Extracorporeal Therapy for Drug Overdose and Poisoning

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Vimal Chadha

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Introduction

Poisoning continues to be a significant cause of morbidity and mortality. The 2008 Annual Report of the American Association of Poison Control Centers (AAPCC) published information on 2,491,049 human exposure cases of poisoning, half of them being children younger than 6 years [1]. Prescription drugs, over the counter medications, illicit drugs, and common household substances can all be responsible for poisoning. As per the 2008 Annual Report, the top four most frequently involved substances in all human exposures were analgesics (13.3%), cosmetics/personal care products (9.0%), household cleaning substances (8.6%), and sedatives/hypnotics/antipsychotics (6.6%). Most (82.8%) poison exposures were unintentional, and suicidal intent was suspected in 8.7% of cases. In 10.6% of exposures (263,942 cases), poisoning resulted due to therapeutic errors such as inadvertent double-dosing, incorrect dosing, wrong medication taken or given, and inadvertent exposure to someone else's medication.

The management of poisoning is a significant burden on health care. In 2008, approximately one-fourth of all cases received treatment in a health care facility. While half of them were treated and released without admission, 93,096 (15.6%) had to be admitted for critical care management. Treatment in a health care facility was provided in a higher percentage of exposures that involved pharmaceutical substances (26.4%) compared with non-pharmaceutical substances (14.1%), and exposures to pharmaceuticals resulted in more severe outcomes. Although children younger than 6 years were involved in the majority of exposures, fortunately they comprised just 2.0% of the exposure-related fatalities.

Management of the Poisoned Patient

The general approach to the management of an acute poisoning includes:

1. Patient stabilization (maintenance of the airway, ventilation, and hemodynamic status)
2. Establishing accurate diagnosis by clinical evaluation which in many cases is aided by

V. Chadha, MD (✉)
Department of Pediatrics, Section of Pediatric Nephrology, Children's Mercy Hospitals and Clinics, Kansas City, MO, USA
e-mail: vchadha@cmh.edu

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identification and determination of blood concentration of the toxic substance
3. Decontamination (removal of poison from site of absorption such as GI tract or skin)
4. Administration of antidotes, if available
5. Supportive care (treatment of hypotension, arrhythmias, respiratory failure, electrolyte imbalance, and seizures)
6. Elimination of poison by manipulation of urinary pH
7. Removal of poison by extracorporeal therapies

It is important to note that a large group of patients can be managed by approaches 1–6 with excellent results. Nonetheless, some of these standard therapies such as usage of ipecac syrup, gastric lavage, and forced alkaline diuresis have recently come under intense scrutiny and fallen out of favor [2]. For detailed information regarding use of oral sorbents, specific antidotal therapies, supportive care, and forced alkaline diuresis, the reader is referred to standard emergency medicine and toxicology texts [3–5].

This chapter will mainly focus on a specific category of poisoned patients in whom active removal of the toxic substance through the use of extracorporeal therapies is deemed necessary. Patients in this category can be divided into three subgroups:

1. Patients intoxicated with poisons that cause direct tissue damage (*vide infra*)
2. Patients intoxicated with poisons that do not cause direct tissue damage, but patient's ability to metabolize or excrete the toxic substance is compromised
3. Patients intoxicated with poisons in which active poison removal is considered to avoid prolonged supportive care and its associated complications

For practical purposes, the toxic substance (poison or a drug) can be divided into two broad categories: those that cause tissue damage and those that do not. Tissue damage is defined as irreversible or slowly reversible structural or functional changes in one or more organ systems that occur as a direct result of the poison (or its toxic metabolite) in the body. Poisons such as aspirin, acetaminophen, and methyl alcohol can cause direct tissue damage despite provision of intensive supportive care [3, 6–8]. In patients poisoned with this group of chemicals, use of specific antidote (if available) and/or active removal of the poison by extracorporeal therapies is necessary to prevent irreversible tissue damage. The second group of poisons such as barbiturates and other common sedative/hypnotic drugs do not have any direct tissue damaging effect but cause harm indirectly due to respiratory compromise or hypotension. These patients can be treated with specific antidote (if available) and supportive care, provided they will metabolize and/or excrete the poison in a reasonable time.

