Recent Advances in Extracorporeal Blood Purifications to manage Poisoning in ICU

Dr Yan Wing Wa
Department of Intensive Care
Pamela Youde Nethersole Eastern Hospital
Main principles of treatment

- Emesis / gastric lavage
- Activated charcoal
- Antidote
- Supportive care
  - Airway
  - Breathing
  - Circulation
  - Organs support
- Elimination
  - Gut irrigation
  - Forced diuresis
  - Extracorporeal elimination
Toxic Exposure Surveillance System
American Association of Poison Centers

- In the year of 2004
- 3% require ICU
- 0.05% extracorporeal treatment
  - (1 out of 60 poisoned ICU patients)
  - (1 out of 2,000 total poisoned patients)
- Many many different kinds of toxins / drugs (toxic dose)

- Evidence on the extracorporeal management of individual poison
  - Single case report / case series
Recent advances

- Not in provision of good evidence in treatment of individual poison

- In advances of different blood purification techniques originally designed for organ support (clearance of metabolic waste products)
  - Potentially effective
    - Many recent studies
  - Enhance toxin removal
  - Sustain life to buy time for natural/artificial removal of toxins
Indications of extracorporeal elimination

- Ingested quantity associated with severe toxicity
- Ingestion of a toxin with serious delayed effects
- Natural removal mechanism impaired
  - Renal / Liver failure / Circulatory failure
- Clinical condition deteriorating
- Clinical evidence of severe toxicity: hypotension, coma, metabolic acidosis, respiratory depression, dysrhythmias or cardiac decompensation
Traditional extracorporeal elimination methods

- >30 years

- Haemodialysis (low flux)
  - For patients with end-stage renal disease

- Haemoperfusion
  - Charcoal
Haemodialysis (low flux)

- Diffusion across a semipermeable membrane down a concentration gradient from blood to dialysate
- Water soluble
- Low molecular weight (<0.5 kD)
- Low protein binding
- Low volume of distribution
- Clearance depends on membrane surface area, $Q_b$ and $Q_d$
- A form of renal replacement therapy
- High clearance but problem of rebound
  - >250ml/min
The most common toxins responsible for cases receiving HD

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Lithium (714)</td>
<td>Lithium (1178)</td>
<td>Lithium (2583)</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Ethylene glycol (649)</td>
<td>Ethylene glycol (1138)</td>
<td>Ethylene glycol (2077)</td>
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<tr>
<td>Salicylates</td>
<td>Salicylates (358)</td>
<td>Salicylates (580)</td>
<td>Salicylates (1490)</td>
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<tr>
<td>Aminophylline</td>
<td>Aminophylline (284)</td>
<td>Methanol (289)</td>
<td>Valproic acid (516)</td>
</tr>
<tr>
<td>Methanol</td>
<td>Methanol (240)</td>
<td>Aminophylline (240)</td>
<td>Acetaminophen (474)</td>
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<tr>
<td>Acetaminophen</td>
<td>Acetaminophen (135)</td>
<td>Acetaminophen (192)</td>
<td>Methanol (463)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ethanol (84)</td>
<td>Valproic acid (170)</td>
<td>Ethanol (297)</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>Phenothiazine (65)</td>
<td>Ethanol (111)</td>
<td>Benzodiazepine (281)</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>Isopropanol (59)</td>
<td>Others (90)</td>
<td>Others (274)</td>
</tr>
</tbody>
</table>
Haemoperfusion

- Cartridge containing sorbent material capable of toxin adsorption
- Charcoal, synthetic resins, anion exchange resins
- Binding affinity with sorbent
- Low volume of distribution
- Charcoal for 1 to 1.5 kD, less effective for protein bound molecules
- Resins effective in protein bound & lipid soluble molecules
- No renal replacement therapy
- Side effects
  - Thrombocytopenia, leucopenia, coagulopathy
  - Embolisation of sorbent particles
  - Febrile reaction, hypotension
  - Hypoglycaemia, hypocalcaemia
The most common toxins responsible for cases receiving HP

