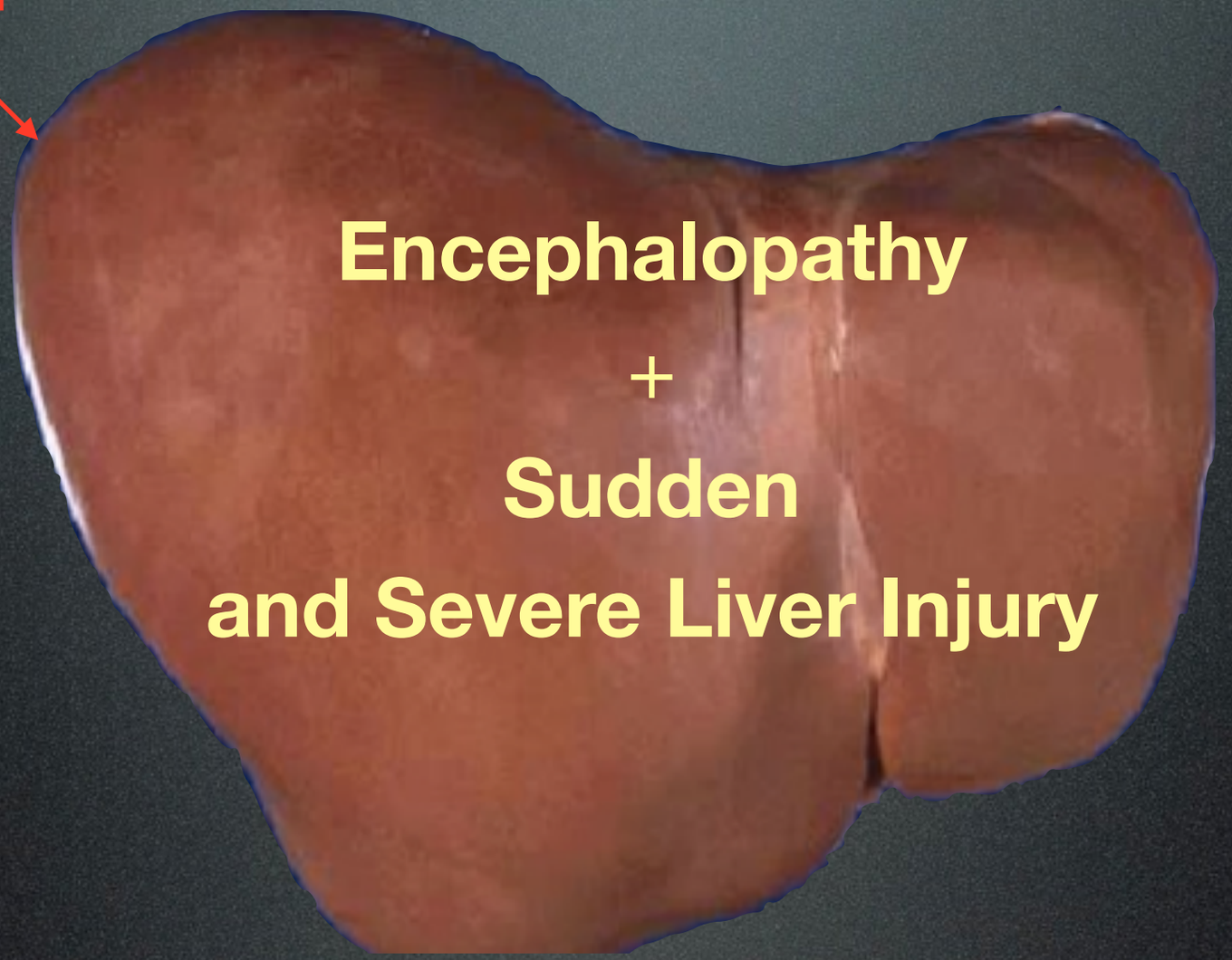
Acute Liver Failure

Introduction - Acute Liver Failure

Healthy liver



Encephalopathy

+

Sudden

and Severe Liver Injury

Introduction - Acute Liver Failure

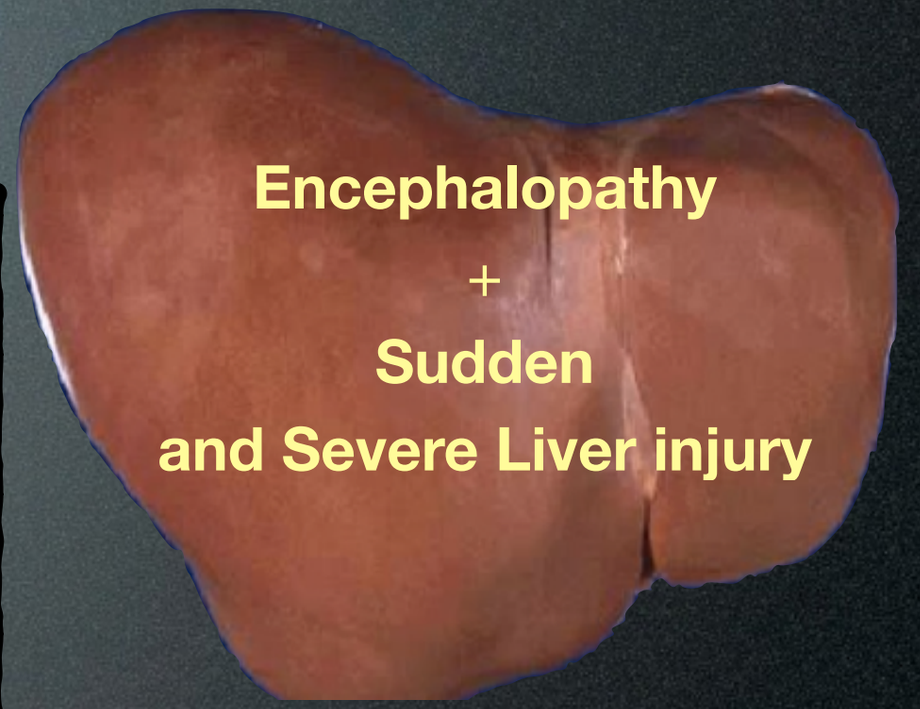
Liver injury?

- Raised transaminases (thousands)
- Impaired synthetic function

  INR > 1.5
- Metabolic derangements

  Hypoglycaemia

  Lactic acidosis



- Rare
- No pre-existing liver disease
- High mortality
- Key is **<u>early</u>** recognition ➙ Liver centre

Acute Liver Failure

Definition

Incidence

Prognosis

Causes

Clinical Management

What your liver does

Synthesis

Protein synthesis
Clotting factors → coagulopathy
Energy regulation → lactic acidosis
Gluconeogenesis → hypoglycaemia

Storage

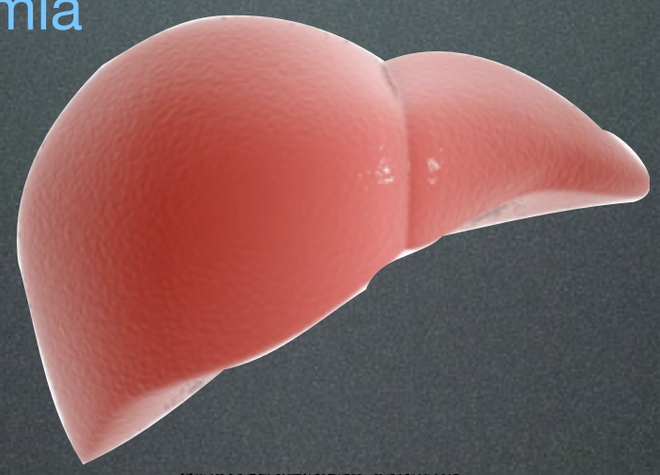
Fats
Glycogen
Vitamins
Minerals

Immunity

Innate
Adaptive
Tolerance
Cytokines → Immunoparalysis/Sepsis/SIRS

Bile

Processing of food
Cholesterol
Hormones



Detox

Drugs
Alcohol
Ammonia → raised art. ammonia
Old RBCs

When it doesn't work

Extra Hepatic

→ Hepatic encephalopathy
→ Cerebral oedema
→ High C.O. state
→ Renal failure
→ ARDS
→ Bone marrow suppression
→ ARDS
→ Reduced leucocyte function
→ Pancreatitis

Clinical features of ALF

Whole body

- SIRS
- hypercatabolic

Liver

- ⬇ metabolic function
- ⬇ gluconeogenesis → hypoglycaemia
- ⬇ lactate clearance → lactic acidosis
- ⬇ ammonia clearance → raised art. ammonia
- ⬇ synthetic capacity → coagulopathy

Portal hypertension

- only in subacute disease don't confuse with chronic liver disease

Bone marrow

- suppression→viral disease

Leucocytes

- ⬇ function and immunoparalysis→sepsis

Brain

- hepatic encephalopathy
- cerebral oedema
- ICH

Heart

- high output state
- subclinical myocardial injury

Lungs

- ARDS

Pancreatitis

- esp with paracetamol O/D

Kidney

- frequent failure

Definition of Acute Liver Failure

“Acute”