Extracorporeal Therapies for Active Poison Removal

To be worthwhile, the rate of poison removal by an extracorporeal method must be significantly greater than the spontaneous rate of elimination by hepatic and/or renal excretion, unless the intrinsic clearance is impaired by the disease process, and extracorporeal method is the only means of providing useful clearance. According to the 2008 annual report of the AAPCC, out of 93,096 patients admitted for critical care management, only 2,177 (<2.5%) were treated with hemodialysis while hemoperfusion was carried out in merely 27 patients [1]. The reason for such restricted usage of extracorporeal therapies despite the fact that techniques such as hemodialysis are highly efficient in removal of small molecular weight chemicals from circulation is that in relatively few cases, such as poisoning with methanol, ethylene glycol, valproic acid, carbamazepine, acetylsalicylic acid, and lithium, does the extracorporeal removal have a significant impact on patient outcome.

Since poisons achieve their toxic effects on target organs via the blood stream, it seems logical that their elimination from the blood should result in amelioration of the patient's condition. Accordingly, changes in the serum drug levels are the most frequently used parameters of response to extracorporeal therapy in intoxication; however,

this pretext can be misleading and provides false assurance of dialysis efficacy. To better understand these perplexities, the nephrologist ought to be well versed with the basic concepts of drug kinetics and principles of detoxification when dealing with the management of an acutely poisoned patient. These concepts also help in determining the usefulness of extracorporeal therapy as well as selection of the optimum modality for drug removal.

General Pharmacokinetic Concepts and Principles of Extracorporeal Therapy

Volume of Distribution

Volume of distribution (V_d) is an imaginary space that represents the volume of fluid in which a known amount of drug would have to be diluted to yield the measured serum concentration. Theoretically, if body is presumed to be a single compartment and a substance is homogenously distributed in body water without binding to protein or accumulating in tissues, it would have an apparent V_d equal to the total body water.

$$V_d\,(\text{Liters}) = 0.6\ \text{L/kg} \times \text{body weight}\,(\text{kg}) \quad (42.1)$$

For some substances such as methanol, that distribute in body water without significant binding to tissue or plasma protein and without significant accumulation in adipose tissue, the apparent V_d corresponds to a physiologic space; in this case equivalent to total body water. However, most substances are not homogeneously distributed but rather vary in their concentration throughout the body as a result of lipid solubility, protein binding, active cellular transport, and pH gradients, and as a result V_d can vary over a wide range of values (0.2 L/kg for valproic acid to 20 L/kg for imipramine). A V_d significantly larger than actual body water reflects a high degree of tissue concentration, while a small V_d suggests concentration within the intravascular space.

Volume of distribution is clinically important in two ways. First, knowing the V_d and plasma concentration of a particular drug allows calculation of the total amount of the drug in the body, as:

$$X(\text{mg}) = V_d(\text{L}) \times C_p(\text{mg/L}) \quad (42.2)$$

where X is the total amount of the drug in milligrams (mg) and C_p is the plasma concentration in mg/L. Second, V_d is one of the factors that determines accessibility of a drug to removal by extracorporeal therapy; a large V_d implies that the amount of drug present in blood represents only a small fraction of the total body load. Thus, even if hemodialysis session extracts most of the drug present in blood flowing through the circuit, the amount of drug removed represents a small percentage of the total body drug burden. Volumes of distribution of some of the common substances involved in poisoning are listed in Table 42.1. It is important to note that these values for V_d are derived from general population under normal dosing conditions and may not apply in the situation of a substantial drug overdose. In addition, the presence of renal and/or hepatic dysfunction in a poisoned patient can further alter the value of V_d.

Protein Binding

Many substances bind with varying affinity to plasma proteins, such as albumin or to intracellular proteins in the tissues. Thus, in addition to dissolving in fat, substances can accumulate in tissues according to their degree of protein binding. Protein binding limits the amount of free drug available for removal across dialysis membranes. Highly protein-bound substances are therefore not amenable to therapy with extracorporeal modalities. However, at toxic levels the protein binding sites are usually saturated, resulting in higher percentage of unbound fraction that can be effectively removed by dialysis therapy. In addition, albumin can be added to the dialysate where it acts as a "sink" to bind any free toxin that crosses the dialyzer membrane with a concentration gradient from the blood to the dialysate side [9].

