Clinical Medicine 2012, Vol 12, No 3: 276–80

Sepsis: recognition and treatment

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The American College of Chest Physicians and the Society of Critical Care first published definitions for the wide spectrum of presentations described by sepsis syndromes in 1992 (Fig 1).[1] The driver for this was to facilitate better clinical trials and consolidate the diverse definitions available. However, because of the heterogeneous nature of sepsis these definitions may be too broad for clinical use. The consensus from the 2001 International Sepsis Definitions Conference suggested that these definitions cause difficulty staging sepsis, prognosticating for host response and can be overly sensitive, especially in the case of systemic inflammatory response syndrome (SIRS).

Systemic inflammatory response syndrome (SIRS): current concepts

Multicellular animals have developed means of surveillance, defence and repair when confronted by microbial challenge.[2] The mechanisms behind the activation and co-ordination of this response are complex and not fully elucidated. Exogenous microbial molecules (pathogen-associated molecular patterns (PAMPs)) are recognised by cells of the innate and acquired immune pathway via pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). These in turn activate cell signalling pathways, triggering a SIRS through secretion of inflammatory mediators and activation of leukocytes (Fig 2).

SIRS can be also triggered by tissue or cell damage caused by non-microbial insults, such as trauma, necrosis, extremes of temperature, chemicals (including chemotherapeutics) and lack of nutrients/oxygen.[2] Endogenous molecules (alarmins) are released by tissue damage, triggering a SIRS via PRRs. Alarmins identified to date include uric acid, mitochondrial DNA, advanced glycation end-products and high mobility group box 1(HMGB1). Increased extracellular expression of HMGB1 has been associated with autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis. Together, exogenous PAMPs and endogenous alarmins form a larger set of triggering molecules: damage-associated molecular patterns (DAMPs). In addition, genetic variation in host response to insults (microbial or endogenous) is increasingly recognised as a significant predictor of outcome. Each episode of sepsis has elements of systemic inflammation and immune depression throughout its course.[3]

The severity of SIRS and compensatory anti-inflammatory response syndrome (Fig 3) will vary from individual to individual, depending on their predisposing genetic influences as well as the nature of the pathological insult. For example, genetic polymorphism of TLR 4 predisposes to septic shock in Gram-negative infection.

Extremes of hyper-inflammation or immune depression are associated with poorer outcomes.[4] The implications of host response variations cannot be easily quantified, thus complicating design and evaluation of therapeutic sepsis trials. Studies of host genomic response to sepsis (such as the UK-based GAinS study)[4] are currently underway but it remains uncertain whether the knowledge gained will translate into effective interventions.

Recognising sepsis

The incidence of sepsis in the US is 3 per 1,000 population per year.[5] A large UK

