BHIVA
British HIV Association

BVHG
British Viral Hepatitis Group

Professor Peter Hayes

University of Edinburgh

Hepatology Highlights *for the* Healthcare Specialist

Tuesday 17 April 2019 • Pentland Suite, Level 2, Edinburgh International Conference Centre

Meeting sponsors

abbvie GILEAD

Acute liver failure

BHIVA meeting, April 2018

No disclosures relevant to this presentation

ALF DEFINITIONS

Trey and Davidson, 1970

Potentially a reversible condition that is the consequence of severe liver injury, in which the onset of hepatic encephalopathy occurs within 8 weeks of first symptoms of illness in the absence of pre-existing liver disease

Aetiology of ALF

Drug Causes

- Halothane
- Paracetamol with or without enzyme inducers
- Anti-TB medication (rifampicin, isoniazid, pyrazinamide)
- MAOI
- NSAIDS
- Anticonvulsants (valproate, phenytoin, lamotrigine)
- Antibiotics (cotrimoxazole, ketoconazole)
- Illegal drugs

Non-drug Causes

- Viral; HAV, HBV, HCV (?), HDV, HEV, CMV, Coxsackie.
- Autoimmune hepatitis
- Pregnancy; AFLP, HELLP.
- Ischaemia.
- Budd-Chiari.
- Malignancy.
- Wilsons Disease.
- *Amanita phalloides*

Paracetamol Poisoning- epidemiology

- Commonest discharge diagnosis for over dose
- Slight reduction in discharges to 100 per 100 000 population since 1998 in Scotland
- Commonest cause of acute liver failure in the UK and US
- Legislation changes led to reduction in admissions with severe overdose by 30% in England

Paracetamol toxicity

- Approx 10-15 gm of paracetamol is sufficient to induce hepatotoxicity
- Related to metabolic activation of paracetamol
- Toxic metabolite identified as N-acetyl-p-benzoquinoneimine
- Glutathione binds NAPQI and limits toxicity
- N-acetylcysteine is an effective antidote within the theraputic window

Severity of liver damage

- ALT markedly increased- not good marker
- Prothrombin time best marker
- Often early acidosis before fluid resuscitation
- Hypoglycaemia

Predictors of severity

- Quantity of paracetamol
- Time to NAC
- Age
- Chronic alcohol misuse

Initial Management

- Clear history of time of overdose and any additional tablets
- If around 12 hours or unclear start NAC
- Monitor blood glucose
- Routine bloods including PT and paracetamol level
- Intravenous fluids- 5% dextrose and N-saline