Table 42.1 Properties of substances frequently involved in poisonings

Substance	Molecular weight (Da)	Volume of distribution (L/kg)	Protein binding (%)	Preferred extracorporeal modality
Acetaminophen	151	0.95	25	MARS
Aminoglycoside	*	0.2–0.3	<5	HD
Amphotericin B	924	4.0	90	–
Benzodiazepine	*	0.3–6.6	85–98	–
Carbamazepine	228	0.8–1.6	75	HDF[a], PP
Digoxin	765	5–8	20–30	–
Ethanol	46	0.7	0	–
Ethylene glycol	62	0.6	0	HD, HF
Indomethacin	327	0.12	99	–
Isopropyl alcohol	60	0.7	0	HD, HF
Lithium	7	0.5–0.9	0	HF, HD
Methanol	32	0.7	0	HD, HF
Methotrexate	456	0.76	45–50	HP
Narcotic	*	3–16	*	–
Phenobarbital	232	0.7–1.0	40–60	HD, HP
Phenytoin	252	0.55	90	–
Salicylate	138	0.1–0.2	80–90	HD, HF
Theophylline	*	0.4–0.7	55	HD, HP
Tricyclic antidepressants	*	6–50	90–97	? PP
Valproate	144	0.19–0.23	90	HDF[a], PP

MARS Molecular adsorbent recirculating system, *HD* hemodialysis, *HF* hemofiltration, *HP* hemoperfusion, *HDF* hemodiafiltration, *PP* plasmapheresis

[a]Addition of albumin to the dialysate has been shown to enhance the elimination of carbamazepine and valproate [10, 11]

*Variable depending on specific drug

?Questionable efficacy

This technique has been shown to be very efficient in enhancing the clearance of valproic acid and carbamazepine [10, 11]. It is also important to note that most drug-protein bonds are weak and easily reversible, and protein binding can be altered by a number of variables such as pH, and drug competition for the binding sites.

Membrane Transport

Transport across dialyzer membrane can occur by diffusion or by convection. Diffusive transport is the average of the random motion of the huge number of individual molecules with a net movement down their concentration gradient. As the random motion of smaller molecules is faster than those of larger molecules, small molecules diffuse and equilibrate faster than large molecules. Concentration gradient and membrane surface area are the two other major determinants of diffusive transport. During convective transport, dissolved molecules are carried along with the fluid (solvent drag). The transport of the molecules across the membrane is limited by the membrane pore size. The ratio of the substance concentration in the filtrate to its plasma concentration is known as sieving coefficient which along with ultrafiltration rate is the major determinant of convective transport.

Lipid Solubility

Lipid solubility affects the accumulation of drug in lipid-rich tissues such as adipose tissue and brain. The degree of lipid solubility of a substance is expressed by its partition coefficient, which is an in vitro measurement of the ratio of lipid (nonpolar) phase to aqueous (polar) phase concentration of its nonionized form. Lipid-soluble drugs can accumulate extensively in the adipose tissue and act as reservoir with poor accessibility due to decreased vascular perfusion.

Ionization

Nonionized substances are more lipid soluble and, therefore, more easily transported across cellular membranes in the body than their ionized form. The pK of the substance is the pH at which it is half ionized and half nonionized. An acid is increasingly ionized as the pH rises above its pK, and a base is increasingly ionized as pH falls below its pK. pH gradients across cell membranes can affect the extent of diffusion by trapping the ionized form on one side. In stomach and kidney, where large pH gradients exist (or can be induced) with respect to plasma, this has therapeutic implications.

Intercompartmental Transfer

In a single compartment model, a change in plasma level would reflect similar change in levels throughout body. Unfortunately, most substances in the body are distributed in multiple compartments and movement across these compartments is variable and dependent on several factors. Knowledge of these parameters is crucial in understanding the relationship between blood level and drug removal during extracorporeal therapies [12].

