemical tests. A consensus must be developed regarding the minimal list of tests that should be performed on an emergency basis and the more sophisticated tests that can be ordered later on if needed (full agreement).

4.2. Which body fluid is best for toxicological tests?

Toxicological tests are best done on blood, the body fluid in which the presence and concentration of medications or illicit substances correlate best with toxicity (severity factor or outcome factor) (full agreement).

Toxicological tests on urine may supply complementary information on xenobiotic exposure within the 24 to 48 hours preceding sample collection (cumulative data), as well as on exposure to medications or illicit substances that are rapidly cleared from the bloodstream because they have a short half-life and/or bind strongly to tissues (full agreement).

Samples for plasma and urine banks should be collected at admission when the cause of the manifestations is in doubt or signs indicating severe poisoning are present (full agreement).

4.3. Which tests, for which substances?

When acetaminophen (paracetamol) poisoning is suspected or detailed data on the nature of the toxic substances are lacking, a serum acetaminophen (paracetamol) assay should be obtained (full agreement).

Immunochemical detection in blood of benzodiazepines, tricyclic antidepressants, amphetamines, cocaine, and opiates does not contribute to the immediate management (full agreement).

In patients with severe poisoning by illicit substances, when blood immunoanalysis screening is not available, urine can be used for immunoanalysis detection of amphetamines, cocaine, and opiates (poor agreement).

Blood assays of toxic substances are in order when the results are likely to influence patient management. Examples include valproate, carbamazepine, iron, digoxin, digitoxin, lithium, acetaminophen (paracetamol), phenobarbital, salicylates, and theophylline (full agreement).

Chromatography used to detect a broad array of toxic agents in blood or urine should be reserved for patients who have severe neurological abnormalities or unexplained coma, in the absence of diagnostic orientation (full agreement).

5. Decontamination and elimination of toxic agents

5.1. Induced vomiting

Vomiting induced by oral ipecac syrup has not been shown to yield clinical benefits and should not be used (full agreement).

5.2. Gastric lavage

Gastric lavage should not be performed routinely after acute oral poisoning, as there is no evidence that this procedure improves the clinical outcome. The appropriateness of gastric lavage should be examined, with careful attention to the risk/benefit ratio, in patients seen within 1 h after ingestion of a substance that is not adsorbable by charcoal (e.g. iron or lithium), in an amount that may be life-threatening. Contraindications related to the substance or patient (inability to effectively protect the airways) should be sought (full agreement).

5.3. Activated charcoal

Administration of a **single oral dose of activated charcoal** should not be performed routinely after acute oral poisoning but instead should be considered in the light of the risk/benefit ratio. Activated charcoal may be useful when given within 1 hour of ingestion of toxic agents that are adsorbable by charcoal. There is no evidence supporting or militating against the effectiveness of charcoal given more than 1 hour after ingestion. Airway protection should be considered when examining the appropriateness of activated charcoal administration (full agreement).

Administration of **multiple doses of activated charcoal** can be considered after ingestion of sustained-release preparations and potentially life-threatening amounts of carbamazepine, dapsone, digitoxin, phenobarbital, quinine, or theophylline (full agreement).

5.4. Accelerating intestinal elimination

Available data do not support the use of **cathartics** in patients with poisoning (poor agreement).

There is no evidence that **intestinal irrigation** influences the outcome of poisoning. Intestinal irrigation may be considered after ingestion of potentially toxic amounts of substances that are not adsorbable by charcoal and are formulated as sustained-release preparations or enteric-coated tablets, as well as after ingestion of significant amounts of iron (full agreement).

5.6. Urine alkalinization

Urine alkalinization should be considered as first-line treatment for patients with salicylate poisoning who do not meet criteria for hemodialysis (full agreement). Urine alkalinization is not recommended in the management of phenobarbital poisoning (poor agreement).

5.7. Dialysis

Hemodialysis is chiefly recommended in acute-on-chronic and clinically severe chronic lithium poisoning in patients with impaired lithium elimination (increased serum half-life and decreased renal excretion). Another indication for hemodialysis is severe salicylate poisoning with severe metabolic acidosis despite sodium bicarbonate administration (full agreement). Hemodialysis has not been proved beneficial in the treatment of poisoning with other agents (poor agreement).

At present, there is no convincing evidence that continuous **hemodiafiltration** is useful for enhancing the elimination of medications (full agreement).