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>(162)</td>
<td>Aminophylline (58)</td>
<td>Carbamazepine (38)</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>(24)</td>
<td>Carbamazepine (16)</td>
<td>Lithium (30)</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>(12)</td>
<td>Benzodiazepine (14)</td>
<td>Ethylene glycol (22)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>(11)</td>
<td>Valproic acid (13)</td>
<td>Acetaminophen (19)</td>
</tr>
<tr>
<td>Salicylates</td>
<td>(8)</td>
<td>Other (12)</td>
<td>Valproic acid (17)</td>
</tr>
<tr>
<td>Mushroom</td>
<td>(6)</td>
<td>Ethylene glycol (9)</td>
<td>SSRI (17)</td>
</tr>
<tr>
<td>Unknown</td>
<td>(5)</td>
<td>SSRI (9)</td>
<td>Phenothiazine (15)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>(5)</td>
<td>Barbiturate (8)</td>
<td>Ethanol (12)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>(4)</td>
<td>Lithium (7)</td>
<td>Biguanide (11)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>(4)</td>
<td>Methanol (7)</td>
<td>Other (10)</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>(4)</td>
<td></td>
<td>Salicylate (10)</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>(4)</td>
<td></td>
<td>Carisoprolol (10)</td>
</tr>
<tr>
<td>Bee/wasp/hornet</td>
<td>(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>irritant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HD vs. HP (from 1985 to 2005)
Hemoperfusion: Mechanism of Action

Blood containing poison molecules (P), some free and some bound to albumin (A), passes through hemoperfusion column, which contains particles of coated activated charcoal or special adsorbent resin (CR). Charcoal or resin absorbs free poison and detaches and adsorbs albumin-bound poison. Poison remains in cartridge. Cleansed blood is then filtered, heparinized to prevent clotting, and returned to patient.
MANAGEMENT OF SEVERE POISONING CASES BY HAEMODIALYSIS AND HAEMOPERFUSION

CHUNG-PING HO
M.B.,B.S. (H.K.), M.R.C.P. (U.K.),
Senior Medical & Health Officer

KAM-KWONG YAM
M.B.,B.S. (H.K.), M.R.C.P. (U.K.),
Senior Medical & Health Officer

S.C.R. KAPOOR
M.B.,B.S. (Punjab), M.R.C.P. (London),
Consultant Physician

RENAI UNIT,
PRINCESS MARGARET HOSPITAL,
HONG KONG
Table I: No. of Cases of Accidental Poisoning by Drugs, Medicaments and Biologicals Each Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Government Hospitals</th>
<th>All Hospitals</th>
<th>Deaths</th>
<th>Mortality Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>1,656</td>
<td>1,831</td>
<td>22</td>
<td>1.2</td>
</tr>
<tr>
<td>1980</td>
<td>1,727</td>
<td>1,844</td>
<td>23</td>
<td>1.2</td>
</tr>
<tr>
<td>1981</td>
<td>1,663</td>
<td>1,757</td>
<td>37</td>
<td>2.1</td>
</tr>
<tr>
<td>1982</td>
<td>2,073</td>
<td>2,196</td>
<td>47</td>
<td>2.1</td>
</tr>
</tbody>
</table>
NATURE OF THE POISON AND INDICATIONS FOR HD AND HP

The nature of the drugs or chemicals and the mortality are tabulated below:

<table>
<thead>
<tr>
<th>Poison</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylate</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lithium Carbonate</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paraquat</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dettol</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>11</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>
### Necessary properties for extracorporeal removal

<table>
<thead>
<tr>
<th>Property</th>
<th>Haemodialysis</th>
<th>Haemoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Water</td>
<td>Water or lipid</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt; 0.5 kD</td>
<td>&lt; 40 kD</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Low (&lt;80%)</td>
<td>Low or high</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>&lt;1l/kg</td>
<td>&lt;1l/kg</td>
</tr>
<tr>
<td>Endogenous clearance</td>
<td>&lt;4ml/min/kg</td>
<td>&lt;4ml/min/kg</td>
</tr>
<tr>
<td>Distribution time</td>
<td>Short</td>
<td>Short</td>
</tr>
</tbody>
</table>
## Commonly Dialyzed Intoxications