Drug Removal

The efficacy of any extracorporeal therapy is assessed by the accurate determination of the amount of drug removed from the body. Several parameters such as dialysance or clearance, efficiency ratio, extraction ratio, and mass removal are commonly utilized to scientifically assess drug removal from the body in an attempt to determine the success or failure of the intervention.Dialysance (D) is a measure of solute removal by dialysate, and in most modern systems is technically same as clearance (C), as concentration of the toxic substance in the dialysate is minimal in single-pass dialysis with high dialysate flow rates. Clearance (C) for hemodialysis is expressed as:

$$C = Q_b \times (A - V)/A \qquad (42.3)$$

where Q_b is the blood flow rate, A is the arterial or inlet concentration, and V is the venous or outlet blood concentration of the toxic substance. Note that (A – V)/A is termed as extraction ratio (E_x) that represents the solute removed as a fraction of the maximum it is theoretically possible to remove. For continuous renal replacement therapy, clearance (C) is expressed as

$$C = E/P \times Q_e \qquad (42.4)$$

where E is the effluent concentration, P is the plasma concentration of the toxic substance, and Q_e is the effluent flow rate which can be Q_{uf} (ultrafiltrate), or Q_d (dialysate), or $Q_{uf} + Q_d$. The term E/P is also known as sieving coefficient that is equivalent to extraction ratio (E_x). As is apparent, these clearance calculations are based on plasma concentration of the substance and the results can be misleading in terms of effectiveness of dialysis therapy unless drug distribution and inter-compartmental kinetics are also taken into account. To understand this better, consider a drug "x" with a large volume of distribution of 20 L/kg. One gram of this drug when given to a 30 kg child will yield a plasma concentration of 0.0016 mg/mL (42.2). With maximal extraction at a blood flow rate of 200 mL/min, clearance could theoretically be 200 mL/min, which is equivalent to drug removal of 0.32 mg/min or 76.8 mg in 4 h, which is less than 10% of the total given dose. As illustrated by this example, the dialysis is highly efficient, but it is not very effective as the reduction in drug burden is minimal.

For clinical efficacy, one can compare the drug half-lives, or their clearance rates from the body with and without treatment; this is also known as efficacy ratio. Half-life is calculated as:

$$\text{Half-life } (t\,½) = 0.693/K_e$$
$$K_e = [\log(C_{peak}) - \log(C_{trough})]/t_{interval} \qquad (42.5)$$

where K_e is the elimination rate constant, C_{peak} and C_{trough} are two plasma levels separated by time interval "t" (these levels need not be "true" peak and trough as long as they are separated in time and realizing that the longer the interval the better the estimate). Drug clearance is calculated as:

$$C = 0.693 \times V_d/t\,½ \qquad (42.6)$$

where V_d is the volume of distribution of drug in question. Efficacy ratio can then be calculated as t′½/t½ or C′/C, where t′½ and C′ are half-life and clearance with treatment, and t½ and C are half-life and clearance without treatment, respectively.

Specific Toxicological Issues in Neonates and Young Infants

The implications and management of poisoning in newborns and young infants requires understanding of their unique physiology. Primarily, the organs that play an important role in susceptibility to and moderation of toxic reactions such as the liver and kidney are immature in their function. Their gastric emptying is slower and gastric pH is higher which can enhance absorption of certain drugs thus increasing their susceptibility to toxicity. Once absorbed, the drug distribution varies considerably during the neonatal period and infancy largely due to age-related variations in protein binding, body fat, and total body water [13]. Overall, protein binding of drugs is reduced and body fat and total body water are increased in the neonate. This may result in an increase in the apparent V_d and consequent increase in the elimination half-life of the drug. Furthermore, the reduction in protein binding may result in an increased concentration of free (unbound) drug with a potentially augmented pharmacological response for a given drug concentration in the plasma. As mentioned before, due to the immaturity of their liver function, this group of patients has a decreased capacity to metabolize drugs in the liver due to significantly lower activity of cytochrome P-450–dependent mixed-function oxidases. In addition, the renal clearance of drugs is reduced and various tubular functions are suboptimal.