No previous liver disease

"**Short**" time between
encephalopathy and symptoms

Hyperacute < 7days

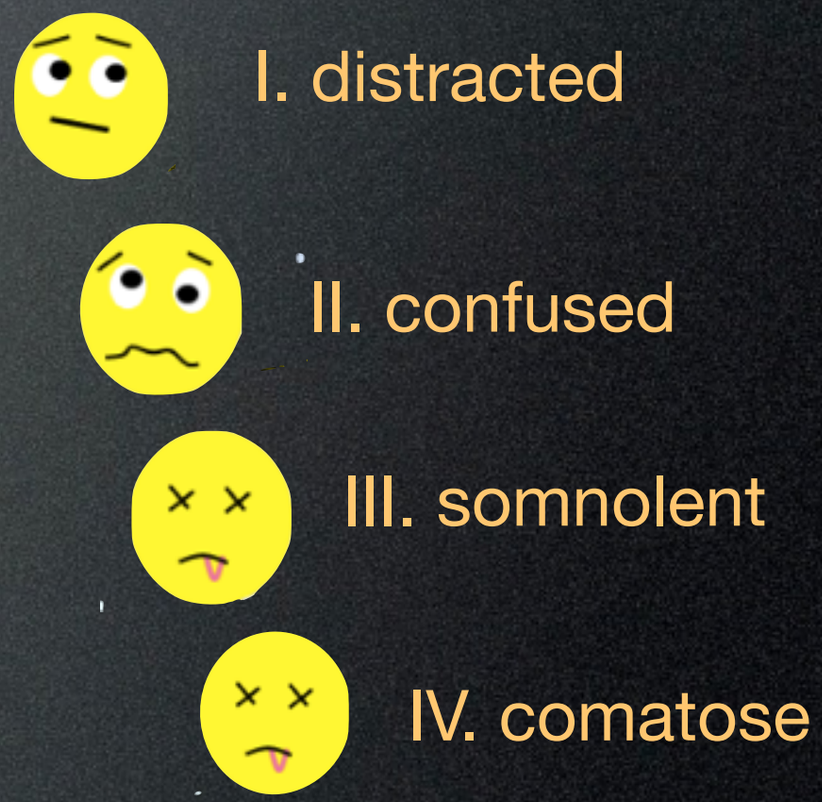
Acute 1-4 weeks

Subacute 4-12 weeks

“Liver failure”

INR >/= 1.5

Encephalopathy
(any grade)



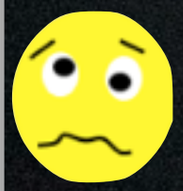
AASLD definition (Polson and Lee, Hepatology 2005)

Interval between symptoms ↔ encephalopathy

- identifies **cause**
- aids in **prognosis**

	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	***< 7 days***	***1-4 weeks***	***4-12 weeks***
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of ICH	++	++	+/-
Survival rate without Tx	Good	Moderate	Poor
Typical cause	Paracetamol, Hep A / E	Hep B	Non paracetamol drugs

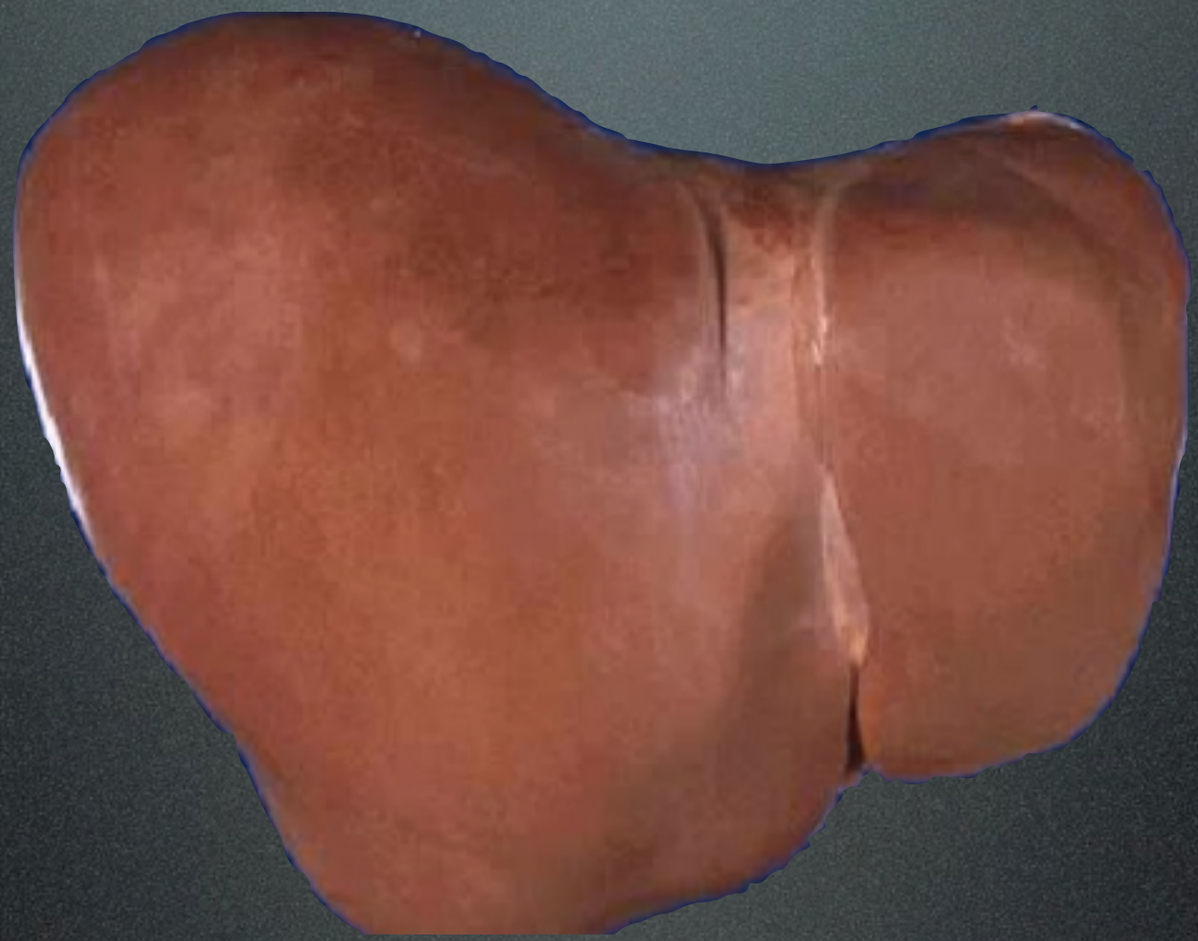
Hepatic Encephalopathy

Grade	Level of consciousness	Personality/ Intellect	Neurological signs
 I	**Restless**	Forgetful, reduced attention, mild confusion,agitation, irritability	Tremor, apraxia, impaired handwriting
 II	**Drowsy** but awake	Disorientation to time, loss of inhibition, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoactive refexes
 III	**Somnolence** but responds to stimulation, confusion	Disorientation to place, aggressive behavior	Asterixis, muscular rigidity, hyperactive reflexes
 IV	**Coma**	None	Decerebration Signs of ICH