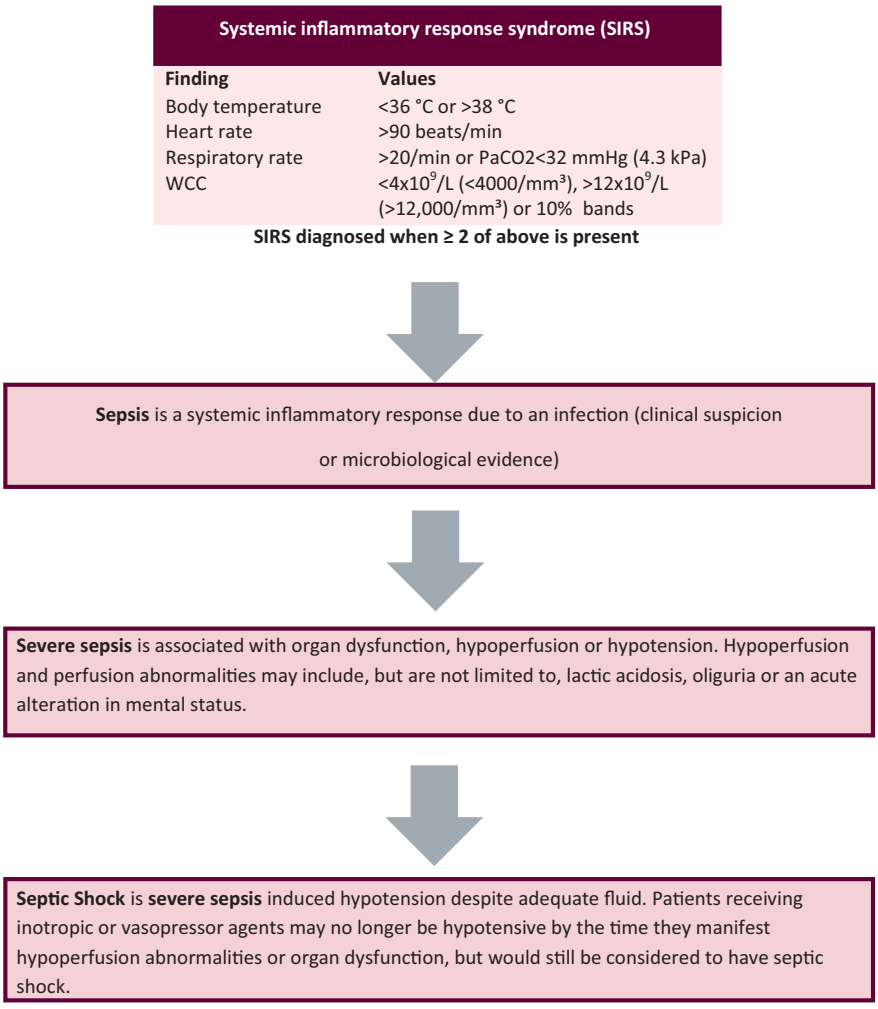

Fig 1. The spectrum and definitions of sepsis syndromes. SIRS = systemic inflammatory response syndrome, WCC = white cell count.