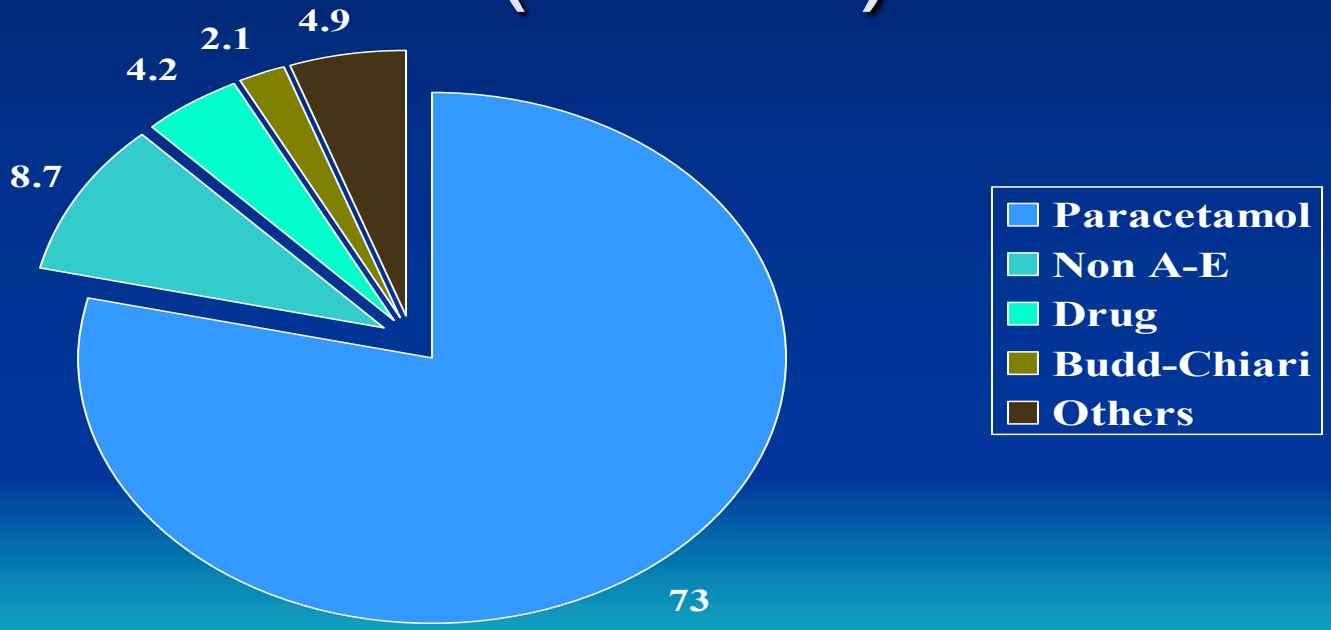
Progress

- Monitor prothrombin time and creatinine
- Monitor neurological state
- Psychiatric evaluation as early as possible
- If PT rising rapidly SLTU contacted and transferred early-if PT =hrs post OD-50% risk of FHF

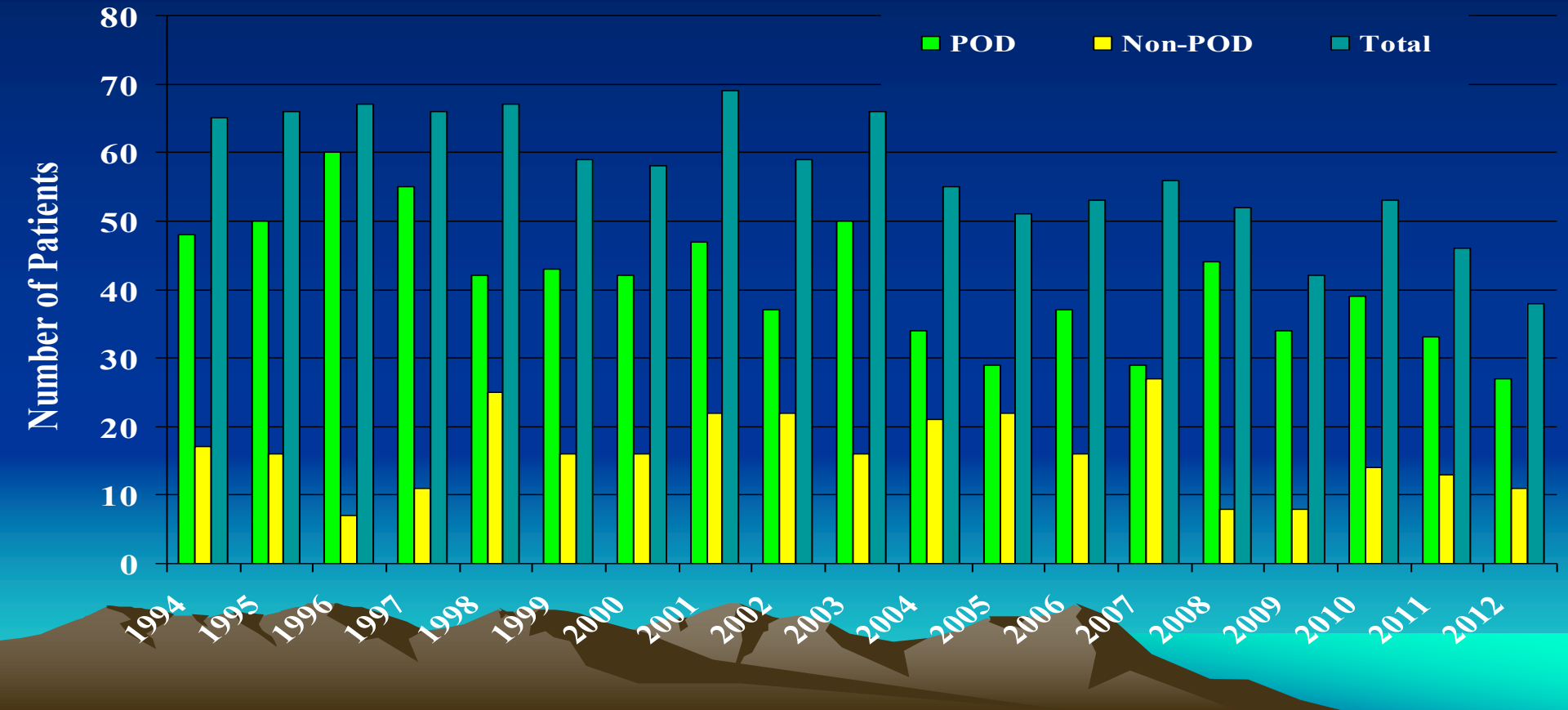
On transfer

- Main thrust initially to ascertain suitability for transplantation
- Psychiatric evaluation
- Contact with GP and family
- Continue intravenous fluids and monitoring PT, creatinine and glucose