III - IV protect airway

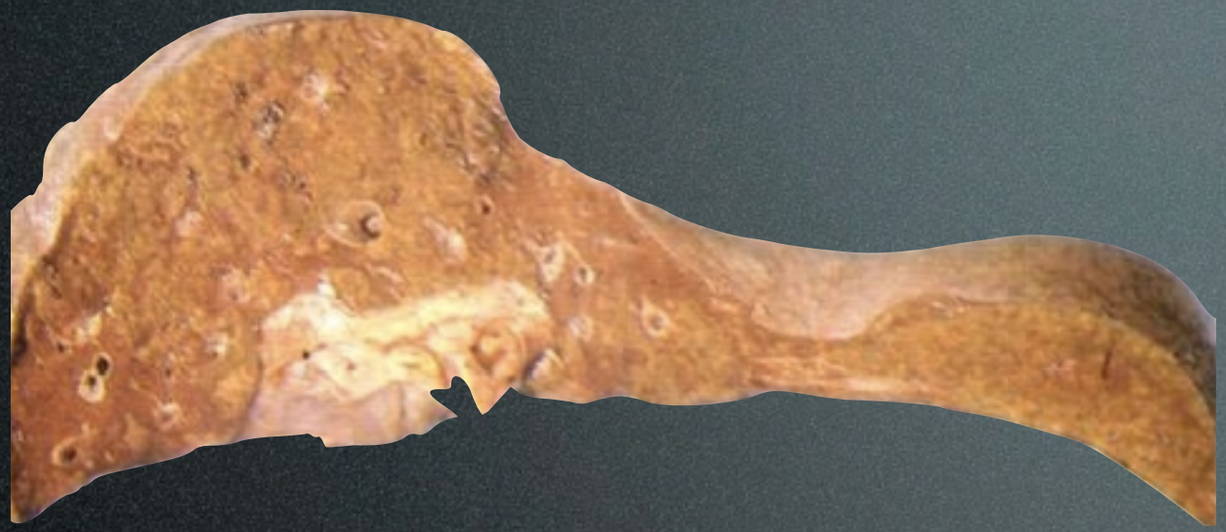
Pathology

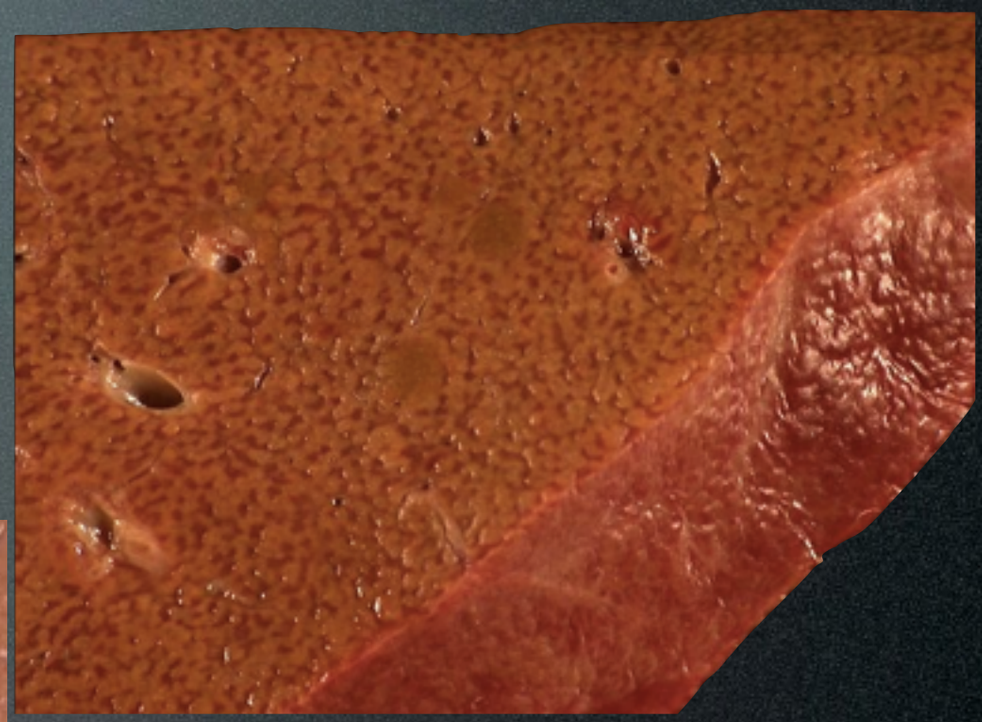
Pathology

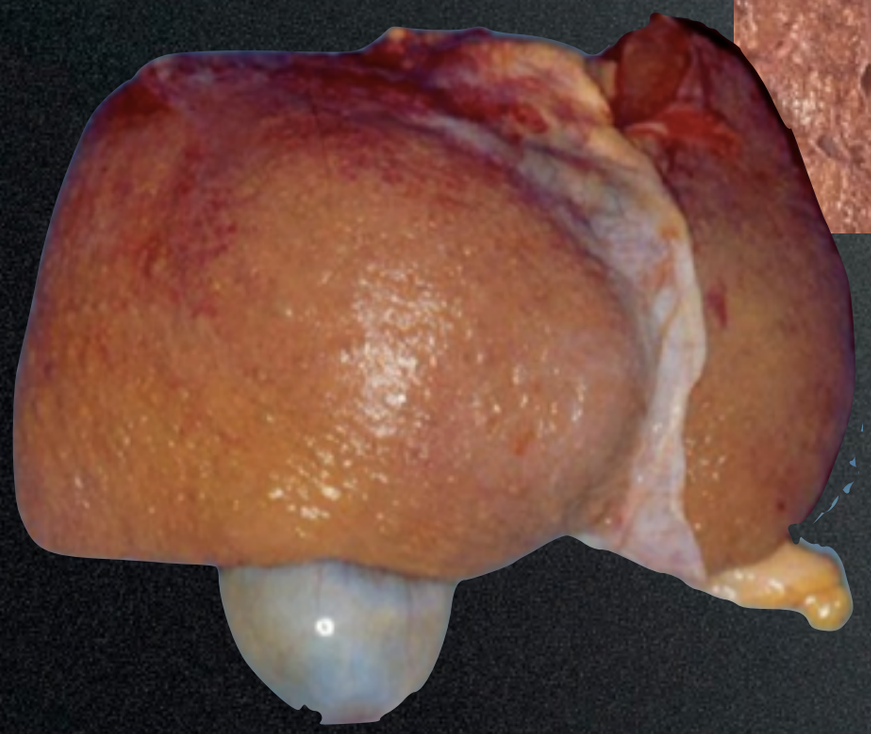


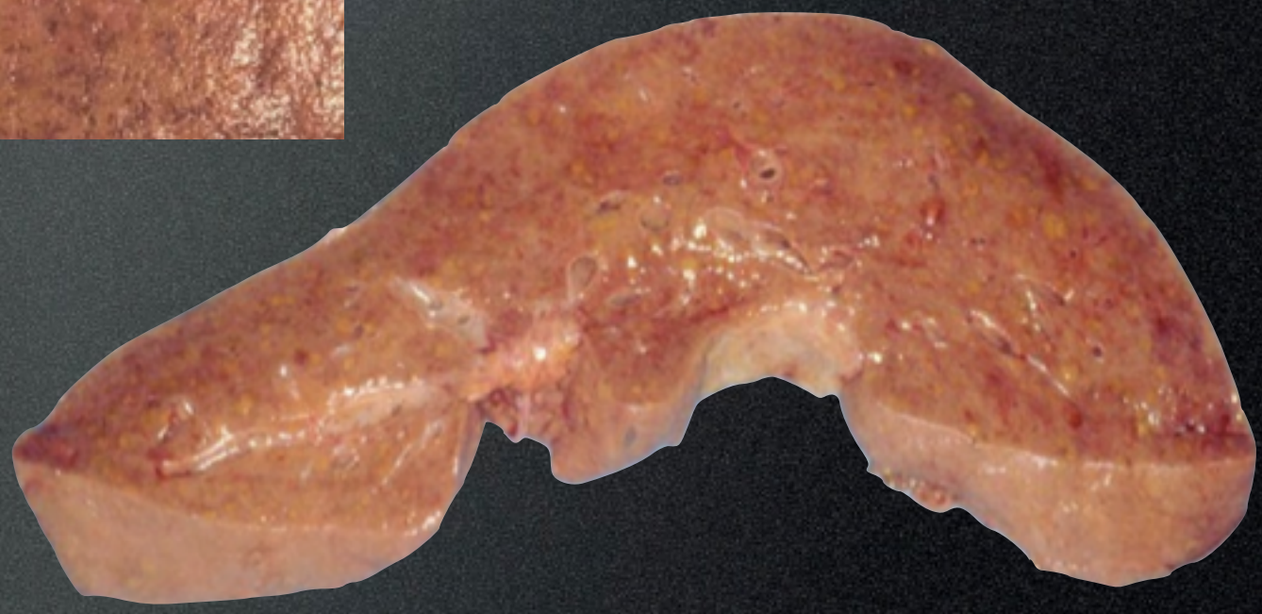
Normal liver

Pathology







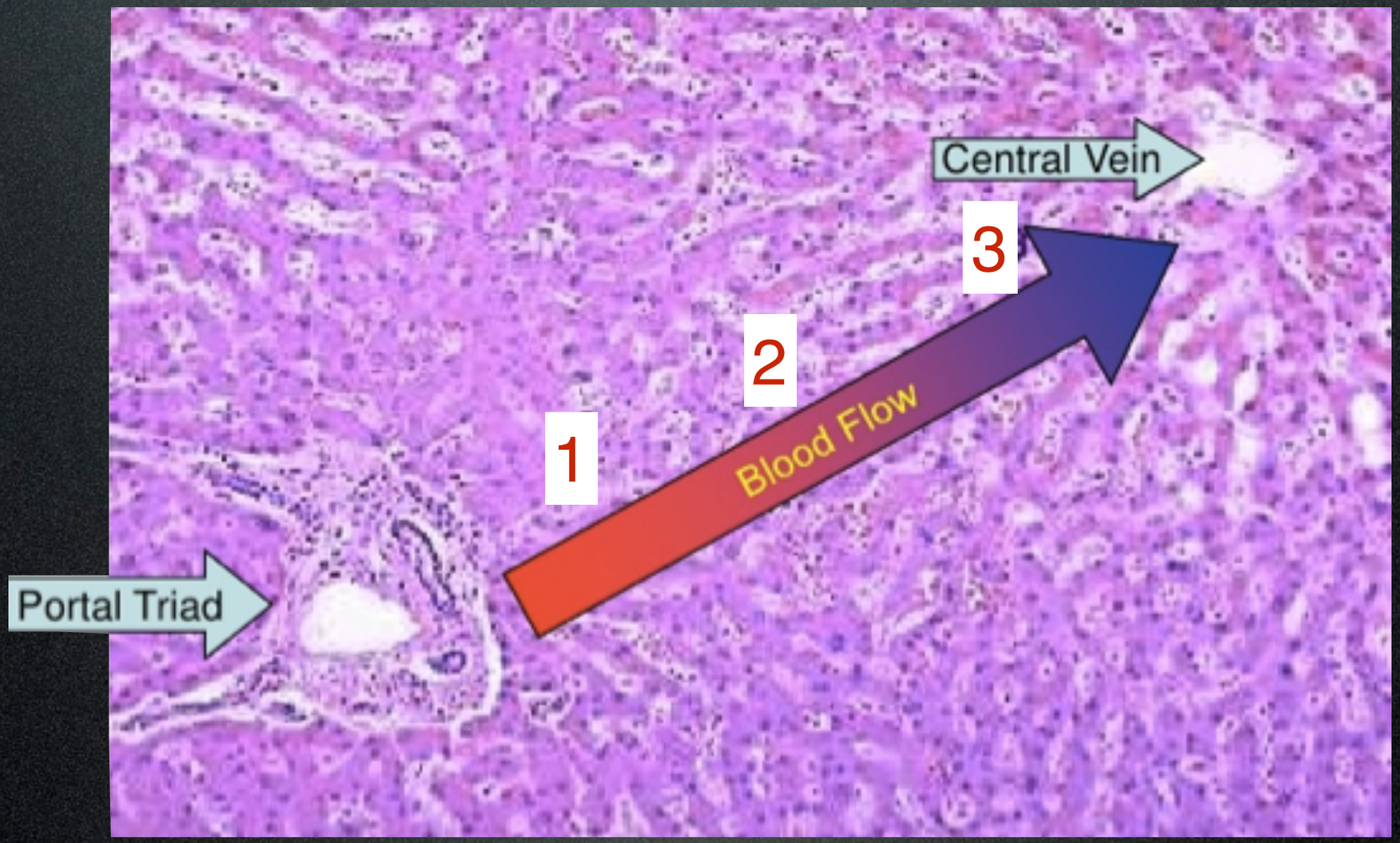


Fulminant hepatitis

Histopathology

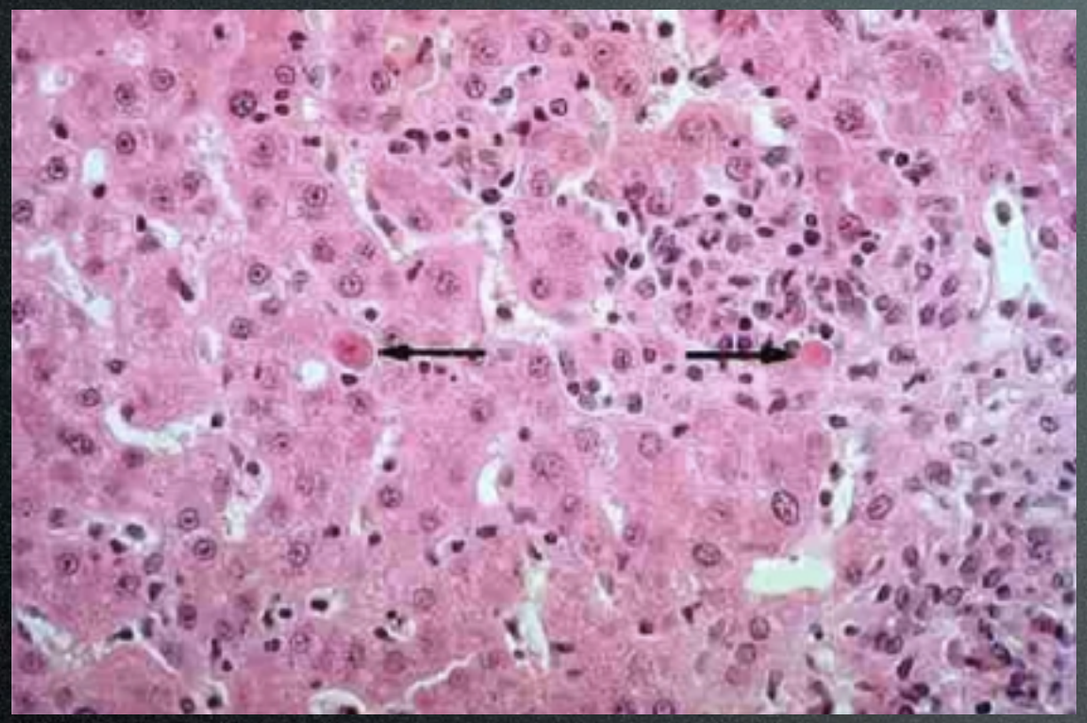
Normal liver microscopy

showing acinus zones 1,2,3



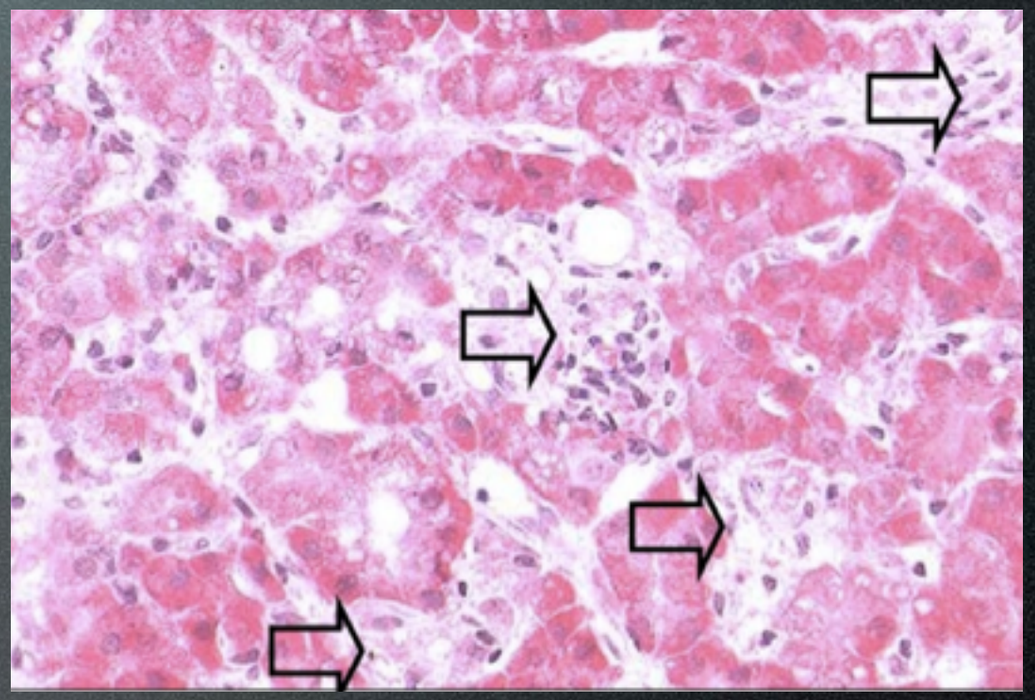
Histopathology

Acute hepatitis



Apoptotic cells

- Swelling and apoptosis
- Diffuse inflammation
  - lymphocytes, macrophages