<table>
<thead>
<tr>
<th>Substance</th>
<th>Methanol</th>
<th>Eth. Glycol</th>
<th>Salicylate</th>
<th>Lithium</th>
<th>Theophylline</th>
<th>Acetaminophen(??)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (Daltons)</td>
<td>32</td>
<td>62</td>
<td>138</td>
<td>7</td>
<td>180</td>
<td>151</td>
</tr>
<tr>
<td>&amp; Protein Bound</td>
<td>0</td>
<td>0</td>
<td>50-90</td>
<td>0</td>
<td>56</td>
<td>0-25</td>
</tr>
<tr>
<td>Vd (L/Kg)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.2</td>
<td>0.8</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Endog. CL ml/min/kg</td>
<td>0.7</td>
<td>2</td>
<td>0.88</td>
<td>0.35</td>
<td>0.65</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Recent advances in Extracorporeal techniques

- Haemodialysis (high flux)
- Haemofiltration (CVVH / CVVHDF)
- High volume haemofiltration
- Super-high flux haemofiltration
- MARS
- Prometheus
- Single pass albumin dialysis
- Coupled plasma filtration adsorption
- Plasmapheresis
- Extracorporeal life support
  - VV-ECMO
  - VA-ECMO
Haemodialysis (High flux)

- Mechanism similar to low flux haemodialysis
- Allow removal of larger size molecules (<5kD)
  - Still much less as compared with haemofiltration (40kD)
- Ultrapure dialysate required (lower level of endotoxin)
Haemodialysis (High flux)

- Barbiturate
- Salicylate
- Ethylene glycol
- Valproic acid
- Carbamazepine
- Cephalosporin induced neurotoxicity
Haemofiltration

- In form of continuous therapy
  - Continuous veno-venous haemofiltration (CVH)
  - Continuous veno-venous haemodiafiltration (CVHDF)
- Blood passing through haemofilter
- Allow convective removal of molecules of up to 40kDa
- Lower Qb, stable in haemodynamics
- Prolonged duration of therapy
  - Lower rebound
  - Protein bound or second compartment
- Low clearance
  - ~ effluent rate 20-40 ml/min
  - Not good for highly toxic substance which requires rapid removal
Protein binding equilibrium

\[ \ae \equiv a + e \]

If long distribution time: HD not effective but CVVH is more favourable.
Haemofiltration (cont.)

- Anticoagulation required
  - Systemic anticoagulation
  - No anticoagulation
    - Pre-dilution replacement
    - Saline flush
  - Regional anticoagulation
    - Regional citrate anticoagulation
<table>
<thead>
<tr>
<th></th>
<th>Haemodialysis</th>
<th>Haemofiltration</th>
<th>Haemoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solubility</strong></td>
<td>Water</td>
<td>Water</td>
<td>Water or lipid</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>&lt; 0.5 kD</td>
<td>&lt; 40 kD</td>
<td>&lt; 40 kD</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 kD (high flux)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>Low (&lt;80%)</td>
<td>Low (&lt;90%)</td>
<td>Low or high (&gt;90%)</td>
</tr>
<tr>
<td><strong>Volume of distribution</strong></td>
<td>&lt;1l/kg</td>
<td>&lt;1l/kg</td>
<td>&lt;1l/kg</td>
</tr>
<tr>
<td><strong>Endogenous clearance</strong></td>
<td>&lt;4ml/min/kg</td>
<td>&lt;4ml/min/kg</td>
<td>&lt;4ml/min/kg</td>
</tr>
<tr>
<td><strong>Distribution time</strong></td>
<td>Short</td>
<td>longer</td>
<td>short</td>
</tr>
</tbody>
</table>
CVVH / CVVHDF

- Metformin associated lactic acidosis
- Star-fruit poisoning in chronic renal failure patients (with charcoal HP)
- Barbiturate
- Theophylline
- Methanol
- Valproic acid
High Volume Haemofiltration

- Higher clearance (compared with CVVH)
  - Continuous or pulsed
  - 40-100 ml/min (still low vs. HD)
- Effective in lowering the cytokines mediated toxicity
- Immunomodulation
- Additional renal replacement therapy
High Volume Haemofiltration

Disadvantages

- Technically difficult, high nursing workload
- High cost
- High blood flow required, maybe a challenge to haemodynamic unstable patients
  - If pre-dilution, reduce efficiency
- Loss of essential small molecules, aminoacids, glucose, vitamins, ...etc.
High Volume Haemofiltration