In patients with lithium poisoning, **hemodiafiltration** may be an alternative when hemodialysis is not available (poor agreement).

Hemoperfusion has a very limited role. It may be indicated in a small number of cases of severe theophylline or carbamazepine poisoning when repeated-dose activated charcoal decontamination is either not available or not feasible. However, the ability of hemoperfusion to reduce morbidity and mortality has not been established (full agreement).

Molecular absorbent regenerating system (MARS) therapy has no role at present in enhancing the elimination of toxic agents (full agreement).

Plasma exchange has no role in toxic agent elimination (full agreement).

Exchange transfusion is appropriate only in patients with intravascular hemolysis or severe methemoglobinemia unresponsive to symptomatic treatment (full agreement).

6. Antidotes

6.1. General principles

Antidotes for dysfunction-inducing poisons (benzodiazepines, opiates, digitalis) are defined as agents capable of improving the clinical symptoms and laboratory test abnormalities related to poisoning (full agreement).

For lesion-inducing poisons (e.g. acetaminophen [paracetamol]), the antidote should be administered before the organic lesions develop. Otherwise, even when used in effective dosages, the antidote cannot induce beneficial effects (full agreement).

The appropriateness of an antidote should be examined in the light of the expected benefits and risk of adverse iatrogenic events, and the best mode of administration should be chosen based on the respective durations of action of the poison and antidote (full agreement).

6.2. Flumazenil

Flumazenil administration is appropriate in patients requiring ventilatory assistance for a coma due to benzodiazepines or related agents (zolpidem, zopiclone), in the absence of other substances. Buspirone poisoning is not recognized as an indication for flumazenil therapy. Flumazenil should not be given on a routine basis to patients with coma of unknown origin (no toxic agent or unknown toxic agent) or when poisoning with more than one agent cannot be ruled out (full agreement).

Relative contraindications of flumazenil therapy include a history of epilepsy or co-ingestion of pro-convulsant agents (full agreement).

Flumazenil administration should be titrated and conducted under clinical monitoring. One possible dosing schedule is an initial dose of 0.3 mg in 1 min followed by additional doses of 0.1 mg per min up to a cumulative dose of 1-2 mg. Absence of a clinical response despite administration of a dose greater than 2 mg should lead to reappraisal of the diagnosis of benzodiazepine poisoning (full agreement).

Flumazenil administration as a continuous infusion has not been validated. This administration modality requires prolonged monitoring, in a continuous monitoring unit or ICU (full agreement).

6.3. Glucagon

The positive chronotropic and inotropic effects of glucagon may be helpful in the early management of beta-blocker poisoning (poor agreement).

The role for glucagon in the management of calcium-channel-antagonist poisoning is not well defined (full agreement). An initial bolus of 5–10 mg followed by a continuous infusion of 1-5 mg/h has been suggested. Glucagon cannot suffice to treat the hemodynamic complications of calcium-channel antagonist poisoning (full agreement).

6.4. Insulin-glucose

Insulin-glucose administration may be used as adjunctive treatment for acute calcium-channel-antagonist poisoning (full agreement).

A suggested insulin dosing schedule is a 10-U bolus followed by a continuous infusion of 0.5 U/kg/h. Blood glucose should be assayed hourly and blood potassium at regular intervals (full agreement).

6.5. Hypertonic sodium salt solutions

Administration of a hypertonic sodium salt solution (molar sodium lactate or bicarbonate) is appropriate at the early stage of poisoning responsible for intraventricular conduction disturbances (QRS widening) and hypotension. However, hypertonic

sodium salt solution cannot suffice to treat the hemodynamic complications seen in this situation (full agreement).

A suggested dosing schedule is administration of fractionated doses of 100 to 250 ml of molar sodium bicarbonate up to a total dose no greater than 750 ml, with serum potassium monitoring. Efficacy criteria include QRS normalization and correction of the hypotension (full agreement).

6.6. N-acetylcysteine

N-acetylcysteine has been proved effective in preventing liver damage induced by acetaminophen (paracetamol) poisoning. N-acetylcysteine therapy is appropriate in patients with severe acetaminophen (paracetamol) poisoning (estimated ingested dose ≥ 125 mg/kg) confirmed by an acetaminophen (paracetamol) assay interpreted using the Rumack and Matthew nomogram (possible or probable hepatic toxicity zones) (full agreement).