Confluent necrosis

- Panacinar necrosis
- Mild fatty change
- Portal inflammation and cholestasis

Acute Liver Failure

Definition

Incidence

Prognosis

Causes

Clinical Management

Incidence

Rare

1-6 cases / million /year

Consequently

- Small evidence base
- Few **experienced** centres /doctors
- **Often missed** at initial medical contact

(often confused with septic shock)

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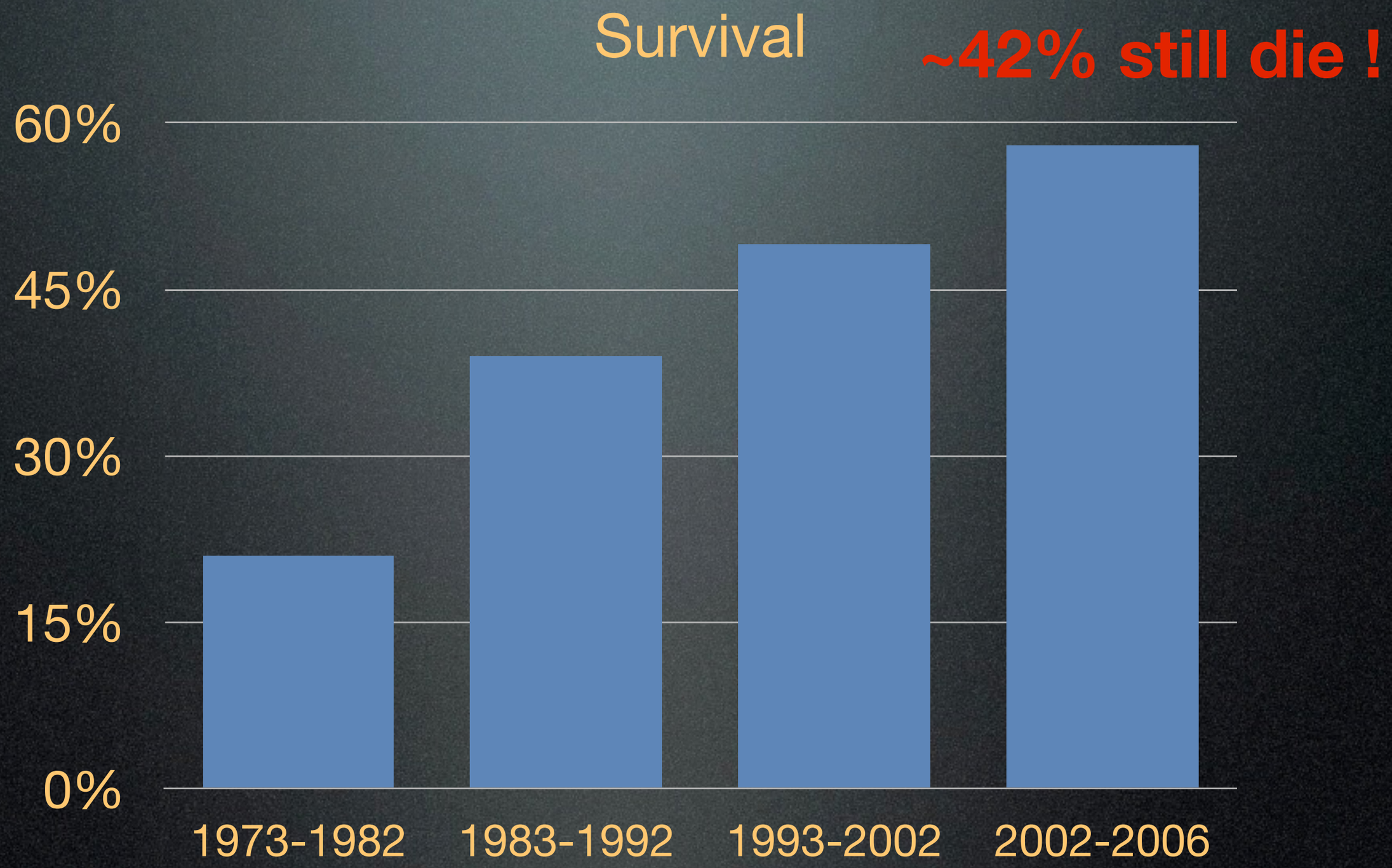
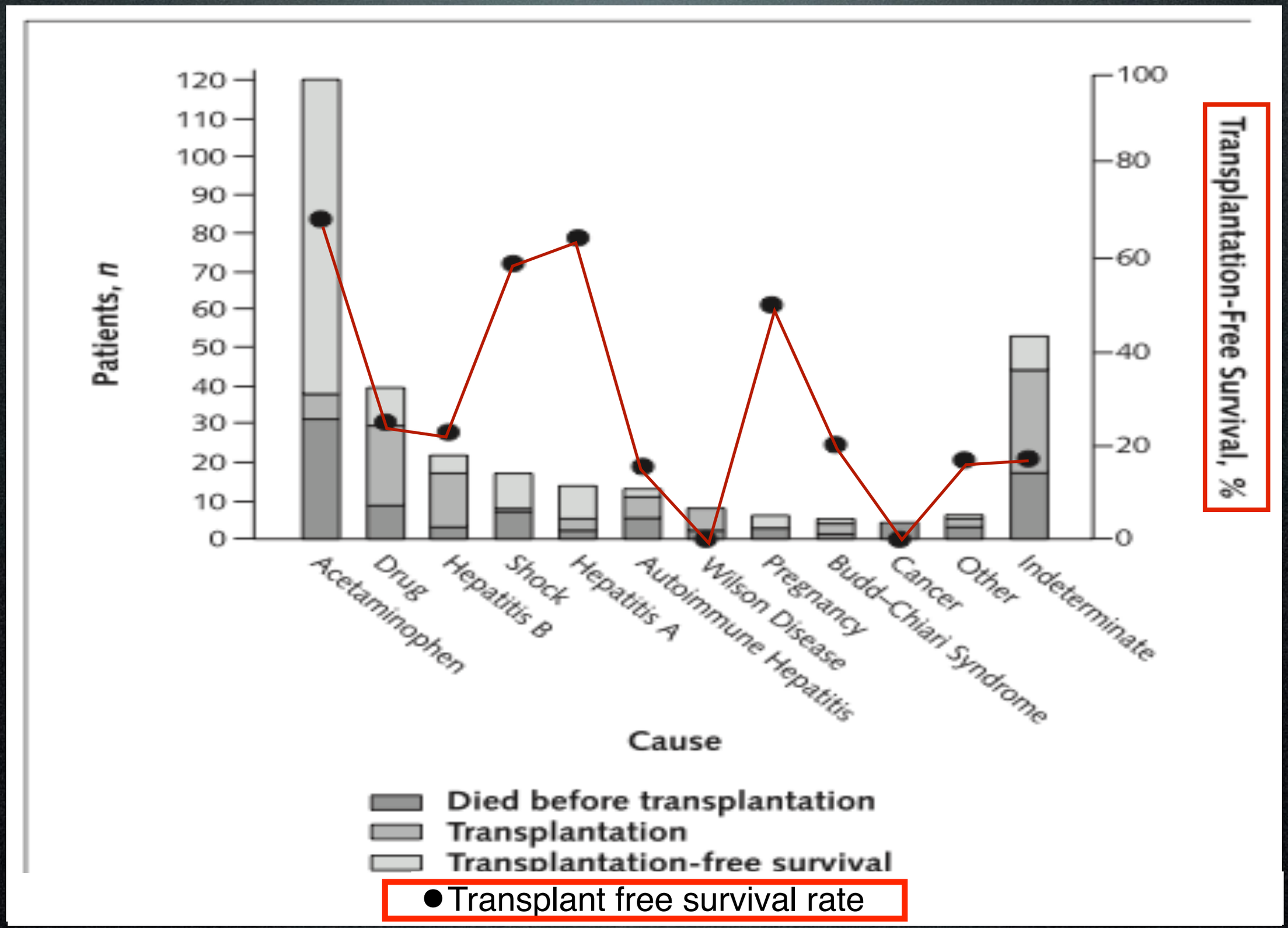
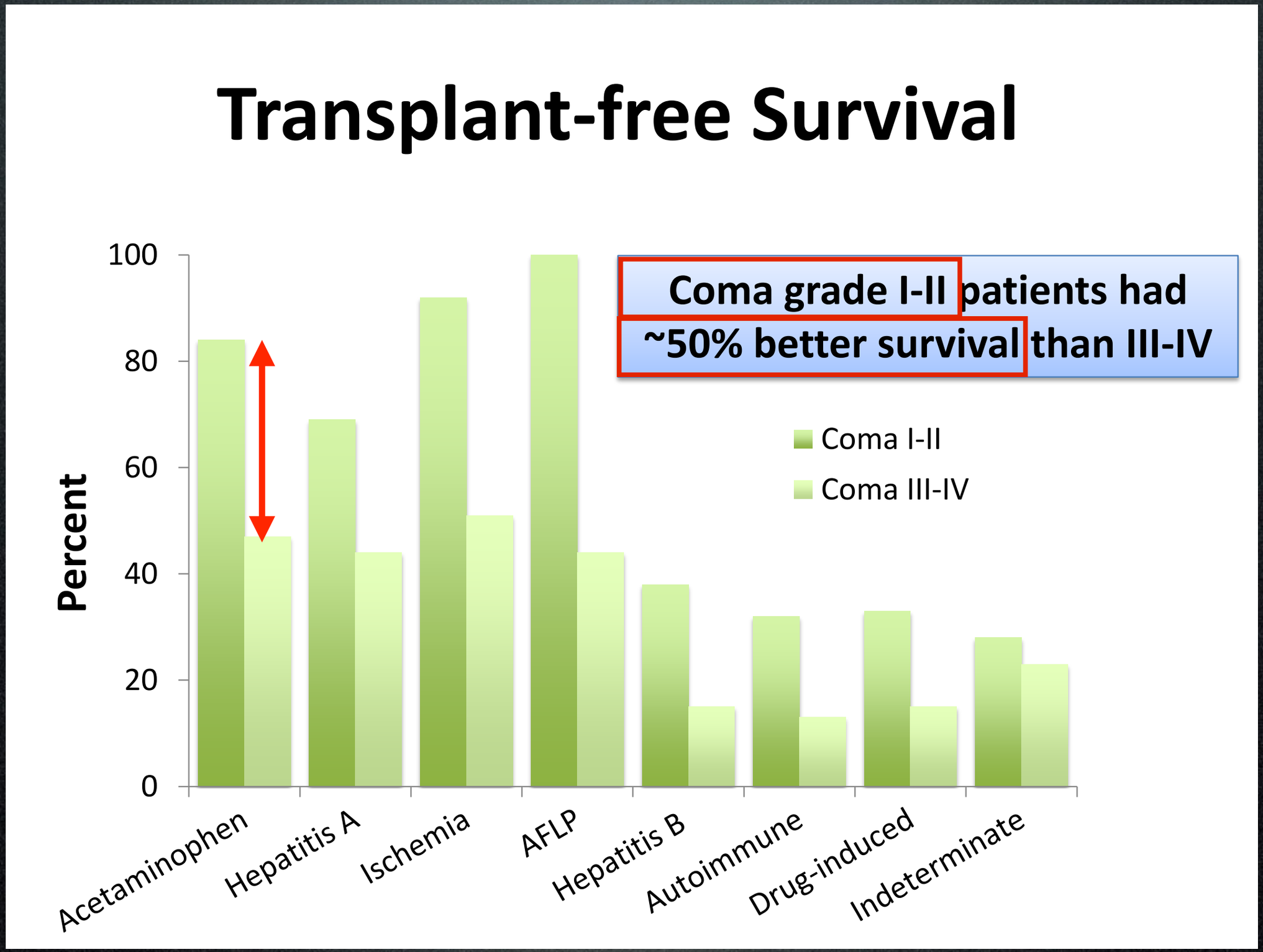