- Any poisoning with CVH/CVHDF

- Cephalosporin induced neurotoxicity

- Lithium toxicity

- Tetramine poisoning (charcoal haemoperfusion)
  - Chau CM et al, Hong Kong Med J, 2005;11:511-514
Super High Flux Haemodialysis / Haemofiltration
High Cut-off Protein-permeable Membrane
Super High Flux Haemofilter
High Permeability Haemofilter
High Cut-off Haemofilter
Super High Flux Haemodialysis / Haemofiltration

- High cut off > 50 kD
- Efficient removal of free light chain immunoglobulin for multiple myeloma
- Effective cytokine removals
  - Lamberton et-al, Artificial Organs 2006;30(7):560-564
- Rhabdomyolysis (myoglobin 17kD)
  - Marked increased clearance
    - Naka et-al, Critical Care 2005;9:R90-R95
- Albumin loss requiring replacement
Molecular Adsorbent Recirculating System (MARS)

- Liver support system
- Have been shown to remove
  - Ammonia
  - Bilirubin
  - Bile salts
  - Aromatic amino acids
  - Short & medium chain fatty acids
- Have been shown to improve
  - short term survival
  - hepatic encephalopathy
  - Haemodynamics
  - intracranial pressure and
  - coagulopathy in patients with liver failure
Molecular Adsorbent Recirculating System (MARS)
Circuit

- Blood circuit
- Albumin detoxification circuit
- Haemodialysis circuit

Removing albumin bound toxic molecules and e.g. phenytoin, theophylline, diltiazem

- Small water molecules too
- Provide temporary liver and renal support too

Limitations

- High cost
- Technically complicated
- Availability
- Theophylline
- Phenytoin
- Diltiazem
Prometheus
Fractionated Plasma Separation, Adsorption (FPSA)
Prometheus
Fractionated Plasma Separation, Adsorption (FPSA)

- Plasma filtration with adsorption, run in series with high flux haemodialysis
- Remove
  - Albumin bound (unconjugated bilirubin, bile salts, hydrophobic amino & fatty acids)
  - Small and middle molecules
- Only small scale clinical studies
- Temporary liver and renal support
Single Pass Albumin Dialysis

Modified CWHD with albumin dialysate
Infrastructure similar to CWHD
Qb (180 - 270 ml/min)
Qd (1 – 4 L/h)
Haemofilter / high flux haemodialyser
Addition of 2.5% to 5% albumin in dialysate
Adding albumin in dialysate compartment
  - Increase valproic acid and carbamazepine clearance
  - Not pheytoint clearance
Single Pass Albumin Dialysis

Dialysate + 2.5 or 5% albumin
1-4 L/h

Haemofilter / High Flux haemodialyser

Qb 180-270 ml/min
Molecular Adsorbent Recirculating System (MARS)
Coupled Plasma Filtration with Adsorption

- Effective removal of sepsis related endotoxins and inflammatory mediators
  - Improved survival in animal trials
  - Improved haemodynamic in clinical trials

- Similar to haemoperfusion
- Plasma instead of whole blood passing through sorbent
  - Less complication like thrombocytopenia (should be considered in patients still requiring HP but with severe thrombocytopenia)
  - Less efficient in clearance
Coupled Plasma Filtration with Adsorption

- **Plasma filter**
  - **Qb** 100-200 ml/min
  - **Qp** 30-60 ml/min

- **Sorbent**
  - **Qb** 100-200 ml/min

- **haemoperfusion**
  - **Qb** 100-200 ml/min
Coupled Plasma Filtration with Adsorption
Plasmapheresis or Therapeutic plasma exchange (TPE)

- High MW > 100 kD
- Water / Lipid soluble
- High plasma protein binding (>80%)
- Low volume of distribution (<0.21 l/kg)
Plasmapheresis or
Therapeutic plasma exchange (TPE)

Qb 100-200 ml/min

Plasma filter

Qp 30-60 ml/min

FFP / albumin solution / synthetic colloids
Plasma Separator

- **Centrifugal separation**

  ![Figure 2: Haemonetics rotating bowl](image)