Finally, successful usage of extracorporeal techniques in infants and young children is technically complex and can be carried out only in few specialized centers. Obtaining a suitable vascular access can also become very challenging. In these situations, exchange transfusion that can be easily performed in neonates may be used successfully for eliminating certain toxins that have a low V_d.

Modalities of Extracorporeal Therapy

Hemodialysis

Hemodialysis is widely available and has been used for detoxification purposes for a long period of time. To be effectively removed by hemodialysis, a substance must have favorable pharmacokinetic profile such as small molecular weight (<500 Da; currently available high-efficacy dialyzers can provide useful clearance for molecular weights up to 2,000 Da), should be water soluble with a small V_d (<1 L/kg), without significant protein binding, and rapid equilibration with the plasma water compartment. In addition the substance must be nonionized so that it can easily diffuse across the dialysis membrane. For drugs such as methanol, ethylene glycol, aspirin, and lithium which have these pharmacokinetic characteristics, hemodialysis is an effective treatment for drug clearance.

Hemodialysis has been commonly used for alcohol (methanol, ethylene glycol, isopropyl alcohol) and salicylate poisoning. Methanol has a low molecular weight, is water soluble, and has a V_d of 0.6 L/kg. In addition, methanol is metabolized to more toxic substances such as formaldehyde and formate that are also dialyzable. Historically, a plasma concentration of 50 mg/dL has been used as a threshold for the need for dialysis in both ethylene glycol and methanol poisonings [6, 14, 15]. Adjunctive management has traditionally included correction of acidosis and administration of ethanol which competitively inhibits the metabolism of methanol by alcohol dehydrogenase [16]. Similar use of hemodialysis and ethanol could be considered for ethylene glycol, while hemodialysis alone would be useful for isopropyl alcohol and severe ethanol intoxication. However, the availability of fomepizole, a safe and effective inhibitor of alcohol dehydrogenase, has altered the indications for HD [17–20]. While HD continues to be a useful and often necessary adjunct in the treatment of toxic alcohol poisonings, an elevated blood concentration of the alcohol alone is no longer considered sufficient to require HD.

Although highly protein bound, salicylates have very low V_d and are amenable to removal by hemodialysis. The decision to perform hemodialysis is usually made on clinical parameters rather than plasma salicylate concentration. Clinical indications for hemodialysis include the presence of coma, seizures, cerebral or pulmonary edema, renal failure, refractory acid–base disturbances, or clinical worsening despite treatment. While sole reliance on the plasma salicylate concentration is not advised, serious consideration for hemodialysis, however, should be given to acutely poisoned patients with salicylate concentrations of at least 100 mg/dL or chronic patients with salicylate concentrations of at least 60 mg/dL [21].

While hemodialysis has a long track record for safety, it is associated with many potential complications that are outlined elsewhere in the text. In particular, one must be aware that the dialysis process may remove other drugs, such as antibiotics and cardiomimetics. Thus, these drugs must be delivered distal to the dialyzer and will perhaps require higher doses to be effective.

Continuous Renal Replacement Therapy (CRRT)

Continuous renal replacement therapies provide clearance through both convection and diffusion mechanisms, either alone or in combination. For larger molecules, convection can provide better clearance than that achieved by diffusion. Due to its continuous nature, CRRT is beneficial in the removal of drugs that distribute in multiple compartments with slow equilibration. Continuous removal of the drug from the vascular compartment maintains a favorable gradient and facilitates its release from the inaccessible compartments into the vascular compartment. As a result, the typical rebound phenomenon resulting in high serum levels due to redistribution seen after HD is not seen with CRRT modalities. Lithium is a substance known to have a large volume of distribution due to its intracellular distribution. Although it is not highly protein bound, its large V_d coupled with its slow transcellular diffusion, makes CRRT the preferred modality for its elimination [22–24]. In addition, patients with hemodynamic instability may benefit from a slower form of dialysis.