Acute Liver Failure admitted to SLTU (n=621)



Referrals ALF to SLTU



KCH criteria-paracetamol

- pH < 7.30 after fluid resuscitation

- or all 3 of following: PT >100s
  creat>300
  grade 3 encephalopathy

Bernal et al. Lancet 2002

- Arterial lactate >3.5 mmol/l before resuscitation
- Arterial lactate >3.0 mmol/l following resuscitation

As good as KCH as indicating poor prognosis in ALF

Clinical Progress

- Encephalopathy worsens
- Patient becomes agitated and difficult to manage
- Oligoanuric
- Require ITU assessment

MEDICAL CONTRAINDICATIONS TO TRANSPLANTATION

- Untreated or progressive infection
- Clinically apparent extrahepatic or metastatic malignancy
- Progressive hypotension, resistant to vasopressor support
- Clinically significant ARDS, $FiO_2 > 0.8$
- Fixed dilated pupils > 1 hour in the absence of thiopentone
- Severe coexistant cardiopulmonary disease, AIDS

PSYCHIATRIC CONTRAINDICATIONS TO TRANSPLANTATION

- Multiple episodes of self harm (>5) within an established pattern of behaviour (esp. if non-drug methods used)
- Consistently stated wish to die, in the absence of established mental illness
- Chronic refractory schizophrenia or other mental illness, resistant to therapy
- Incapacitating dementia or mental retardation
- Active intravenous drug abuse or oral polydrug use
- Alcohol dependence or abuse
- Established pattern of non-compliance with treatment

Clinical problems in acute liver failure

Encephalopathy

Cerebral oedema

Cardiovascular disturbance

Deranged coagulation

Renal failure

Gut failure

(Respiratory problems)

SEPSIS

Hepatic encephalopathy

Grade	Conscious level	Personality	Neurological signs	EEG
1	Sleep reversal Restless	Forgetful Agitated Irritible	Tremour Apraxia Incoordination Impaired handwritting	Triphasic waves (5Hz)
2	Lethargy Slowed	Disorentated Loss of inhibition Inappropriate behaviour	Asterixis Dysarthria Ataxia Hyporeflexes	Triphasic waves (5Hz)
3	Sleepy Confused	Disorentation Aggressive	Asterixis Muscular rigidity Extensor planters Hyperreactive reflexes	Triphasic waves (5Hz)
4	Coma	None	Decerebration	Delta slow waves