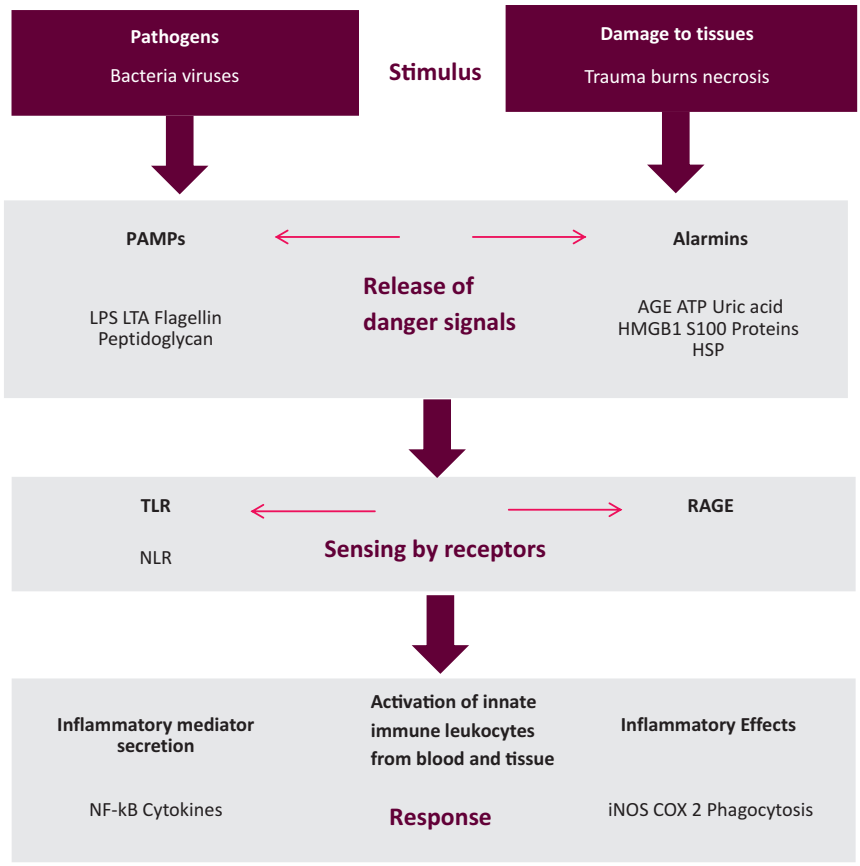

Fig 2. Concepts in sepsis: inflammation and response to various danger signals. PAMPs = pathogen-associated molecular patterns; DAMPs = damage-associated molecular patterns; LPS = lipopolysaccharide; LTA = lipotechoic acid; AGE = advanced glycation end products; ATP = adenosine triphosphate; HMGB1 = high-mobility group box 1; HSP = heat shock proteins; TLR = toll-like receptor; NLR = NOD-like receptor; RAGE = receptor for advanced glycation endproducts; PRRs = pattern recognition receptor; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS = inducible nitric oxide synthase; COX 2 = cyclooxygenase-2.

clinical database study[6] suggests that both the number of critical care admissions with severe sepsis and the total number of deaths from severe sepsis and septic shock are rising. Overall mortality for those admitted with severe sepsis is decreasing through advances in medical care, but it remains unacceptably high (>30%) with approximately 37,000 deaths annually in the UK.[7]

In a recent international survey investigating the views of physicians regarding sepsis,[8] 86% of responders felt that the symptoms of sepsis could easily be misattributed to other medical conditions, leading to delayed diagnosis and treatment, while 81% felt that a clear, globally accepted clinical definition would help.

Improving sensitivity of identification

Strategies which improve the sensitivity of identifying patients at risk include

Key points

- The heterogeneous nature of sepsis may result in current definitions of sepsis being too broad for optimal clinical use
- Systemic inflammatory response syndrome can be triggered by tissue or cell damage caused by non-microbial insults, such as trauma, necrosis, extremes of temperature, chemicals (including chemotherapeutics) and lack of nutrients/oxygen
- Genetic variation in host response to insults (microbial or endogenous) are increasingly recognised as a significant predictor of outcome of sepsis
- The combination of physiological early warning systems and biochemical markers serve to aid early recognition of sepsis and therefore improve outcome
- Timely delivery of appropriate antibiotics is associated with higher survival rates; it is estimated that every hour of delay equates to a 6% increase in mortality
- There is robust evidence for evidence for early goal-directed haemodynamic support
- Care bundles are small (3–5) sets of evidenced-based interventions that require healthcare systems to deliver all components consistently, the rationale being that their reliable implementation will yield better results than their inconsistent individual adoption. Recent evaluation of healthcare centres participating in the surviving sepsis campaign shows improvement in performance measures and adjusted odds ratio for mortality

KEYWORDS: bundles, immunogenetic concepts, recognition, sepsis, treatment

complementary systems that capture physiological parameters,[9] routine biochemical measurements[10] or a combination of both. Scoring systems that allocate weighted points based on the degree of deviation of a patient's physiological parameter (eg heart rate) from the normal range are commonly employed.[9]

'*Track and trigger systems*' TTS use the following indicators to trigger a review and indicate the level of care and frequency of monitoring:

- summation of the points from the scoring systems (often termed Early Warning Score) above a predefined threshold
- trends of rising summated points, and/or
- degrees of deviation of a single physiological parameter.

Numerous locally derived aggregate weighted TTS are currently in widespread use, with poor evidence for their utility, reliability and validity.[11]

National standardisation. A national TTS that allows for standardisation of care and homogeneous training of medical personnel is likely to be beneficial.[12] The Royal College of Physicians is leading the development of a national early warning scoring system, to be published in 2012.

Biomarkers. The role of biomarkers to prognosticate, stage and diagnose sepsis is a work in progress. Serial serum lactate has prognostic value for mortality[13] (40% for lactate >4 mmol/l vs <15% for lactate <2 mmol/l) and predictive value for critical care admission. Similarly, serum procalcitonin[14] may be more specific for bacterial-induced severe sepsis and thus aid early diagnosis. Mediators currently being investigated include adrenomedullin, cellular adhesion molecules and interleukin-6.

In the future, the combination of physiological early warning systems and biochemical markers may aid early recognition and treatment.