Hemoperfusion

In hemoperfusion, blood is percolated through a cartridge packed with activated charcoal or other resin coated with a semipermeable membrane [25]. Typical cartridges have 150–300 g of activated charcoal or 650 g of resin. Substances are adsorbed onto the charcoal or polystyrene resin despite protein binding, making this modality a better choice for highly protein-bound poisons [26]. These cartridges can also absorb lipid-soluble substances and substances with molecular weight up to 40,000 Da are effectively removed by this technique. A standard hemodialysis machine can generally be used for hemoperfusion with a cartridge inserted in place of the dialyzer. Most cartridges come sterilized, and must be flushed with saline prior to use.

Complications with hemoperfusion have been well documented and include platelet depletion and clotting in the cartridge. Other substances such as calcium, glucose, and white cells can be depleted during hemoperfusion. As with any extracorporeal therapy, desirable drug levels of other therapeutic agents may require increased dosing. Cartridges can become saturated and must be changed every 4–6 h. Finally hemoperfusion does not correct acid–base or electrolyte abnormalities, nor volume overload. Thus, it may be necessary to perform hemodialysis in addition to hemoperfusion.

Despite the theoretical appeal of hemoperfusion for the treatment of intoxications, its use remains quite limited. The cartridges are not freely available in all hospitals and modern dialyzers with highly porous membranes and large surface area may give clearance rates approaching those achieved with hemoperfusion.

Peritoneal Dialysis

In peritoneal dialysis, the clearance kinetics are dependent on intrinsic characteristics of the

membrane and the mesenteric circulation, and not amenable to significant external adjustments. In cases with intoxication, peritoneal dialysis is only 10–25% as effective as hemodialysis and further more its efficacy is compromised if the patient is hypotensive. Thus the role of peritoneal dialysis in detoxification is limited to situations where other modalities are contraindicated or not possible due to lack of vascular access.

Molecular Adsorbents Recirculating System (MARS)

The Molecular Adsorbents Recirculating System (MARS) is a relatively new method of extracorporeal decontamination, which employs dialysis across a membrane impregnated with albumin and a 20% albumin dialysate, thus attracting highly protein-bound substances. In addition, charcoal and anion exchange resin cartridges are employed to filter the dialysate, regenerating it for continued use [27]. MARS may be of interest in the setting of poisons that have a predilection for liver toxicity, as the system is capable not only of removing certain hepatotoxins, but also reducing hyperbilirubinemia, restoring hemodynamics, diminishing hepatic encephalopathy, and improving renal function [27]. MARS has been used to maintain patients in liver failure during the peritransplant period [28–30]. The existing data for MARS in general are encouraging, but the evidence base is limited [31].

Plasmapheresis

Plasmapheresis is the extracorporeal blood purification technique used for removal of large molecular weight substances from plasma such as pathogenic autoantibodies, immune complexes, and endotoxins. In general, a single exchange of 1 plasma volume (3 L for a 70-kg patient) removes approximately 63% of all solutes in the plasma and an exchange of 1.5 plasma volume removes about 78% [32], which under normal conditions corresponds to removal of 40–60 mL of plasma/kg over 2–3 h [33]. While evidence-based indications on the role of plasmapheresis in the management of intoxications is lacking, several publications (mostly case-reports) have reported its successful usage in the treatment of phalloid mushroom intoxication, tricyclic-antidepressant (amitriptyline), L-thyroxin, phenbromate, verapamil, diltiazem, carbamazepine poisoning, and some heavy metals such as mercury intoxications [34–42]. It is important to note that plasmapheresis is most useful for drugs with a low V_d and a high protein binding. Accordingly, it has been suggested that plasmapheresis should be considered only when plasma protein binding of a substance is greater than 80% and V_d is less than 0.2 L/kg [43].