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SEPSIS

Cause of cerebral oedema

Multifactorial

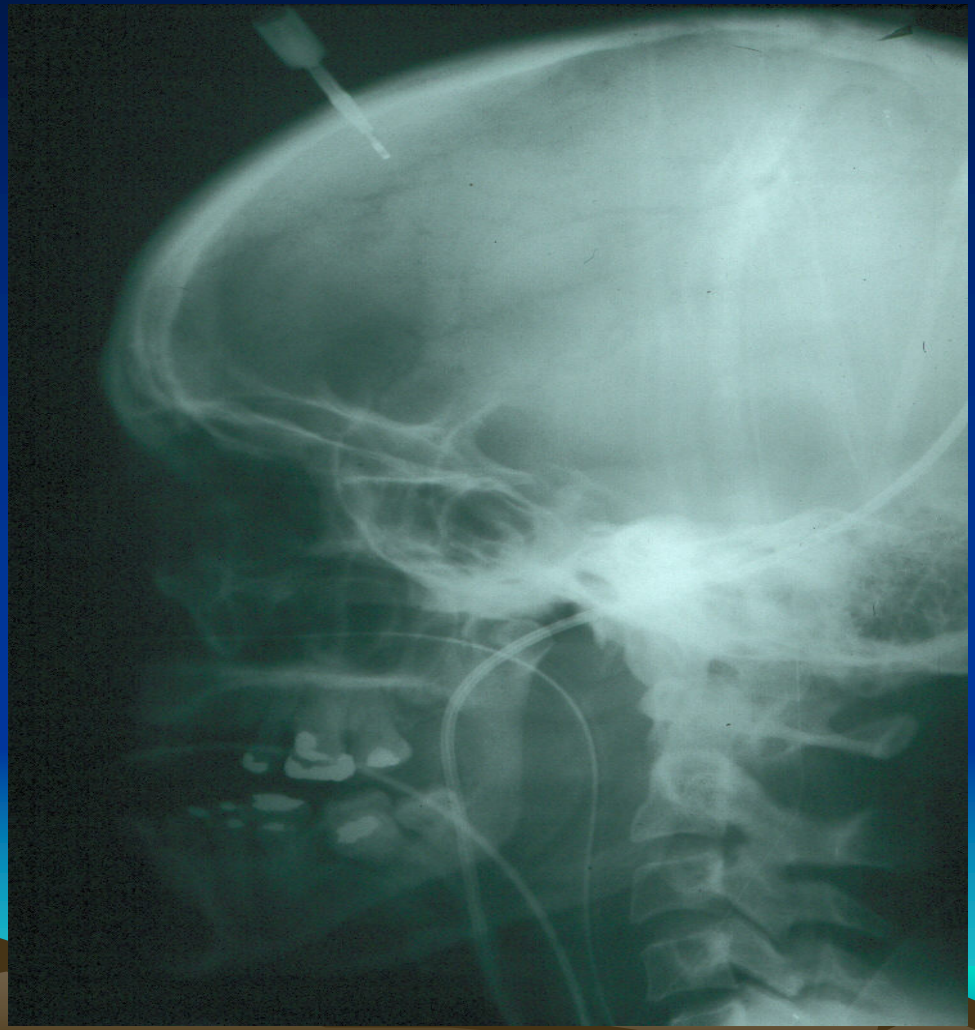
Cytotoxic problem rather than disruption of blood-brain barrier

1. Ammonia metabolism to glutamine in astrocytes

   - osmotic effect

2. Cerebral hyperaemia

3. Inflammatory mechanism



Management of cerebral oedema

Basic measures:

patient position, venous drainage, adequate sedation, adequate ventilation, hypervent