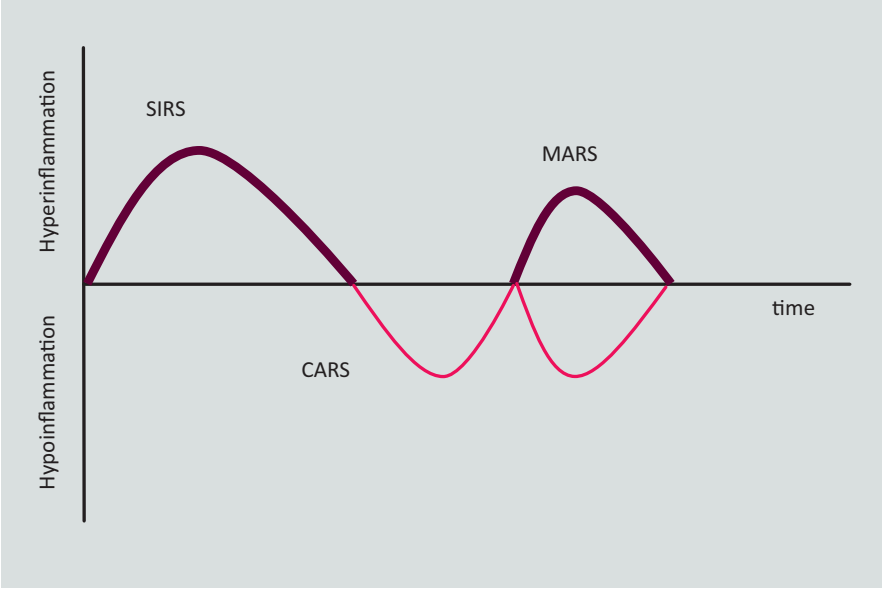

Fig 3. Concepts in sepsis: systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and mixed antagonist response syndrome (MARS) (adapted from Ref 3).

Table 1. Sepsis resuscitation bundle (within the first six hours) (adapted from the Surviving Sepsis Campaign material).

- Measure serum lactate.
- Obtain blood culture prior to antibiotic administration.
- Administer broad-spectrum antibiotic within three hours of A&E admission and within one hour of non-A&E admission.
- In the event of hypotension and/or serum lactate >4 mmol/l:
  - deliver initial minimum of 20 ml/kg crystalloids or equivalent
  - apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP >65 mmHg.
- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/l achieve:
  - CVP 8 mmHg
  - $ScvO_2$ 70% or SvO_2 65%.

A&E = Accident and Emergency; CVP = central venous pressure; MAP = mean arterial pressure; $Scv0_2$ = central venous oxygen saturation; $Sv0_2$ = mixed venous oxygen saturation.

Table 2. Sepsis management bundle (within the first 24 hours) (adapted from the Surviving Sepsis Campaign material).

1. Administer low-dose steroids for septic shock in accordance with standardised ICU policy.
2. Maintain glucose control (aiming for 8.3–9.9 mmol/l).
3. Maintain tidal volume of 6 ml/kg of estimated lean body weight; median inspiratory pressure <30 cmH_20 for mechanically ventilated patients.

ICU = intensive care unit.

Treating sepsis

The International Surviving Sepsis Campaign was launched in 2002, with the ambitious aim of reducing sepsis-associated mortality by 25% over five years. The main objectives were to:

- increase awareness
- define standards of care informed by evidence from clinical trials, and
- produce management policy.

These standards were translated into care bundles for implementation in partnership with the Institute for Healthcare Improvement. Care bundles are small (3–5) sets of evidenced-based interventions that

require healthcare systems to deliver all the components consistently, the rationale being that failure to implement even one component would yield poor outcomes. Compliance is therefore measured in an 'all-or-nothing' manner. A recent study shows improvement in performance measures and adjusted odds ratio for mortality.[15]

Care bundles

The recommended care bundles were organised in two phases: sepsis resuscitation and sepsis management (Tables 1 and 2), each set of performance measures requiring completion within six and 24 hours, respectively. Broadly speaking, the resuscitation bundle can be divided into two distinct strategies.