The toxic threshold of acetaminophen (paracetamol) is lowered in patients with chronic alcohol abuse, malnutrition, use of cytochrome P450 inducers, repeated acetaminophen (paracetamol) use, or concomitant use of trimethoprim/sulfamethoxazole or zidovudine (full agreement).

When the time of acetaminophen (paracetamol) ingestion is unknown, a second assay should be obtained 4 hours after the first to measure the plasma elimination half-life. Its value, usually 2-3 hours, is increased in patients with acetaminophen (paracetamol) poisoning, and hepatotoxicity is likely when the plasma elimination half-life exceeds 4 h (full agreement).

Several treatment schedules can be used in adults and children (full agreement):

- intravenously, 150 mg/kg in 1 h, followed by 50 mg/kg in 4 h then 100 mg/kg over 16 h (full agreement);
- orally, in the absence of vomiting or activated-charcoal administration, 140 mg/kg followed by 70 mg/kg/4 h for 72 h (poor agreement).

The protective effect is greatest when N-acetylcysteine is given within 10 h after acetaminophen (paracetamol) ingestion. When the patient is seen more than 24 hours post-ingestion, or evidence of cytolytic hepatitis is already present, N-acetylcysteine can be used according to the same schedule followed by 300 mg/kg/24 h until recovery (full agreement).

Anaphylactoid reactions may occur, most notably during administration of the loading dose of N-acetylcysteine, especially in patients with asthma. They are often related to excessively rapid administration of the antidote (full agreement).

6.7. Naloxone

Naloxone is indicated to treat poisoning with preferential mu-agonists, partial agonists, and agonist-antagonists. It is not effective in buprenorphine poisoning. Naloxone can be used to treat opiate-induced coma or alterations in consciousness of unknown origin with bradypnea and bilateral miosis (full agreement).

The initial dose is necessarily empirical and should be sought by titration. After correction of hematosis abnormalities by oxygen therapy or facemask ventilation, a slow intravenous injection can be given in doses of 0.1 mg (titration) every 2–3 minutes until reversal of the respiratory depression (respiratory rate ≥ 15/min). Failure to respond to a cumulative dose of 2 mg should prompt a search for another cause of coma. Full antagonism with a single bolus can induce withdrawal symptoms and is therefore not advisable (full agreement).

The duration of the clinical antagonist effect of naloxone is unpredictable, and continuous monitoring is therefore in order after the injection (full agreement).

A continuous naloxone infusion is recommended after the initial bolus when there is a risk of delayed toxicity related to a long-acting opiate (e.g. methadone) or massive heroin dose (rupture of heroin packages in the bowel) (full agreement).

6.8. Methylene blue

In patients with methemoglobinemia, methylene blue should be given when blood methemoglobin levels are ≥ 20% or when evidence of hypoxia is found, provided there are no contraindications (known allergy to methylene blue, renal failure with anuria, or glucose-6-phosphate dehydrogenase (G6PD) deficiency (full agreement).

The dosage is 1 to 2 mg/kg (0.1–0.2 ml/kg) over 10 minutes as a strictly intravenous injection. A second infusion of 1 mg/kg can be given without exceeding a total dose of 7 mg/kg (full agreement).

Failure of methylene blue therapy suggests continued absorption of the toxic agent, sulfhemoglobinemia, concomitant hemolysis, or congenital G6PD deficiency (full agreement).

6.9. Octreotide

Octreotide can be used as an antidote in patients with sulfonylurea poisoning that is unresponsive to glucose administration (full agreement).

A suggested schedule is subcutaneous injection of 50 to 100 μg octreotide every 8-12 hours, starting as soon as hypoglycemia refractory to hypertonic glucose solution administration is noted. Blood glucose levels should be monitored at least until 12 hours after the last octreotide injection (full agreement).

6.10. Antidigitalis antibodies

Evidence supporting the clinical efficacy of Fab fragments of antidigitalis antibodies is sufficiently strong that cardiac pacing should no longer be used in this situation (full agreement).

An equimolar neutralizing dose (one 80-mg bottle of Fab antidigitalis antibodies neutralizes 1 mg of digitalis in the

body) is recommended in patients with any of the following adverse criteria: ventricular fibrillation or tachycardia, severe bradycardia ≤ 40/min unresponsive to intravenous injection of 1 mg of atropine, serum potassium ≥ 5.5 mmol/L, cardiogenic shock, or mesenteric infarction (full agreement).