Survival
~42% still die !
60%
45%
30%
15%
0%
1973-1982
1983-1992
1993-2002
2002-2006

Aetiology determines prognosis



Ann Intern Med. 2002;137:947-954

Severity of encephalopathy determines prognosis



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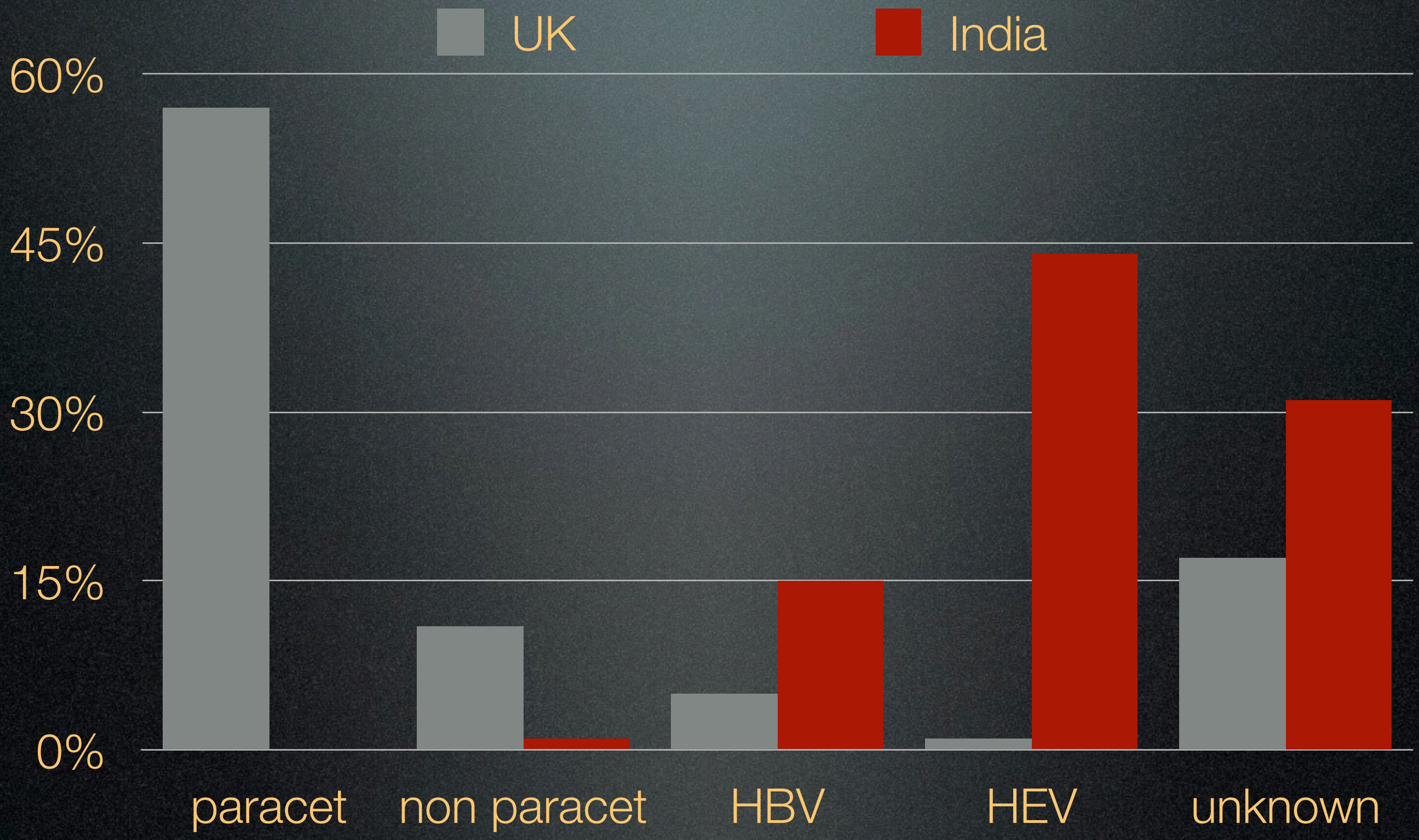
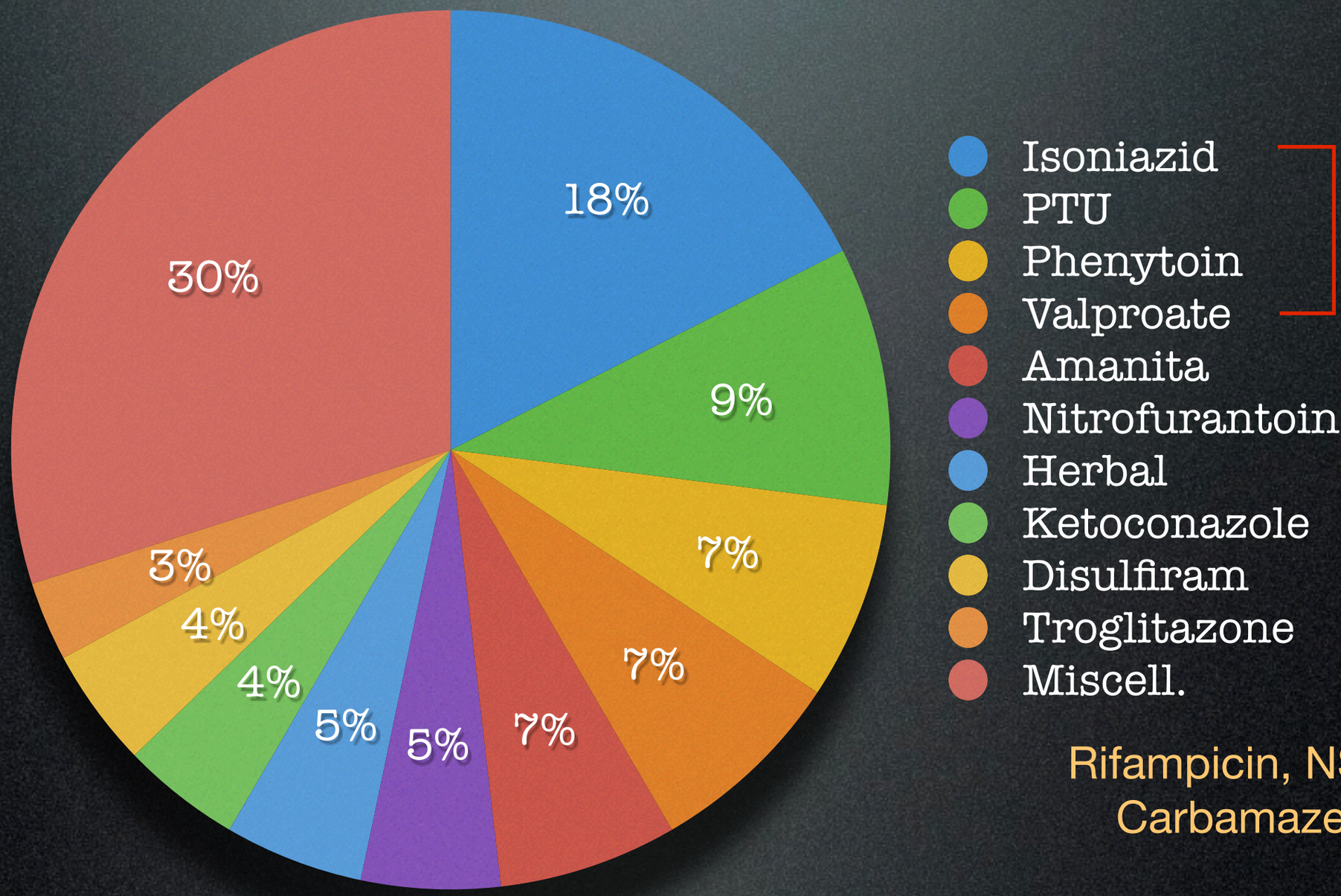
Aetiology