1 *Expedient source isolation/control and early administration of empirical broad-spectrum antibiotics*

Timely delivery of appropriate antibiotics is associated with higher survival rates. It is estimated that every hour of delay equates to a 6% increase in mortality.[16] Source control is vital, but is determined in part by aetiology. For example, a patient with bacterial peritonitis from a perforated diverticular abscess would be likely to require urgent surgical intervention, whilst another with bacterial meningitis would require prompt clinical diagnosis, judicious and expedient antibiotic administration as well as excellent supportive care.

2 *Early goal-directed haemodynamic support with appropriate monitoring*

The evidence for early goal-directed therapy stems from a single randomised control trial (RCT) of protocolised haemodynamic support, involving both diagnostic and therapeutic interventions, for patients presenting to an emergency department in the US with severe sepsis or septic shock.[17] The 90-day hospital mortality was significantly reduced (46.5–30.5%). The UK-based multicentre PRoMIse RCT is currently underway to investigate further the efficacy of early protocolised management in sepsis, with added examination of cost-effectiveness.

Evolving evidence

The evidence for interventions in the management bundle (Tables 1 and 2) is evolving and some interventions need adjusting. For example, there is robust evidence[18] for lung protective strategies in mechanically ventilated patients but, following the multicentre CORTICUS trial, the survival benefit of universal low-dose glucocorticoid therapy in septic shock is uncertain. The recent PROWESS-SHOCK trial failed to show 28-day survival benefit in patients with septic shock, leading to drotrecogin alpha (activated) being withdrawn in October 2011. The NICE-SUGAR trial unexpectedly showed excess mortality for critically ill patients in the tightly controlled arm; earlier guidance has been revised to recommend a higher glucose threshold (<9.9 mmol/l or 180 mg/dl). The current 2008 guidelines are under revision to incorporate recently published evidence. The implementation of sepsis care bundles has shown benefit and they must evolve as new evidence emerges.

The hunt for a magic bullet

The collective term 'sepsis' predicates the premise that a common final pathway for systemic inflammation exists which may be targeted and will improve outcome if suppressed.[19] Many potential agents have been trialled. Those currently being investigated in sepsis RCTs include:

- statins, which seem to have pleiotropic effects extending beyond their favourable action on lipid profiles
- talactoferrin alpha, a recombinant form of the protein lactoferrin found in human breast milk, which seems to have immunomodulatory power via action on gut-associated lymphoid tissue.

The central premise of a common final pathway has never been proven; such a pathway may either not exist or be too final a point to be effectively targeted. Sepsis is a broad-based heterogeneous condition consisting of many disease entities, all with individual natural histories and variations in host response. Sepsis syndromes may therefore lack genuine homogeneity and be the wrong point of entry for study – in which case, there may be no magic bullet.

Conclusions

For the moment, and for the foreseeable future, the evidence lies with early recognition, source control, early antibiotic administration and excellent supportive care.

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Poisoning and self-harm

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This article will deal with several areas in which there have been recent problems or developments in knowledge and practice in relation to poisoning and self-harm.

Initial triage, consent and management

A confidential deaths enquiry conducted on patients who died in English hospitals in 2005 from poisons-related events suggested that the major initial errors in care were delay in appropriate rapid assessment and airway management.[1] A reduced conscious level, in particular a Glasgow Coma Scale below 8, is a recognised risk factor for increased mortality in poisonings with central nervous system (CNS) effects. Rapid changes in conscious level early in admission are a recognised additional risk factor. Therefore careful monitoring and management of these patients in the initial phases are essential.