Semi-molar neutralization is recommended in patients with at least one of the three following factors: male gender, pre-existing heart disease, age ≥ 55 years, atrioventricular block of any degree, bradycardia < 50 bpm unresponsive to intravenous injection of 1 mg of atropine, or serum potassium ≥ 4.5 mmol/L (full agreement).

Recurrence of clinical evidence of digitalis toxicity in combination with a factor of adverse significance indicates a need for a second dose of Fab antibodies (full agreement).

Routine monitoring of serum digitalis levels after antibody administration is unnecessary (full agreement).

6.11. Vitamin B6 (pyridoxine)

Pyridoxine can be used to treat isoniazid poisoning with seizures, as an adjunct to symptomatic treatments (full agreement).

The dosage is 4 to 6 g/day or 1 g of vitamin B6 per gram of ingested isoniazid in adults (70 mg/kg in children), as a 30-minute intravenous infusion in glucose solution. The infusion can be repeated every 30 minutes until the seizures stop (full agreement).

6.12. Diazepam

In the treatment of chloroquine poisoning, a combination of artificial ventilation, epinephrine (adrenaline), and diazepam has been found beneficial in patients with factors of adverse prognostic significance (systolic blood pressure < 100 mm Hg, QRS > 0.10 s, and rhythm and/or conduction disturbances) (full agreement).

Diazepam used alone does not have proven antidotal effects in patients with chloroquine poisoning (full agreement).

6.13. Vitamin K

Vitamin K therapy is in order when accidental ingestion of an overdose of vitamin K antagonist is associated with an INR > 5 and non-minor bleeding (i.e. not gingival bleeding or induced nosebleed). The suggested dosage is 1-2 mg of vitamin K as a slow intravenous injection (full agreement).

In patients on vitamin K antagonist therapy, the INR should be brought into the target zone and checked every 24 hours (full agreement).

Vitamin K therapy is appropriate after intentional vitamin K antagonist overdosing with an INR >5 and non-minor bleeding (i.e. not gingival bleeding or induced nosebleed) or an INR > 20 without bleeding. The suggested dosage is 10 mg of vitamin K1 as a slow intravenous injection. The dose can be repeated every 12 hours (full agreement).

Immediate correction of severe bleeding (most notably cerebral hemorrhage) rests on administration of vitamin-K-dependent factor concentrate or, when not available, of fresh virus-inactivated plasma (full agreement).

After treatment with high doses of vitamin K, vitamin K antagonists may be ineffective for some time. Therefore, when vitamin K antagonist therapy must be resumed, a period of heparin therapy should be arranged (full agreement).

7. Symptomatic management (neurological, respiratory, and hemodynamic support)

Organ failures must be managed on an emergency basis, without waiting for investigations or decontamination–elimination procedures (full agreement).

7.1. Neurological complications

Good knowledge of the array of mechanisms by which poisoning can lead to neurological complications is essential to ensure appropriate management. The outcome is closely dependent on the mechanism – functional impairment or lesion – of the central-nervous-system abnormalities (full agreement).

Medication-induced alterations in consciousness are usually related to functional disturbances responsible for a transient and reversible abnormality in central-nervous-system function (full agreement).

Neurological abnormalities may be related to concomitant organ failure (cardiovascular or respiratory failure for instance) or metabolic disturbances (e.g. hypoglycemia, acidosis, or hypoxia), which must be looked for and treated immediately (full agreement).

An obvious toxic cause does not rule out another cause to the neurological abnormalities (full agreement).

A careful neurological examination is essential to evaluate the depth of the coma and its presentation and to look for focal or brainstem signs, which suggest an organic cause (full agreement).

Although the Glasgow Coma Scale score (GCS) is ill-suited to poisoning settings, it is widely used to assess coma severity and changes over time. The GCS score is also a useful guideline for intubation, although it should be used in combination with other criteria (full agreement).

The GCS is not reliable for evaluating toxic encephalopathy, because it fails to accurately estimate the severity of poisoning in this situation (full agreement).

Capillary blood level measurement and urine dipstick testing (for glucose and ketone bodies) should be performed routinely, even when poisoning is obvious (full agreement).

Airway protection is a foremost concern and should be achieved prior to evacuation (gastric lavage) and/or inactivation if these are indicated (full agreement).