- **Membrane separation**

  ![Figure 3: Principle of membrane plasma separation](image)
Centrifugal Separation
Therapeutic Plasma Exchange with Prismaflex
**Plasmapheresis**

Nenov et-al, Nephrol Dial Transplant 2003;18[Suppl 5]:v56-v58

- **Phalloid mushroom intoxication**
  - When compared with charcoal HP
    - mortality reduced from 30-50% to <20% in general
  - From >20% to 4.8% in a series of 21 patients
    - Ther Apher 2000;4:303-307

- **Tricyclic and tetracyclic antidepressant**
  - In life threatening cardiac and CNS toxicity, plasmapheresis can be life saving
    - Nephrol Dial Transplant 1996;11:743
  - After a single plasmapheresis, amitriptyline level drop from 4.03 to 1.49ug/ml; 63% reduction in plasma level

- **L-thyroxine**
Amanita Phalloides mushroom
Plasmapheresis (2)
Nenov et-al, Nephrol Dial Transplant 2003;18[Suppl 5]:v56-v58

- Verapamil
- Diltiazem
- Carbamazepine
- Adjunctive therapy with antidigoxin antibodies for digitalis intoxication
  - In patients with renal failure
  - To prevent rebound caused by dissociation of digoxin-antidigoxin complexes
- Theophylline
- Heavy metals (mercury & vanadate)
Exchange transfusion

- Not new technique but it is potentially useful
- Severe malarial falciparum infection
- Neonatal jaundice
  - Unconjugated bilirubin
- Quinine intoxication in a child
  - *Archives of Disease in Childhood* 1972;47:304-305;
Extracorporeal Life Support

VA-ECMO

- Cardiovascular drug toxicity
  - 5.8% (3.5%) of total poisoning
  - 19% (16.4%) of total poison mortality

- Antidotes,
  - digoxin specific Fab fragment
  - Calcium
  - Dobutamine
  - Glucagon
  - Insulin high dose + dextrose

- VA-ECMO
  - Percutaneous cardiopulmonary support peripherally without the need of sternotomy
  - Severe drug-induced cardiotoxicity
    - Persistent hypotension
    - Cardiogenic shock
    - Pulseless ventricular tachycardia
    - Asystole
  - Temporal circulatory support to vital organs
    - Unloading the heart to encourage recovery
**Drugs having “membrane stabilising activity” with potential for severe cardiotoxicity**

EJ Baud et al., Critical Care 2007, 11:207

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 anti-arrhythmics</td>
<td>Flecaainide, disopyramide, propafenone, quinidine, lignocaine, procainamide</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Propranolol, acebutolol, nadolol, pindolol, labetalol, oxprenolol, metoprolol</td>
</tr>
<tr>
<td>Polycyclic antidepressants</td>
<td>Imipramine, desipramine, amitriptyline, clomipramine, doxepine</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Venlafaxine, citalopram</td>
</tr>
<tr>
<td>Dopamine and noradrenaline uptake inhibitors</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Thioridazine</td>
</tr>
<tr>
<td>Opioids</td>
<td>Dextropropoxyphene</td>
</tr>
<tr>
<td>Antimalarial agents</td>
<td>Chloroquine, quinine</td>
</tr>
<tr>
<td>Anaesthetic-recreational agents</td>
<td>Cocaine</td>
</tr>
</tbody>
</table>
Extracorporeal life support in severe drug intoxication: a retrospective cohort study of seventeen cases

Critical Care 2009, 13: R138

- A case series of 17 cases
  - 10 refractory shock & 7 prolonged cardiac arrest
  - 15 (88%) wean off ECLS
  - 13 (76%) hospital discharge without sequelae

- Consider ECLS as a last resort, efficient, and relatively safe therapeutic option
Paraquat poisoning

- A lady of 27 year-old with good past health took 100ml 24% concentrated paraquat solution after quarrel with her boy friend
- 24g (480mg/kg) paraquat