Osmotic agents

Hypothermia

Hepatectomy

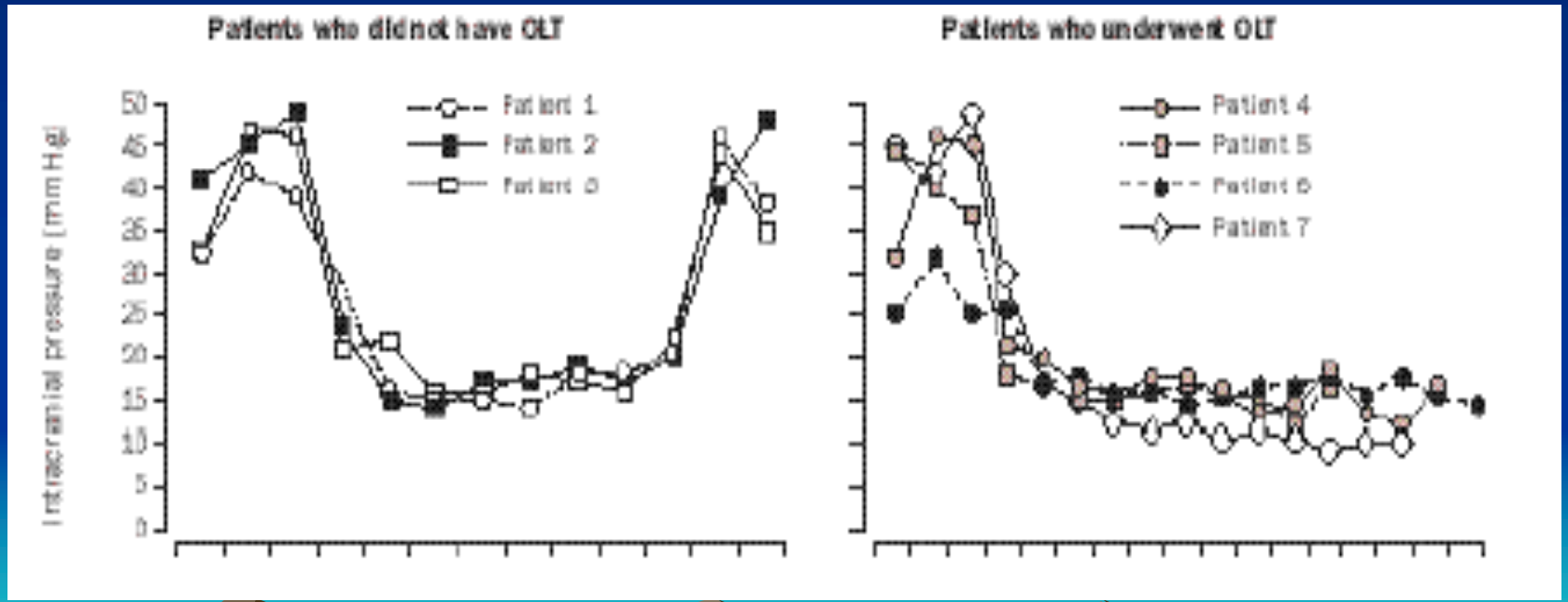
?Barbiturate coma

Detoxification using liver support system

Treatment objectives

- Cerebral perfusion pressure = mean arterial pressure – intracranial pressure
- Cerebral oedema increases ICP therefore aim to reduce ICP
- Other manoeuvres to increase MAP
- Aim for CPP>50mmHg

Hypothermia and ICP



Jalan et al Lancet

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SEPSIS

Cardiovascular support

Hyperdynamic circulation

Hypotension, vasodilatation, elevated cardiac output, low SVRI

- resuscitation
- use of N-acetylcysteine
- norepinephrine

Clinical problems in acute liver failure

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SEPSIS

Coagulopathy

Coagulation disturbance vs bleeding

Invasive procedures and coagulopathy

Bleeding unusual complication

Thromboelastography helpful at operation

Clinical problems in acute liver failure

Encephalopathy

Cerebral oedema

Cardiovascular disturbance

Deranged coagulation

Renal failure

Gut failure

(Respiratory problems)

SEPSIS

Renal support

Haemofiltration vs haemodialysis

Nutritional support

Enteral / jejunal feeding?

Clinical problems in acute liver failure

- Encephalopathy
- Cerebral oedema
- Cardiovascular disturbance
- Deranged coagulation
- Renal failure
- Gut failure
- Respiratory problems
- Sepsis

Respiratory Problems

- Common
- Pneumonia, aspiration
- Atelectasis
- Ventilation related
- ARDS

SEPSIS

Incidence- common (80%)

Organisms- gram positive in 70% of cases

fungal infection in up to 30%

Time course- often cause of late death

Antibiotic and anti-fungal prophylaxis is given when patients ventilated

LIVER SUPPORT SYSTEMS

Cell mass

90% of liver mass is hepatocytes

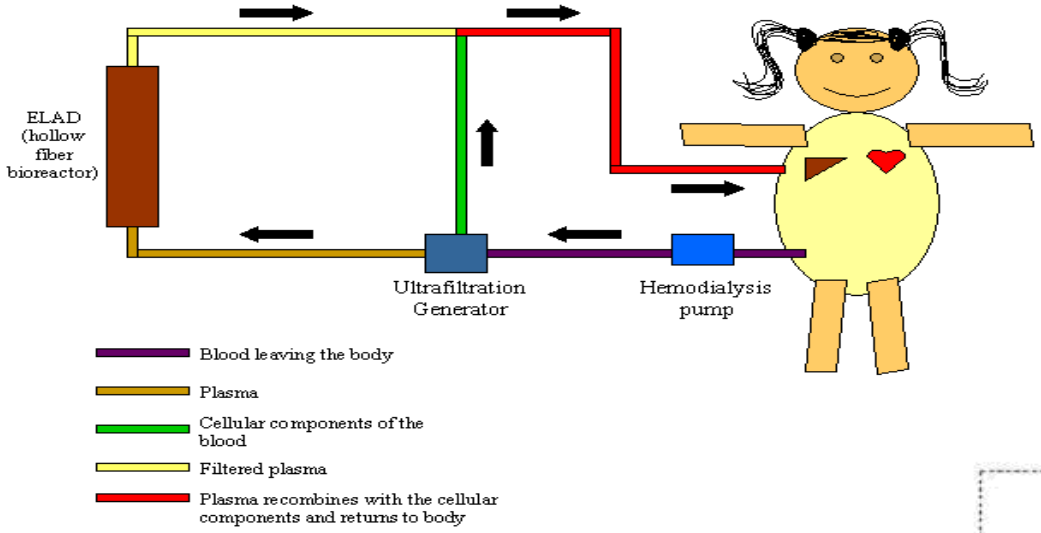
Approximately 20% of liver mass is required in patients undergoing hepatic resection