Rapid-sequence anesthesia induction is recommended for intubating patients with poisoning, in the absence of contraindications (full agreement).

Seizures caused by poisoning or occurring in the setting of poisoning should be treated with benzodiazepines initially then with barbiturates if they persist (full agreement).

Metabolic abnormalities and/or profound hypoxia associated with poisoning and possibly responsible for the seizures must be corrected (full agreement).

There is no evidence supporting the empirical routine use of an antidote combination (coma cocktail: glucose, thiamine, naloxone, and flumazenil) in patients with unexplained coma (full agreement).

Antidotes such as naloxone and flumazenil can be given to patients with poisoning and neurological abnormalities, in compliance with recommended indications and modalities of use (full agreement).

Hypertonic glucose solution is appropriate in all patients with coma and hypoglycemia, regardless of the presumed cause of the coma (full agreement).

Brief sedative treatment may be appropriate in a patient with poisoning and coma or encephalopathy, in order to control agitation or to allow mechanical ventilation (full agreement).

Oxygen therapy is recommended in patients with alterations of consciousness and should be monitored (full agreement).

7.2. Respiratory complications

Bradypnea should prompt a search for opiate poisoning. Naloxone lifts opiate-induced respiratory depression and improves consciousness (full agreement).

Using blood gas values to differentiate Type I and Type II respiratory failure is important to guide the initial treatment: improving oxygenation is the priority in Type I respiratory failure, and in Type II mechanical ventilation should be started immediately (poor agreement).

The parameters used to monitor mechanical ventilation in patients with poisoning are the same as in other conditions. Mechanical ventilation requires close monitoring initially given the risk of hemodynamic failure (toxin-induced vasoplegia syndrome), barotrauma (cocaine), or acid-base imbalance (full agreement).

Noninvasive respiratory assistance is not appropriate, since consciousness is altered. Orotracheal intubation is the technique of choice for ensuring airway patency during respiratory assistance (full agreement).

Neuromuscular blockade is appropriate in patients with malignant hyperthermia or when chest-wall muscle hypertonia contributes to the mechanism of poison-induced respiratory failure (full agreement).

Rapid weaning is often possible in patients with Type II respiratory failure. In Type I, a stepwise decrease in oxygenation conditions is in order (poor agreement).

7.3. Circulatory complications

An essential step is careful identification of each potential mechanism of toxicity: the substance may exert direct toxic effects on the heart and blood vessels and/or indirect toxicity (hypovolemia, hypoxia, metabolic disturbances …) (full agreement).

Cardiac arrest may occur very early as a result of asystole, cardiac inefficacy, or ventricular fibrillation. Cardiac arrest requires immediate and prolonged management (full agreement).

In patients with serious intraventricular conduction disorders, 8.4% sodium bicarbonate is recommended in a dose of 100 to 250 ml over 15 to 20 min, without exceeding 750 ml (full agreement).

External cardioversion is recommended to treat serious ventricular rhythm disorders. When these recur, most notably after poisoning with membrane-stabilizing agents, most of the antiarrhythmic agents are contraindicated. Circulatory assistance should be considered in this situation (full agreement).

Magnesium sulfate (2-g bolus as a slow intravenous injection then maintenance infusion of 3-20 mg/min) is recommended in patients with torsades de pointes; should this event recur, isoprenaline (1 mg in a titratable infusion) and pacing are in order (full agreement).

Beta-blocker therapy (e.g. esmolol, 500 μg/kg bolus in 1 min then 50 μg/kg/min for 4 min) is often effective in correcting tachycardia induced by theophylline, amphetamines, or thyroid hormones (full agreement).

Atropine (0.5 to 1 mg) is the first-line treatment of sinus bradycardia or low-degree atrioventricular block. Atropine may be effective in the higher-degree atrioventricular blocks that are often seen in poisoning with beta-blockers or calcium channel antagonists. Betamimetics (isoprenaline or adrenalin) or pacing should be considered (full agreement).

Severe rhythm and conduction disorders in a patient with digitalis poisoning indicate an absolute need for Fab antidigitalis antibodies in addition to symptomatic measures (full agreement).

Cardiovascular collapse or shock is a dreaded complication. Knowledge of the underlying mechanism (hypovolemia, vasodilation, contractility disorders) is essential to guide the choice of treatment. In severe cases, invasive or noninvasive hemodynamic investigations are warranted (full agreement).