Transplantation for substance and drug reactions/toxicity (non-paracetamol)



Rifampicin, NSAIDS, Carbamazepine

Russo et al, Liver Tranpl 2004

Paracetamol

Paracetamol

Therapeutic doses

Oxidation by cytochrome P450 is a **minor** route (5%)

Paracetamol → Paracetamol conjugates

Conjugation is the **major** route of metabolism

Paracetamol → **NAPQI**

Reacts with **SH-** group in **glutathione**

NAPQI → **NAPQI** conjugates

Overdose

Oxidation by cytochrome P450 becomes a **major** route

Paracetamol → Paracetamol conjugates

Conjugation is saturated

Paracetamol → **NAPQI**

Excess **NAPQI** covalently binds to **SH** in cellular proteins causing **injury**

NAPQI → **NAPQI** conjugates

Glutathione supply exhausted

NAPQI → SH

Paracetamol

Beware co-pharmacy

Paracetamol

- Hyperacute
- Rapidly progressive MOF
- Compared to other causes:
  - greater **severity** of illness injury
  - those **NOT** meeting transplant criteria **do better**

Paracetamol

Effects of legislation restricting pack sizes of paracetamol in UK

9/16/1998 : British law mandated that paracetamol be sold in blister packs, max 16 per pack (8 gm) at stores and 32 (16 gm) at pharmacies

Deaths from paracetamol poisoning **fell 21%** in first year

Non fatal paracetamol self-poisoning fell 11% in first year

Hawton, BMJ 2001

Paracetamol

THE LANCET

Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults

"…paracetamol ... the **most important cause** of acute liver failure……the dose taken can be as low as **7 g a day**."

Paracetamol: are therapeutic doses entirely safe?

A total of 4 g of paracetamol repeated daily may be hepatotoxic in malnourished adults with low body weight

"….beware people who are likely to be at **high risk** ….."

Lancet Vol 368 December23/30,2006 BMJ | 11 DECEMBER 2010 | VOLUME 341

Increased risk of injury from paracetamol :

Glutathione depletion

- Malnourished
- Alcoholism
- Eating disorder (ex. anorexia or bulimia)

Beware

- Low BMI
- Urinalysis + for ketones, low se. urea

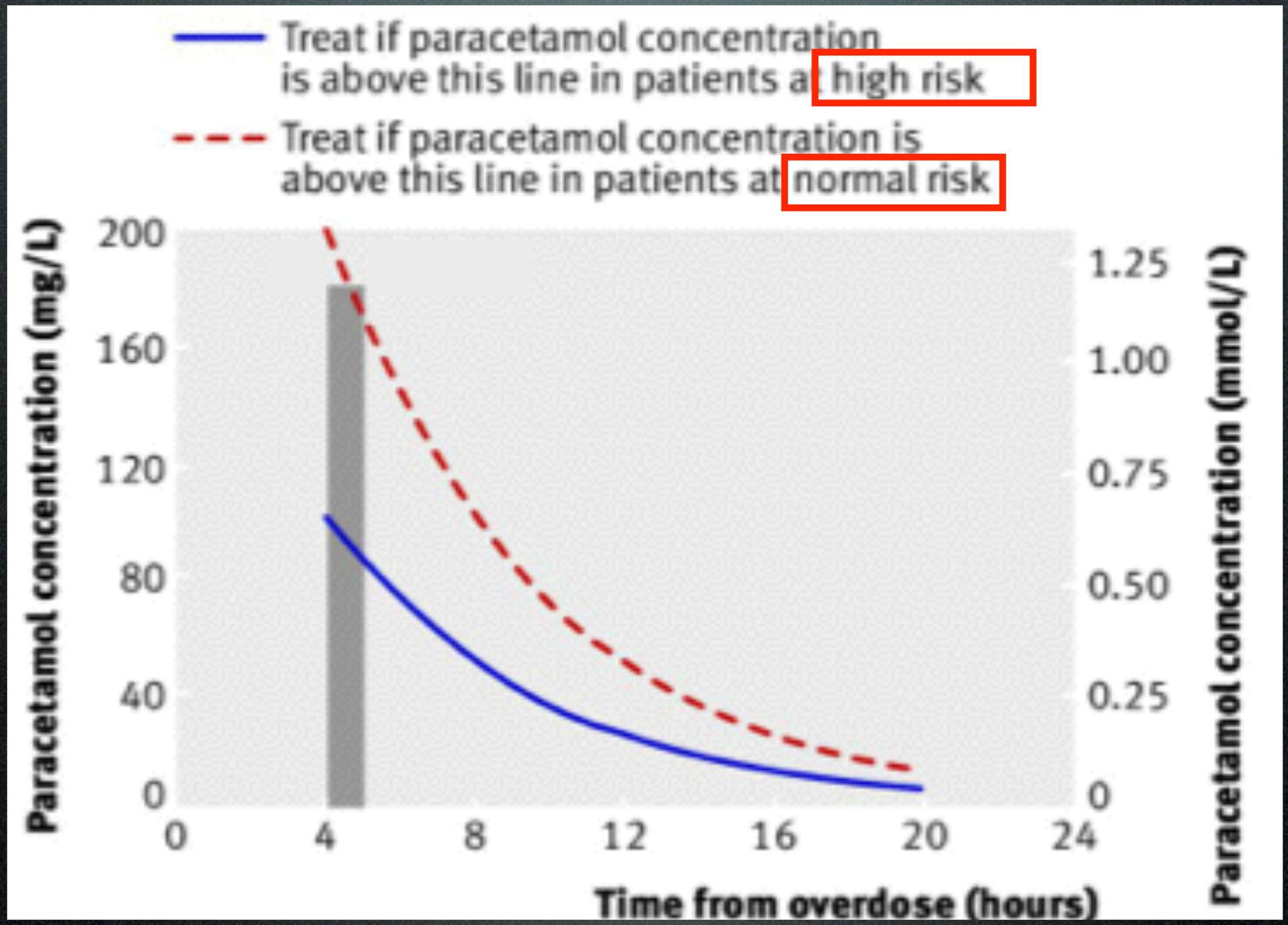
Hepatic enzyme induction

Chronic use of :