- > 40mg/kg universally fatal
<table>
<thead>
<tr>
<th>#</th>
<th>Sex/age</th>
<th>Amount</th>
<th>Presenting time and symptoms</th>
<th>Urine Dithionite</th>
<th>GI deconpression</th>
<th>CHP</th>
<th>Immunosuppression</th>
<th>NAC</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/78</td>
<td>? 2100 ml</td>
<td>25 mins</td>
<td>×</td>
<td>Cannot tolerate AC</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Developed gasping and cardiac arrest in AED</td>
</tr>
<tr>
<td>2</td>
<td>M/49</td>
<td>Ocular contact</td>
<td>3 hrs</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Uneventful with local irrigation</td>
</tr>
<tr>
<td>3</td>
<td>M/46</td>
<td>Inhaled diluted soln Left knee contact</td>
<td>19 hrs vertigo</td>
<td>-ve</td>
<td></td>
<td>×</td>
<td></td>
<td>✔</td>
<td>Survive with minimal lung fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>M/84</td>
<td>Inhalation during spray Few hours V, D</td>
<td>Few hours V, D</td>
<td>×</td>
<td></td>
<td>×</td>
<td></td>
<td>×</td>
<td>Uneventful</td>
</tr>
<tr>
<td>5</td>
<td>M/38</td>
<td>Ocular contact</td>
<td>2 hrs</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>Uneventful with local irrigation</td>
</tr>
<tr>
<td>6</td>
<td>M/25</td>
<td>One mouthful Immediate throat discomfort. SOB 2/7 later</td>
<td>Immediate throat discomfort. SOB 2/7 later</td>
<td>+ve</td>
<td></td>
<td>×</td>
<td></td>
<td>✔</td>
<td>Survive ARF Cr 141 Decreased DLCO</td>
</tr>
<tr>
<td>7</td>
<td>F/79</td>
<td>Empty bottle</td>
<td>6 hrs</td>
<td>HPLC</td>
<td>AC</td>
<td>✔</td>
<td>15 min</td>
<td>✔</td>
<td>Died 24 hrs after admission</td>
</tr>
<tr>
<td>8</td>
<td>F/63</td>
<td>60 ml oral</td>
<td>12 hrs. V, SOB</td>
<td>+ve</td>
<td>AC</td>
<td>×</td>
<td>✔</td>
<td>✔</td>
<td>Died on D3</td>
</tr>
<tr>
<td>9</td>
<td>F/27</td>
<td>100-150 ml oral</td>
<td>40 mins</td>
<td>+ve</td>
<td>AC</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Died on D15</td>
</tr>
<tr>
<td>10</td>
<td>F/73</td>
<td>Empty bottle</td>
<td>? 8 hrs. V, drowsy</td>
<td>+ve</td>
<td>GL, AC</td>
<td>×</td>
<td>×</td>
<td>✔</td>
<td>Died 8 hours</td>
</tr>
</tbody>
</table>

Courtesy Dr. SH Ng, HKPIC
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Date of attendance</th>
<th>Age/sex</th>
<th>Routes of exposure</th>
<th>Amount of exposure</th>
<th>Specific treatment</th>
<th>Complications</th>
<th>Outcome (survival/death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7/3/1998</td>
<td>58/F</td>
<td>Oral</td>
<td>500 ml</td>
<td>GL &amp; FE</td>
<td>ARF (Cr up to 564 µmol/L), paralytic ileus &amp; respiratory failure</td>
<td>Death (12 hours after admission)</td>
</tr>
<tr>
<td>2</td>
<td>31/3/1999</td>
<td>24/M</td>
<td>Oral</td>
<td>20-40 ml</td>
<td>FE &amp; ST</td>
<td>Renal impairment (Cr 172 µmol/L), PF (normal CXR but abnormal lung function test) &amp; painful dysphagia</td>
<td>Survival, renal function recovered without dialysis, refused endoscopic examination</td>
</tr>
<tr>
<td>3</td>
<td>25/12/2000</td>
<td>23/M</td>
<td>Oral</td>
<td>– One mouthful</td>
<td>FE &amp; HD</td>
<td>ARF (Cr up to 700 µmol/L &amp; progressive PF</td>
<td>Death (15 days after admission)</td>
</tr>
<tr>
<td>4</td>
<td>16/5/2002</td>
<td>20/M</td>
<td>Oral</td>
<td>Half-spoonful</td>
<td>AC, FE, ST, CH &amp; HD</td>
<td>ARF (Cr up to 400 µmol/L) &amp; oropharyngeal erosions</td>
<td>Survival, renal function gradually improved to normal, water soluble contrast study showed no oesophageal involvement</td>
</tr>
<tr>
<td>5</td>
<td>21/7/2003</td>
<td>25/F</td>
<td>Oral</td>
<td>200 ml</td>
<td>FE, ST, CH, HD &amp; AOT</td>
<td>Oropharyngeal excoriation, oesophagitis, haemorrhagic gastritis, ARF (Cr up to 600 µmol/L), acute interstitial pneumonitis &amp; acute hepatic failure</td>
<td>Death (3 weeks after admission), no improvement of renal function</td>
</tr>
<tr>
<td>6</td>
<td>5/12/2004</td>
<td>76/M</td>
<td>Eyes</td>
<td>Few drops</td>
<td>Nil</td>
<td>Nil</td>
<td>Survival</td>
</tr>
<tr>
<td>7</td>
<td>13/2/2005</td>
<td>70/M</td>
<td>Oral</td>
<td>100 ml</td>
<td>FE &amp; HP</td>
<td>ARF (Cr up to 337 µmol/L) &amp; progressive pneumonitis</td>
<td>Death (3 days after admission)</td>
</tr>
</tbody>
</table>