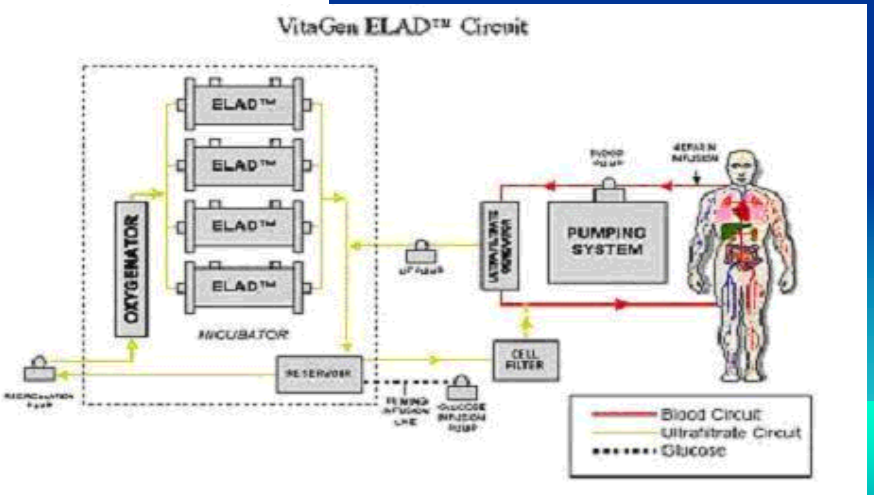
100g – 400g hepatocytes required

- may allow improved function of native liver

ELAD

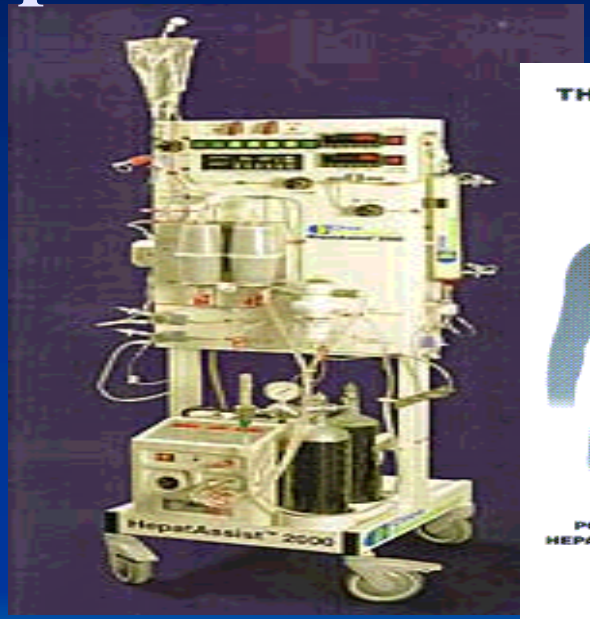
Human hepatoma cells



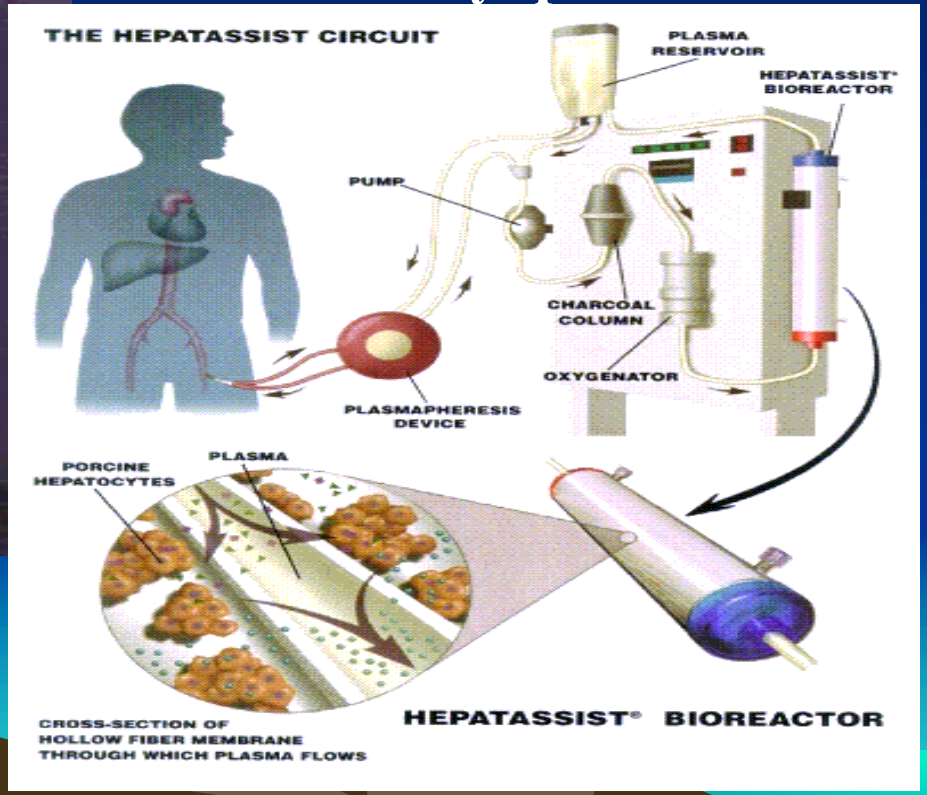