- **ethanol**, carbamazepine, phenytoin, rifampicin, rifabutin, phenobarbitol

Abnormal renal or hepatic function at presentation

Time line for treatment of paracetamol o/d

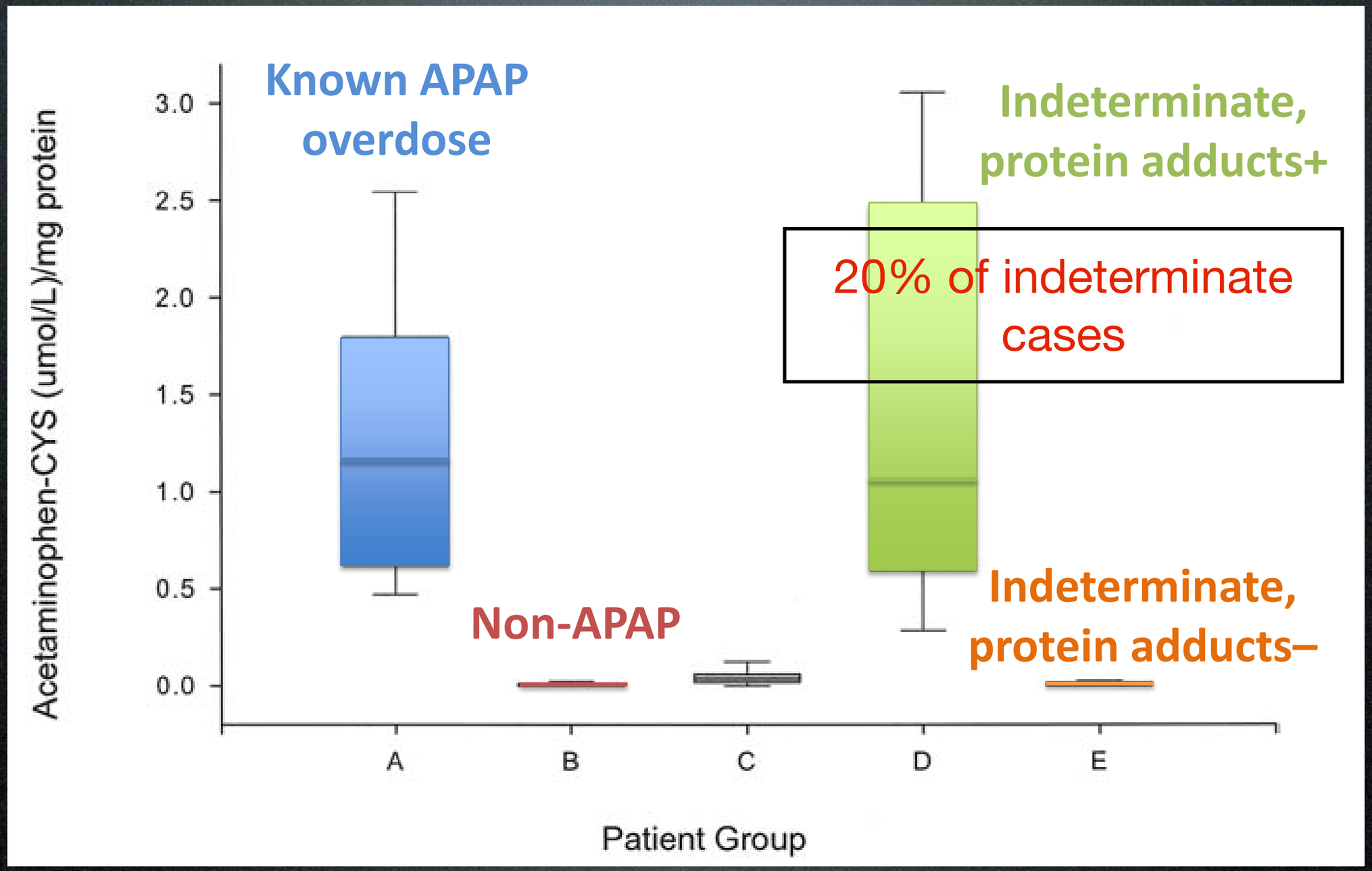


NAC Dosing schedule

Table 2| **Recommended doses of acetylcysteine as antidote to paracetamol poisoning in adults. characteristics for Parvolex17**

	Dose according to patient's weight		
Recommended sequential doses*	**70 kg**	**110 kg**	**140 kg†**
150 mg/kg in 200 mL over first 0.25 hours	10.5 g	16.5 g	16.5 g
50 mg/kg over next 4 hours in 500 mL	3.5 g	5.5 g	5.5 g
100 mg/kg over next 16 hours in 1000 mL	7 g	11 g	11 g
Total dose (300 mg/kg in 20 hours)	21 g	33 g	33 g

Paracetamol - protein adducts in **indeterminate** cases of ALF



Davern et al Gastroenterology 2006; 130:687-694

Aetiology - <u>other causes</u>

Non paracetamol drugs

- **Isoniazid***, **valproate**, **phenytoin,** rifampicin, nitrofurantoin, NSAIDS, carbamazepine,, tricyclics, statins, etc

Viral

- CMV, HSV, Ebstein-Barr

Metabolic

- Wilson's, Reye's

Vascular

- Budd-Chiari, ischaemic hepatitis

Pregnancy

- acute fatty liver, HELLP

Neoplastic

- Lymphoma, metastases

Toxic

- Amanita phalloides mushroom

Acute Liver Failure

Definition

Incidence

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Causes

Clinical Management

Clinical management

multiple critical steps

Complex

not standardized

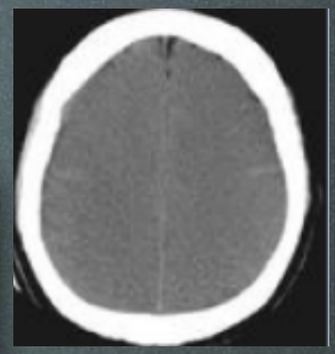
few controlled studies

heterogeneous

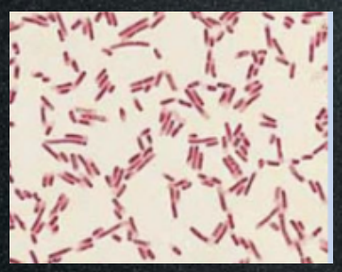
Complications

Complications

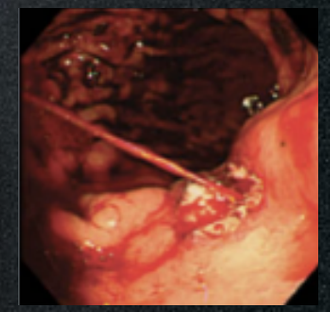
Intracranial hypertension



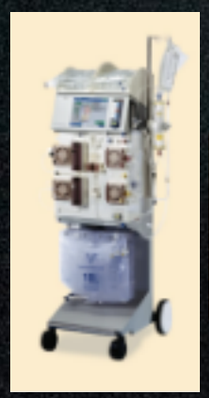
Infection



Bleeding



Renal failure



Shock

Hypoglycaemia

Multi-organ failure

Clinical management

Think ALF !!

- ALF is **rare** so often takes us by **surprise**
- INR is **key** : >/= 1.5
  - especially if **mental status changes**
- Unpredictable + rapid progressive ➔ multiorgan failure

urgent decision for those who are unlikely to survive without liver transplant…**time is of the essence**

Aetiology must be determined

disease-specific therapy may be available.

Clinical Management

Diagnose ALF :
INR, altered mentation, recent onset liver illness

Evaluate **aetiology** :
history/lab

Paracetamol?
history, levels, high AST

+ → NAC

\- ↓

mushroom toxicity
history, muscurinic symptoms

+ → Silibinin, Pen G

\- ↓

Wilsons disease

+ → CVVH, liver transplant

\- ↓

Drug induced, viral, Budd Chiari, unknown
(history, serology, U/S)

\+ ↓

Consider NAC for non-paracet., lamivudine for Hep B, good coma care

Determine **severity**:
labs, aetiology, coma grade

Coma I - II → no sedation

Coma III - IV → intubate, ? transplant

General care:
PPI, ? mannitol,monitor infection, INR, ? transplant

Checklist ?

DO NOT PLACE IN THE MEDICAL RECORD

ADMISSION AND DIAGNOSIS ALF CHECKLIST

THE FOLLOWING ARE TO BE DONE ON ADMISSION AND DAILY IN ALL CASES OF ALF:

- ❑ **Neuro checks every 1-2 hours**
- ❑ **Head of the bed at 30°**
- ❑ **Head in neutral position**
- ❑ **Avoid stimulation (tracheal suctioning, chest physiotherapy, sternal rubbing)**
- ❑ **N-acetylcysteine (NAC) IV until INR <1.5 or resolution of encephalopathy***
- ❑ **CXR and surveillance cultures (blood, urine, sputum) on admission and every 24-48 hrs**
- ❑ **Monitor blood glucose every 1-2 hours**
- ❑ **Avoid nephrotoxic drugs (aminoglycosides, NSAIDs, neomycin, etc) and IV contrast**
- ❑ **DVT prophylaxis (sequential compression device) despite coagulopathy; avoid heparin**
- ❑ **PPI for stress ulcer prophylaxis**
- ❑ **Communication: 1) intensivist and/or transplant hepatologist, 2) nurse, 3) patient's family**

POSSIBLE ETIOLOGY	DIAGNOSTIC ITEMS TO DO IN *ALL* CASES OF ALF	DIAGNOSTIC ITEMS TO *CONSIDER*	SPECIFIC THERAPIES
Drug/toxin	❑ **Obtain 6-month medication/toxin/ingestion history including OTC supplements, herbals, wild mushrooms, weight loss drugs** ❑ **Urine and serum toxicology screens** ❑ **Acetaminophen level**		Acetaminophen toxicity: NAC Mushroom poisoning: Charcoal, NAC, penicillin G and/or silibinin**
Viral	❑ **Anti-HAV IgM** ❑ **HBsAg, anti-HBc IgM, HBV DNA** ❑ **Anti-HCV, HCV RNA**	Anti-HEV HSV DNA EBV DNA CMV DNA Anti-HDV/HDV RNA	HBV: Entecavir HSV: Acyclovir
Autoimmune	❑ **Antinuclear antibody** ❑ **Anti-smooth muscle antibody/anti-actin antibody** ❑ **Immunoglobulin G**	Anti-liver/kidney microsomal antibody Liver biopsy	Corticosteroids
Vascular Budd Chiari Ischemia	❑ **Abdominal ultrasound with Doppler**	CT/MRI Assess for hypercoagulable state including search for malignancy Interventional radiology consultation Echocardiography/ECG	Budd Chiari: Anticoagulation, TIPS
Wilson	❑ **Check for hemolytic anemia (high indirect bilirubin), low alkaline phosphatase, renal failure, acidosis**	Ceruloplasmin 24-hour urine for copper Serum copper Ophthalmology consultation to look for Kayser-Fleischer rings	Consider early CRRT
AFLP / HELLP		β-HCG Obstetrics consultation	Early delivery
Malignancy		CT/MRI Liver biopsy	
Indeterminate		Liver biopsy	

OTC, over-the-counter; NAC, N-acetylcysteine; CRRT, continuous renal replacement therapy