Fluid resuscitation, which is appropriate in patients with true hypovolemia, should be carried out under close monitoring, given the risk of concomitant heart failure. Cardiovascular collapse related to vasodilation requires the administration of vasoconstrictors (norepinephrine [noradrenaline] and, if needed, dopamine). Heart failure due to contractility disorders should lead to the administration of betamimetic amines: adrenaline, isoprenaline, or dobutamine. High doses may be needed in patients with severe shock (full agreement).

Use of other agents that exhibit inotropic effects (glucagon, phosphodiesterase inhibitors, calcium salts, euglycemic insulin) may deserve consideration, with or without catecholamines. However, they are inconsistently effective (full agreement).

When the above-discussed treatments fail, in patients with persistent circulatory arrest or refractory shock, circulatory assistance should be considered (full agreement).

7.4. Hepatic complications

In patients with fulminating hepatitis (encephalopathy, prothrombin time TP < 30% and factor V < 30%, lactic acidosis, renal failure), a liver transplantation center should be contacted promptly (full agreement).

Liver assistance methods (MARS, ELAD) can be used while waiting for the transplantation (full agreement).

8. Psychiatric management

8.1. General considerations

Patients with intentional poisoning should be kept under adapted and continuous surveillance in the ICU, as a repeat attempt, although rare, may occur rapidly (full agreement).

Contact with the family should be facilitated and should occur in the presence of ICU staff. Visits should be allowed providing the patient consents (full agreement).

All patients admitted to the ICU for intentional poisoning should be evaluated by a psychiatrist as soon as clinically possible, in a manner that complies with a high standard of care, most notably regarding the protection of patient confidentiality (full agreement).

Agitation, aggressive behavior, or anxiety should be managed appropriately (anxiolytic agents, sedatives, or even physical restraint) until a psychiatric evaluation can be performed. Should the patient ask to leave against medical advice, the family and/or close friends (proxy) should be informed, and all events should be recorded in the medical chart while awaiting the psychiatric evaluation (full agreement).

Patients belonging to high-risk groups should undergo a careful psychiatric evaluation and are more likely to be admitted to a psychiatric ward. High-risk groups are defined as meeting any of the following criteria (full agreement):

- Psychiatric disorder;
- multiple suicidal attempts, particularly when closely spaced;
- children and adolescents;
- older individuals;
- social isolation;
- concomitant chronic addictions;
- patients having more than two risk factors for suicide;
- family history of suicide;
- Chronic incapacitating organic disease;

Special attention should be given to criteria for suicidal intent as additional factors of adverse significance (full agreement):

- premeditation;
- dissimulation;
- steps taken to dispose of possessions (e.g. donations);
- delivery to family or friends of a message that is tantamount to a will;
- choice of ingestant;

When a further attempt seems likely in the short term, admission to a psychiatric ward is in order in patients with (full agreement):

- no criticism of their suicidal attempt and persistent active suicidal ideation;
- major anxiety;
- patent psychiatric disorder: major depression, melancholia, acute psychotic disorder or destabilization of a chronic disorder, personality disorder with impulsiveness and organic dementia;
- massive addiction (alcohol abuse, drug addiction);
- traumatic life-changing event;
- recent discharge from a psychiatric ward;
- no possibility of support from family and friends, social isolation, poverty;
- unrecognized drug withdrawal;

When admission to a psychiatric ward is considered appropriate but is declined by the patient, hospital admission should be arranged (according to French law n°90-527 of June 27, 1990) either at the request of a third party or, exceptionally, under compulsion (full agreement).

When planning to discharge a patient admitted for self-poisoning, follow-up psychiatric care should be arranged (post-emergency psychiatric visit, local psychiatric follow-up network, or admission to a psychiatric ward) (full agreement).

The psychiatrist should strive to establish or re-establish a strong therapeutic relationship between the patient and the physician in charge of follow-up. The psychiatrist should evaluate the appropriateness of resuming previous treatment with psychotropic agents and should determine the best dosage and optimal time for restarting, in the light of the effects of the overdose. This last point should be discussed with the intensivists. Temporary treatment with adjusted dosages is often appropriate until the patient's next appointment with the usual psychiatrist (full agreement).