Paraquat poisoning (2)

- Gastric lavage followed by 50g activated charcoal was given at the A&ED
- To ICU for further management
- Charcoal haemoperfusion for 8 hours followed by high volume haemofiltration (64ml/kg/h) for 16 hours daily for the initial two days. Thereafter only HVHF continued
- N-acetylcysteine IV infusion
- Pulse steroid
- Cyclophosphamide
Paraquat poisoning (3)

- The patient regretted for what she had done
- Expressed she want to live. However,
- Her condition gradually deteriorated
  - Impaired renal function
  - Increased pulmonary oedema, increased oxygen requirement
- Intubation & IPPV
  - Oxygenation desaturation with FiO2 100%
- Decided VV-ECMO
  - Support the failing lung
  - To buy time for removal of toxin by HVHF / natural healing process
Paraquat poisoning (4)

- HVHF
  - Toxin removal
    - Serum toxin levels checked (results still pending)
  - To clear cytokines mediated injury
  - Renal replacement therapy

- N-acetylcysteine, steroid and cyclophosphamide
  - Decrease oxidative injury
  - Immune mediated injury
Mechanisms of toxicity

Superoxide radical

regeneration
W -ECMO setup - 1

RIJV

Blood Pump

RFV

Oxygen blender
Heat Exchanger
Membrane oxygenator
ECMO setup: membrane oxygenator
Paraquat poisoning (5)

- Lung continued to deteriorate
- Oxygenation totally dependent on VV-ECMO
- Developed secondary sepsis, DNR and died on day 15
Pathological changes of Lungs

- Acute to subacute lung injury with diffuse alveolar damages, evidenced by:
  - Alveolar haemorrhage
  - Hyaline membrane formation, signifying acute injury
  - Early organization with fibroblastic proliferations in both alveolar space and interstitium
  - Well establish fibrosis was not present

- Overall changes could be explained by lung injury induced by chemicals (Paraquat)
Acute to Subacute Lung Injury

- Diffuse alveolar damage with alveolar hemorrhage and focal fibrin deposition.
- Early organization with loose fibroblasts proliferation in the alveolar spaces and interstitium.
Loose fibroblastic proliferation in the interstitium, could progress to fibrosis.
Paraquat poisoning (6)

- Learning points
  - > 40mg/kg universally fatal
  - Even with aggressive methods
    - Elimination
      - Removal of paraquat by HVHF
    - Organ support
  - Prevention
    - Ban the sales of concentrated paraquat solution
    - 24% paraquat, 40mg/kg == 8 ml for 50kg person
Star fruit intoxication
Star fruit intoxication

- 76 year-old woman with chronic renal impairment, secondary to diabetic nephropathy ([creatinine] ~290 umol/l)
- Presented with sudden onset of seizures and drowsiness at mid-day.
- Patient was perfectly normal hours before
- Developed another seizure attack at the A&ED, generalised tonic-clonic for 10 mins, self aborted
- GCS(E4V1M3), BP207/140, pulse 125
- Afebrile, no neck stiffness, spontaneous movement of all 4 limbs, normal tendon reflexes
- CT scan brain showed old right internal capsular infarct and otherwise normal
Star fruit intoxication (2)