Therapeutic Decisions

When confronted with a case of poisoning, the physician must consider many parameters in choosing the appropriate therapeutic modality. A simplified decision-making approach is provided in the algorithm (Fig. 42.1). The list of toxic substances that have been subjected to extracorporeal therapies is quite long and information is available on more than 200 substances [44]. However, the ability to remove a toxic substance by extracorporeal therapy is not equivalent to an indication for these procedures. One must take into account the patient's underlying health (including any comorbidities), the toxicity of the absorbed substance, the presence of or likelihood of advancing to severe illness, the availability of extracorporeal therapies, and the availability of acceptable alternatives (good supportive care, antidotes). While the availability of antidotes such as N-acytylcysteine, flumazenil, fomepizole, and Fab have significantly changed the clinical management plans, on several occasions it is not possible to identify the small group of patients who will fail to respond to intensive supportive care alone and the decision to institute extracorporeal therapy is based on clinical judgment.

Some of the broad criteria as suggested by Winchester et al. [45] and Rosenbaum et al. [46] for initiating extracorporeal therapy are provided in Table 42.2. Finally, although several studies have shown enhanced drug elimination using several techniques, the data regarding how these methods affect morbidity and mortality are often lacking.

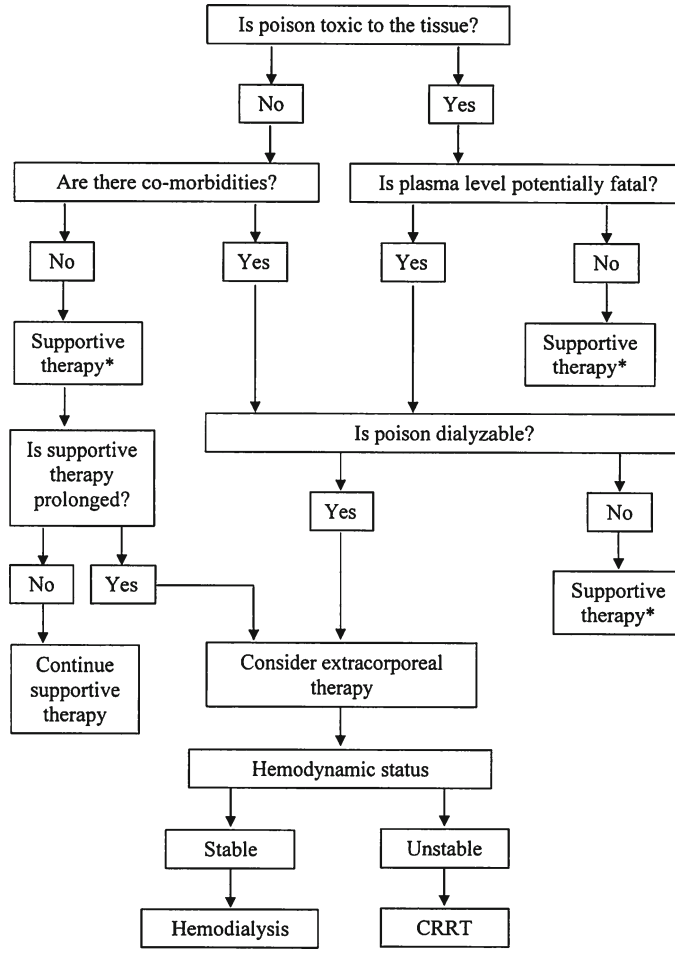

Fig. 42.1 Simplified approach to a patient with poisoning (*specific antidote to be used when available; choice of particular extracorporeal therapy is based on the type of poison and patient's hemodynamic status). *CRRT* continuous renal replacement therapies, *MARS* molecular adsorbents recirculating system

Table 42.2 Criteria for extracorporeal therapy (Modified from Refs. [31, 32])

• Potentially lethal plasma concentration of intoxicant known to be cleared effectively from blood by extracorporeal therapy
• Significant quantity of circulating toxin that is metabolized to a more noxious substance (e.g., methanol, ethylene glycol)
• Ingestion and probable absorption of a potentially lethal dose
• Severe clinical intoxication with abnormal vital signs
• Impairment of normal route of excretion
• Progressive clinical deterioration despite carful medical management
• Prolonged coma with its potential hazards (e.g., aspiration pneumonia, septicemia)
• Need for prolonged assisted ventilation
• Persistent hypotension or need for vasocative therapy
• Poisoning by agents with delayed toxicity (e.g., paraquat)

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