9. Points specific of pediatric patients

9.1. Definition and epidemiology

Severe poisoning is defined as a need to monitor the child in a pediatric ICU either because the amount ingested is potentially lethal or because severe symptoms are present (coma, respiratory distress, and/or hemodynamic instability). Criteria for pediatric ICU admission are the same as in adults (full agreement).

Only 0.5 to 2% of all pediatric cases of medication overdose require admission to the pediatric ICU. The medications most often taken by children admitted to the ICU are agents that affect the central nervous system (sedatives, hypnotic agents, anticonvulsants, antidepressants, opiates …). The medications most often involved in fatal cases are polycyclic antidepressants, anticonvulsants (barbiturates, sodium valproate…), anti-

pyretics (acetaminophen [paracetamol], aspirin…), and iron-based medications (full agreement).

Severe poisoning by medications and illicit substances occurs with two frequency peaks in children, at 36 months and 14 years of age, respectively. These two peaks reflect different mechanisms, with cases in young children being accidental (and occurring either at home or in the hospital as a result of a dosage error) and cases in teenagers being intentional. Accidental cases are more common in males and intentional cases in females. Mortality is less than 2% and increases with age. Intentional poisoning is more likely to involve multiple agents (full agreement).

In children, caution is recommended regarding the ingestion of small amounts of potentially lethal medications (calcium-channel antagonists, clonidine, tricyclic antidepressants, opiates, salicylates, hypoglycemic sulfonylureas) (full agreement).

9.2. Specific diagnostic considerations

Toxidromes have no specific features in pediatric patients (full agreement).

The role for toxicological tests in pediatric patients is the same as in adults (full agreement).

9.3. Specific considerations regarding decontamination and elimination of toxic agents

The indications for gut decontamination and enhanced elimination of toxic agents are the same as in adults. A few features specific of pediatric patients are related to the dosages used:

- ipecac syrup should no longer be used (full agreement).
- for gastric lavage, use 50–100 ml of isotonic fluid for each cycle in children and 250–350 ml in adolescents (full agreement);
- activated charcoal is used in a dosage of 1 g/kg body weight up to a total of 75 g (full agreement);
- to enhance intestinal elimination, give activated charcoal in a dosage of 1 g/kg body weight every 4 h to 6 h (full agreement);
- for intestinal irrigation, the recommended flow rate of polyethylene glycol electrolyte solution is 25 ml/kg/h in children and 1.5–2 L/h in adolescents (poor agreement).

9.4. Specific points related to symptomatic treatments and antidotes

Symptomatic treatment in pediatric patients is the same as in adults (full agreement).

Doses of antidotes may differ between pediatric patients and adults (full agreement).

The recommended flumazenil dosage in children is 10 μg/kg as a slow intravenous injection, followed if needed by a continuous infusion of 10 μg/kg/h if required by the patient's clinical status (poor agreement).

Glucagon therapy is appropriate in pediatric patients with beta-blocker overdose who have refractory hypoglycemia and/or myocardial depression (which usually indicate massive intentional poisoning) in addition to vasopressors (full agreement).

Recommended glucagon dosages are as follows:

- refractory hypoglycemia: subcutaneous, intravenous, or intramuscular injection of 0.5 mg if body weight is < 20 kg and 1 mg otherwise (full agreement);
- myocardial depression: subcutaneous, intravenous, or intramuscular injection of 0.025 mg to 0.1 mg/kg (up to 1 mg per injection) followed by an intravenous infusion of 0.025 mg/kg/h for 5 h to 12 h as dictated by the clinical course (full agreement).

In patients with calcium channel antagonist poisoning and myocardial depression, glucagon can be used as an adjunct to vasopressors in the dosage recommended for severe beta-blocker poisoning (poor agreement).

In children with hypoglycemic sulfonylurea poisoning, glucagon therapy is recommended only after failure of an infusion of hypertonic glucose solution (titrated to obtain a blood glucose level greater than 0.6 g/L) and intravenous octreotide injection if available (full agreement).

The recommended octreotide dosage in children is 1–5 μg/kg/d divided in four injections (maximum: 50 μg/injection). A continuous intravenous infusion may be needed, and the recommended starting dosage is 15 ng/kg/min (full agreement).