Randomised controlled trials have shown no benefit in FHF

HepatAssist



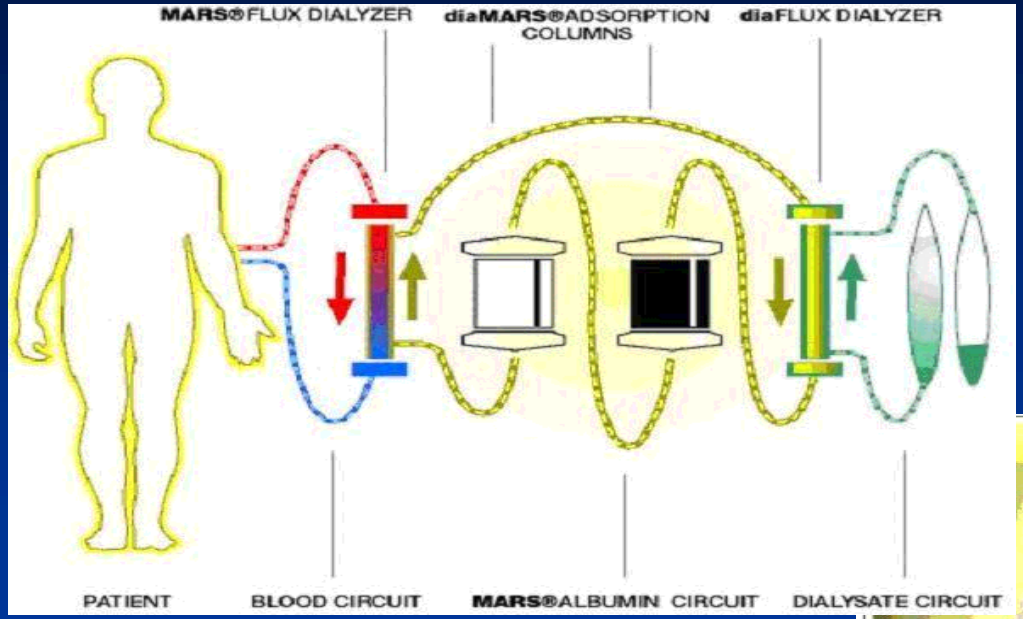
Porcine cryopreserved cells

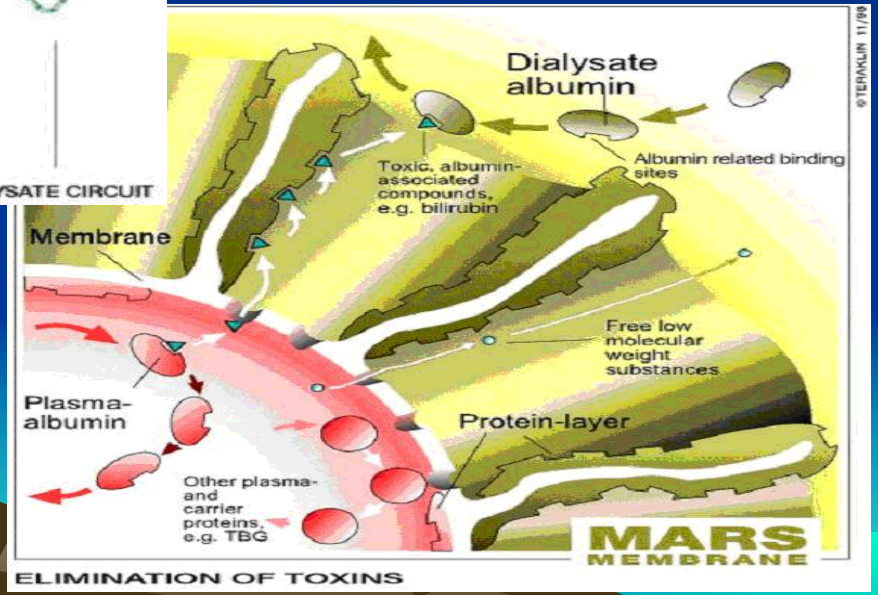


No published randomised trials

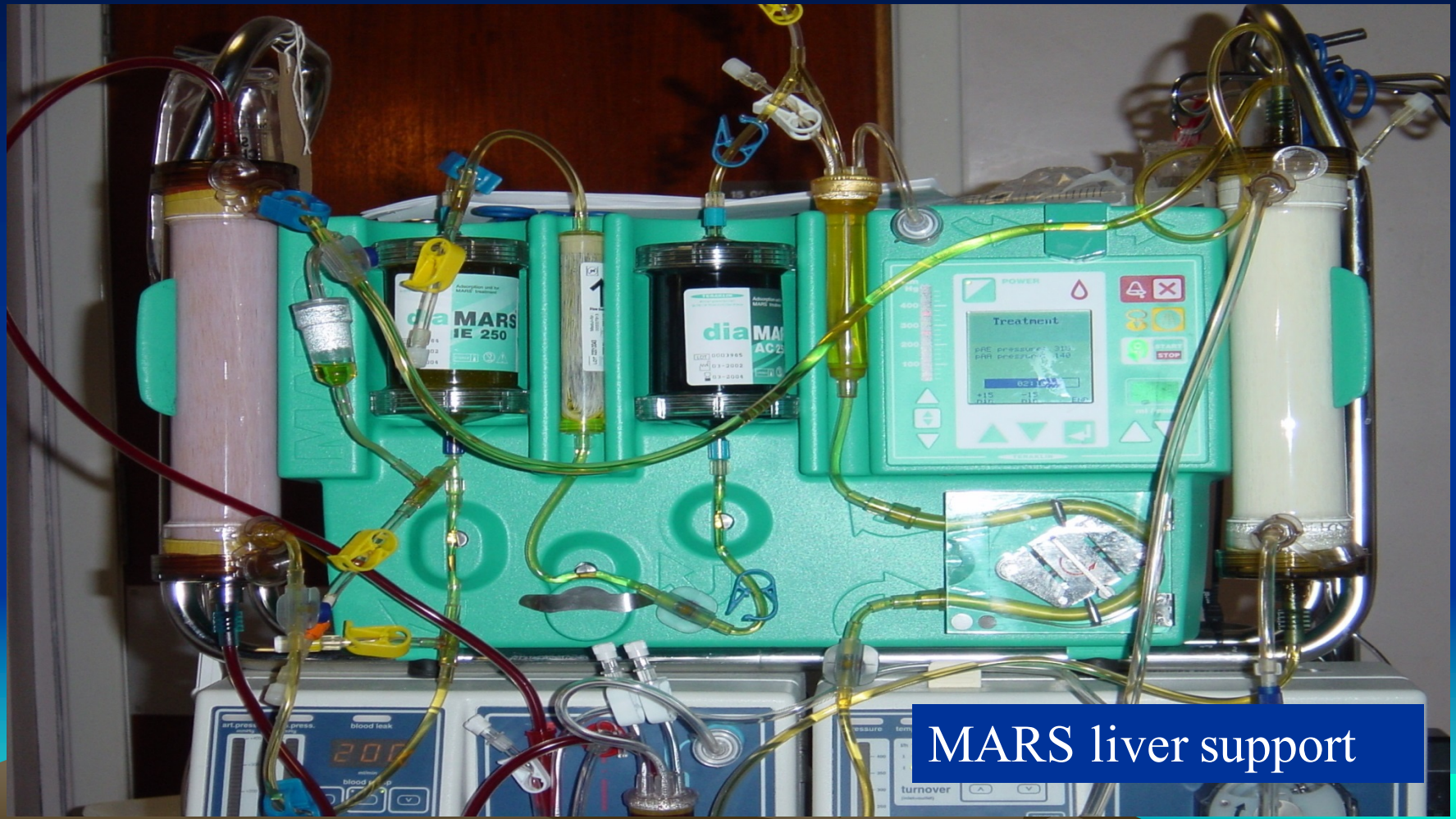
MARS

No hepatocytes





Uncertain role in FHF


MARS liver support

Conclusions

- Paracetamol poisoning is common
- Acute liver failure has reduced in England but not Scotland
- Mortality is high and transplantation may be indicated
- Liver support devices may improve outcome