- GCS deteriorated to E1V1M2 8 hours after admission
- WBC 11.4, Hb10.5, platelet 372
- [urea] 14.1, [creatinine] 319
- Electrolytes normal
- LP done, CSF normal biochemistry and cell count
- MRI brain
  - No radiological evidence of brain, brainstem lesion, or meningoencephalitis
Star fruit intoxication (3)

- History from son
  - Taken two star fruits on the day of admission
- Diagnosis: star-fruit poisoning with severe neurotoxicity
- Supportive care
  - Intubation and IPPV
  - Inotropic support
Star fruit intoxication (4)

- 8 hour charcoal haemoperfusion followed by 30 hours CVVH (33ml/min)
- Her GCS gradually improved back to normal 15/15
- No recurrence of her neurological symptoms upon cessation of CVVH
- Extubated on next day
- Well afterward
Star fruit intoxication (5)

- No consensus on the exact neurotoxin
  - Oxalate
  - Neurotoxin (AcTx)
    - \(<500D\)
    - Excreted largely by kidney
    - Lipophilic, cross BBB, accumulate in the brain
    - Moderate volume of distribution
    - Can be redistributed in different body compartments
<table>
<thead>
<tr>
<th>Studies</th>
<th>Region</th>
<th>No. of patients</th>
<th>Symptoms</th>
<th>Tx modality</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et-al</td>
<td>Taiwan</td>
<td>10, all with impaired consciousness</td>
<td></td>
<td>Intensified HD</td>
<td>8 Deaths, 2 survivors</td>
</tr>
<tr>
<td>Hosp Authority Unpublished, 2001</td>
<td>Hong Kong</td>
<td>1, impaired consciousness</td>
<td></td>
<td>CAPD</td>
<td>Death</td>
</tr>
<tr>
<td>Neto et-al</td>
<td>Brazil</td>
<td>7, all with seizures</td>
<td></td>
<td>Symptomatic(2) CAPD (1) CAPD+2-hour HD (1) IPD (1) IPD+CAVHD (1) HD+15h-CVVHD+daily HD (1)</td>
<td>Death</td>
</tr>
<tr>
<td>Nephrol Dial Transplant 2003;18:120-125</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tse et-al</td>
<td>Hong Kong</td>
<td>1, impaired consciousness</td>
<td></td>
<td>Daily HD</td>
<td>Survived</td>
</tr>
<tr>
<td>Chen et-al</td>
<td>Taiwan</td>
<td>1, hearing impairment, impaired consciousness, coma</td>
<td></td>
<td>2 sessions HD + charcoal HP</td>
<td>Survived, regained consciousness within 1 day after HP</td>
</tr>
<tr>
<td>Clin Toxicol (Phila) 2005;43:197-199</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et-al</td>
<td>Taiwan</td>
<td>2, hiccups, impaired consciousness, status epilepticus (1)</td>
<td></td>
<td>2 sessions HD + charcoal HP</td>
<td>Survived, regained consciousness within 16-20 hours after HP</td>
</tr>
<tr>
<td>Chan et-al</td>
<td>Hong Kong</td>
<td>1, seizures, impaired consciousness, coma</td>
<td></td>
<td>Charcoal HP + 30h CVVH</td>
<td>Survived, regained consciousness within 2-30 hours after HP</td>
</tr>
<tr>
<td>Hong Kong Med J 2009;15:149-152</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et-al</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Learning points

- Toxicology should be one of ddx for unexplained coma
- History is important
- Anything can be toxic, dependent on circumstances
- Extracorporeal elimination is life saving in some condition
  - Should be considered in life threatening condition with unknown diagnosis
Summary

- Haemodialysis (low flux)
- Haemoperfusion (charcoal / resin)
- Haemodialysis (high flux)
- Haemofiltration (CVVH / CVVHDF)
- High volume haemofiltration
- Superhigh flux haemofiltration
- MARS
- Prometheus
- Single pass albumin dialysis
- Coupled plasma filtration adsorption
- Plasmapheresis
- Extracorporeal life support
  - VV-ECMO
  - VA-ECMO
Thank you for your attention