9.5. Specific points related to illicit substances and new drugs

Cases of accidental methadone poisoning have started to occur in pediatric patients, some with a fatal outcome, in parallel with the increasing therapeutic use of methadone in adults. Most of the cases occurred in children whose parents were on methadone therapy. Factors that contribute to increase the severity of methadone poisoning in children include tablet strength (a single dose that is low for an adult, i.e. 10–20 mg, may be lethal in a young child), possible poor parenting, and feelings of guilt that may lead to parents to delay taking their child to the emergency room (full agreement).

Accidental ecstasy (3,4-methylenedioxymethamphetamine) poisoning remains very rare in young children, whereas cases of severe poisoning due to recreational ecstasy use are beginning to be reported in adolescents. The clinical manifestations may develop earlier than in adults (20-30 minutes post-ingestion). Inaugural seizures may be more common in the pediatric population (full agreement).

10. Specific features of poisoning with new drugs

10.1. Cocaine and crack

Hyperthermia related to cocaine must be promptly controlled by cooling. Benzodiazepines may also contribute to combat hyperthermia (full agreement).

Benzodiazepines constitute the first-line treatment for agitation and seizures (full agreement).

Beta-blockers are contraindicated as pharmacotherapy to treat cocaine-related hypertension (full agreement).

Acute coronary syndromes should be treated as usual (full agreement).

Medications that may act synergistically with cocaine should be avoided. They include alpha-adrenoceptor agonists, vasoconstricting agents, tricyclic antidepressants, anticholinesterase agents, local anesthetics, pancuronium, ketamine, and naloxone (full agreement).

10.2. Opiates

In patients with poisoning by opiates or opiate-like agents, two approaches can be considered: intubation and mechanical ventilation or naloxone (except with buprenorphine poisoning) (full agreement).

In heroin and methadone poisoning, naloxone is effective and obviates the need for intubation. With methadone, maintenance treatment and prolonged monitoring in a continuous care unit are in order (full agreement).

10.3. Other drugs

Recreational drugs have emerged (ecstasy, LSD, GHB [gamma-hydroxybutyrate], BD [butanediol], GBL [gamma-butyrolactone], poppers, ketamine, psilocybes, datura, …) and are often encountered in the setting of multiple-drug poisoning and/or dependency. The use of these drugs has increased sharply, most notably among younger individuals (full agreement).

Use of cannabis (active substance, THC ou tetrahydrocannabinol) is not directly life-threatening. Symptoms that suggest cannabis use include tachycardia, confusion, euphoria, and/or psychomotor agitation (poor agreement).

Use of 3,4-methylenedioxymethamphetamine (ecstasy) can lead to severe serotonin syndrome with a risk of death that is independent from the dose and duration of use. Hyperthermia is a consistent feature in severe forms. The overcrowding and physical activity associated with recreational settings increase the risk. Death may occur in a setting of malignant hyperthermia, seizures, and multiple organ failure (full agreement).

The treatment of ecstasy-induced serotonin syndrome relies chiefly on symptomatic measures (external cooling, sedation, neuromuscular blockade using nondepolarizing agents, catecholamines, and correction of fluid and electrolyte imbalances). Cyproheptadine, olanzapine, or chlorpromazine have been suggested but remain unproven. Propranolol, bromocriptine, and dantrolene are not recommended (full agreement).

GHB or its precursors (BD and GBL) should be considered in the setting of chemical submission or recreational drug use. GHB causes a transient coma (< 3 h) with a risk of respiratory depression. The treatment is symptomatic. Naloxone, physostigmine, and flumazenil are ineffective (full agreement).

Poppers (nitrite derivatives) cause methemoglobinemia. Methylene blue is the antidote and should be used in patients with symptoms or with a blood methemoglobin level > 20% (full agreement).

Acute poisoning with datura, a hallucinogenic plant used for recreational purposes, should be considered in patients with anticholinergic syndrome or a coma and seizures. The treatment is symptomatic and includes benzodiazepines. The use of physostigmine is controversial. Decontamination of the gut has not been evaluated (full agreement).

Psilocybes are hallucinogenic mushrooms that are ingested as an addictive behavior. The symptoms develop after 30 min, last 2 to 4 h, and usually resolve within about 12 h. Seizures may occur after massive ingestion. The treatment is symptomatic (full agreement).

A Poison Center or Toxic Exposure Surveillance System should be contacted routinely about patients who develop confusion and hallucinations during recreational activities Nationwide analysis, collation, and synthesis of cases provide valuable surveillance data on new substances (as shown for cocaine/atropine mixtures), as well as on frequency and modalities of use (full agreement).