Do not resuscitate

The study also revealed that a number of patients presented to hospital with documents indicating they did not wish to be resuscitated.[1] Such documents *may* have legal authority, but it is important to be clear about the particular scenarios they cover and whether they *do have* legal authority. Use of such a document in the case of a young woman with repeated self-harm behaviour who subsequently died of ethylene glycol poisoning stimulated an academic exchange in the *British Medical Journal* emphasising the care needed in assessing this type of situation. Decisions made by patients under stress with psychological disorders may not be as clear-cut as they initially appear. Careful psychosocial assessment is an essential cornerstone in the management of self-harm patients.[2,3]

Paracetamol

Paracetamol remains the most common cause of overdose in the UK, yet management errors continue to occur. A recent study demonstrated the benefits of using a multidisciplinary care plan in this frequent clinical scenario.[4] Benefits of this approach include better processes of care, with appropriate use of the antidote N-acetyl cysteine. Copies of this care plan are available for UK health professionals to download from TOXBASE;[5] this provides a comprehensive guide to assessment and management of poisoning.

Drugs of abuse

The most rapidly changing area of clinical toxicology has been the increase in range and toxicity of so-called 'legal highs' (Table 1). As illicit drug regulation changes to take an account of new molecular structures, so new chemicals are marketed to young people to try to get round the legislation. From a clinician's perspective, this creates a particular problem since it occurs increasingly frequently and the names on the products bear little resemblance to their actual contents. Indeed, the same name may be used for different ingredients over a time period as drug regulation changes what is legally permissible to sell.

An example is the 'ivory wave' product that changed drug content as legislation banned its original constituents. It initially contained desoxypipradol, a drug previously appearing in Ireland under the name 'whack'. It had been investigated as a potential antidepressant because of its stimulant effects and was subsequently marketed in the UK as 'ivory wave'. It produced significant physical and psychological symptoms, particularly formication (tactile sensation of being crawled over by insects) and was also associated with rebound self-harm and suicide.[6] Early identification of this product in 'ivory wave' and its potential adverse effects rapidly led to commercial suppliers changing its psychoactive ingredients, while maintaining its 'trade name' on the internet where it continues to be sold.

Other recent examples include the production of more potent cannabinoid compounds which appear to have more psychoactive action than traditional

cannabinoids ('herbal spice'), and the use of pharmaceutical products in 'herbal' pills. The latter products may appear in different countries under different names.[7]

There seem to be at least 150 different chemicals with cannabinoid properties. In overdose they may cause symptoms of extreme cannabis use, but seizures and hypokalaemia are also reported. They appear to have greater affinity for the CB1 cannabis receptor than traditional products which contain delta-9-tetrahydrocannabinol as their active ingredient.[8]

A range of drugs of abuse is available, in general acting as CNS stimulants causing effects similar to amfetamine (Table 1). Key differences appear to be in their duration of action, propensity to cause psychosis, hyperpyrexia, rhabdomyolysis and cardiovascular features. As with desoxypipradol, late after effects may include depressive reaction or continuing psychosis.[6] Patients who ingest these compounds therefore need to be monitored over a period of hours to assess their full impact.

Management of cardiotoxicity

Drugs cardiotoxic in overdose

Many routinely prescribed drugs cause cardiotoxicity in overdose. The most frequent causes of severe heart failure in poisoning include:

- calcium channel blockers (CCB)
- beta-blockers
- sodium channel blockers
- local anaesthetic agents
- tricyclic antidepressants
- drugs of abuse including cocaine.

Cardiotoxicity, like CNS depression, is therefore a major concern in accidental poisoning and overdose. Two new treatment strategies, insulin/glucose (dextrose) and intralipid, have emerged over the past five years with the potential to improve outcome in cases of cardiotoxicity.

In addition, improved technologies such as extracorporeal assist devices make cardiac support more readily available. These may have a role in the most severe poisoning where other treatments have failed to ensure adequate cardiac output and the poison is thought not to have produced irreversible CNS damage.

Table 1. Examples of drugs that have been used in 'legal highs'.

Drug group	Class
Amfetamines and cathinones:	
• mephedrone • methcathinone • methedrone • methylenedioxypyrovalerone (MDPV) • naphyrone	All now Class B substance
Desoxypipradol (2-DPMP) (not an amfetamine or cathinone by structure but similar toxicity)	Now Class B substance
Piperazines:	
• benzylpiperazine (BZP)	Now Class C substance
• meta-chlorophenylpiperazine (mCPP)	Now Class C substance
• methylenedioxybenzylpiperazine (MDBP)	
• trifluoromethylphenylpiperazine (TFMPP)	Now Class C substance

Box 1. Indications and treatment regimen for intra lipid.

Intralipid should be used for drugs with local anaesthetic toxicity at the onset of neurological or cardiovascular symptoms. It should be considered in other haemodynamically significant intoxication from fat soluble drugs (eg propranolol, amitriptyline) after general supportive measures and recognised antidotes have been unsuccessful.

No optimal regimen is established: currently, a 1.5 ml/kg bolus, followed by 0.25–0.5 ml/kg/min over 30–60 min is an appropriate starting approach.

The bolus may be repeated in cases of cardiac arrest. Titrating the infusion rate to the clinical response and repeating lipid administration at the onset of recurrent deterioration is reasonable.

Table 2. Metabolic problems in myocardial function in severe poisoning.

- Switch from free fatty acid to carbohydrate energy sources.
- Relative lack of insulin precludes optimal energy production, resulting in impaired cardiac performance.
- Carbohydrate delivery and glycolysis are impaired due to poor tissue perfusion and acidosis.
- Lactic acidosis results not only from tissue hypoperfusion but also from activation of mitochondrial dehydrogenase.

Key points

Initial assessment and triage of patients with poisoning remains a challenge, particularly with regard to validity and appropriateness of 'advance directives' to this situation

Careful monitoring is required if there is respiratory depression (GCS 8 or less)

Multidisciplinary care pathways improve care of paracetamol poisoning

Stimulant drugs of abuse come in many forms and users are usually unaware of ingredients. Unexpected and delayed toxicity is still seen from new 'legal highs'

Managing severe cardiotoxicity requires critical care input; new management approaches include insulin and intralipid, but their roles in therapy are yet to be clearly defined

Keywords: self harm, poisoning, triage, legal highs, cardiotoxicity, paracetamol

Intralipid

Therapy with intralipid was introduced following initial experimental work on the isolated heart and subsequently on animal models, which suggested that drug partitioning into lipid could change the pharmacodynamics of drug action, resulting in clinical improvement. Subsequent use in clinical case series has confirmed this initial impression and lipid therapy has now been used in the management of a wide range of toxins. At present, it is therefore difficult exactly to place its most effective role. Theoretically, patients who have ingested lipid soluble drugs with actions on sodium channels should benefit.[9] Experimental studies suggest that water-octanol coefficient (ie degree of relative lipid solubility) should predict clinical benefit. Recent *in vitro* studies also suggest that lipid may have a direct effect on sodium channels, modulating their function. Expert advice should be sought. Dose and suggested indications for use of intralipid are shown in Box 1.[9]

Insulin and dextrose

Insulin and dextrose therapy was first introduced in 1999 based on experimental data suggesting insulin has inotropic properties. Its use has subsequently become more widespread, particularly in the management of CCB poisoning, the severity of which relates to the degree of hyperglycaemia, causing a complex effect on the heart with several metabolic consequences (Table 2). Interestingly, insulin appears to act on all these mechanisms, increasing cardiac efficiency and hence cardiac output.

Hypoglycaemia is a potential risk of using insulin, but can be readily managed in the clinical scenario of CCB poisoning by the additional use of glucose. In a case series of 12 patients, hypoglycaemia was the greatest risk but outcomes were generally good. The only poor outcome in this series resulted from a failure to comply with the agreed management protocol involving insulin.[10]

The exact dose of insulin required can be titrated; doses up to 10 U/kg/hr are well described as efficacious and safe.

Conclusions

The key to the treatment of any patient is careful observation, clinical management and preparedness for response to expected complications. Thirty years ago gastric lavage was the norm, whereas it is now virtually never used in North America, the UK and Western Europe. Changes in management mandate the need for appropriate clinical studies which remains a problem for much of clinical toxicology. Multicentre clinical trials of the new treatments mentioned in this article are required. Until appropriate funding and resource can be identified, it seems reasonable to base changes in treatment on well conducted carefully reported case studies. New drugs of abuse are likely to continue to be developed, and it is important to share experiences with others as these case reports and series arise.

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