*For all patients with ALF and encephalopathy grade I/II regardless of etiology, and for all cases of suspected acetaminophen toxicity

**Not FDA approved

Instructional video: http://youtu.be/H6yyTA-yNqc

Standard ITU management

Standard ITU management

- **Circulation**

  Aggressive fluid resuscitation (avoid hypo-osmotic / lactate containg fluids)
  +/- Noradr or terlipressin +/- steroids

- **Renal / acid-base /metabolic**

  Renal failure in 50-80%
  CVVHF - high dose (90ml/kg/hr)
  Beware hypos (glycaemia, Na, PO4, Ca,)
  IAH

- **Respiratory**

  Intubate and ventilate if Grade III - IV encephalopathy
  ARDS in ~30%

Standard ITU management

- **Coagulation**

  critical in **triage** for transplant

  FFP not indicated unless clinical bleeding as spontaneous haemorrhage rare and **INR** is **valuable prognostic marker**

  relative **balance** in coagulation as clotting and fibrinolysis equally defective

- **Sepsis**

  bacteraemia (20-80%) and fungal (32%) infection common (‘immune paralysis”)

  prophylactic antimicrobials/ antifungals (ex. Tazocin / fluconazole)

  SIRS correlates strongly with encephalopathy

- **GI / Nutrition**

  feed early (enteral if possible)

  no protein restriction

  PPI

Standard ITU management

- **Cerebral protection**
  - Treat like Traumatic Brain Injury
  - **Beware cerebral oedema** (rare in chronic liver disease)

III 25-35%

IV 65-80%

- **greatest risk with high <u>arterial</u>** ammonia

  100-200 µmol/l (30% cerebral oedema)

  >200 µmol/l (50% cerebral oedema)

Encephalopathy and ammonia

↑ **arterial ammonia** concentration → ↑ **cerebral ammonia**
➜ astrocytic glutamine accumulation

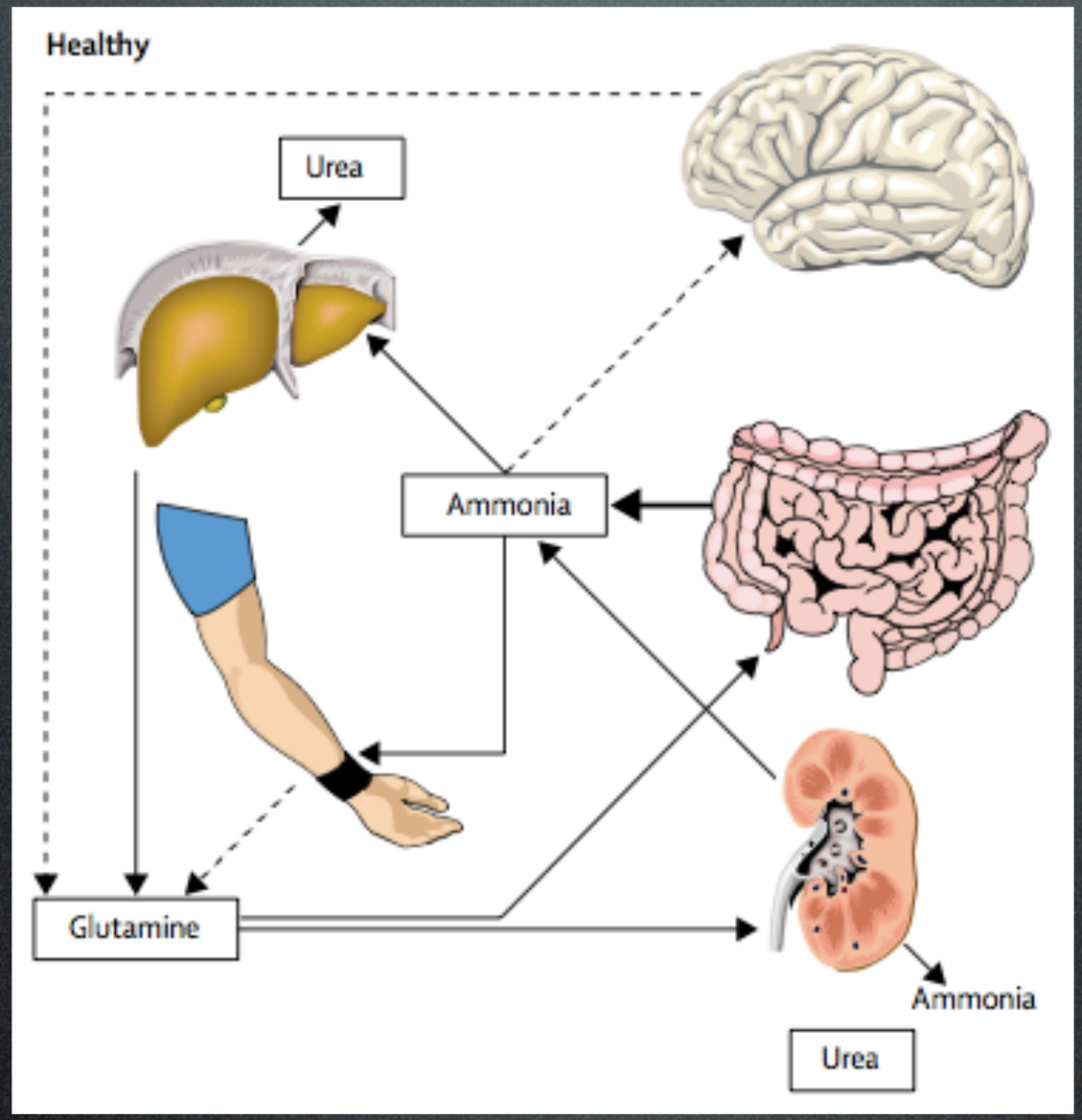
The **speed** of onset **overwhelms** any adaptive process to control intracellular osmolarity.

Arterial ammonia level **above 200mmol/l** was associated with **cerebral herniation**

Gut 2006 55: 98-104

Ammonia metabolism

Ammonia formed in **small intestine** from glutamine , healthy liver removes ammonia by detoxification into urea.



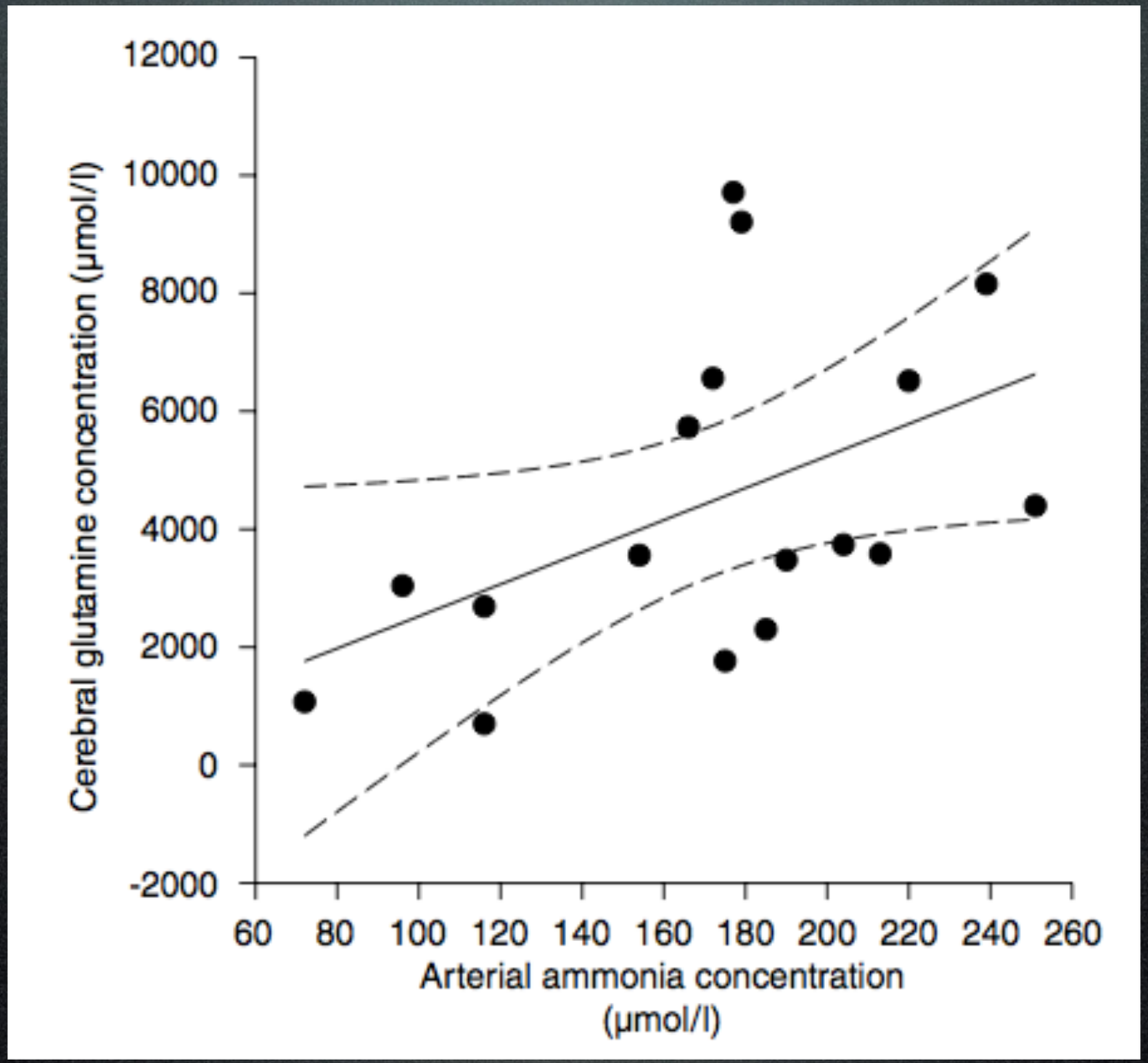
In liver disease, ➜ hyperammonaemia:

Muscle becomes important organ of ammonia **detoxification** into **glutamine**.

Glutamine acts as temporary **buffer** that can both **regenerate** ammonia (enterocytes) and **excrete** ammonia (kidney)

Lancet Vol 365 Jan 29, 2005 431-433

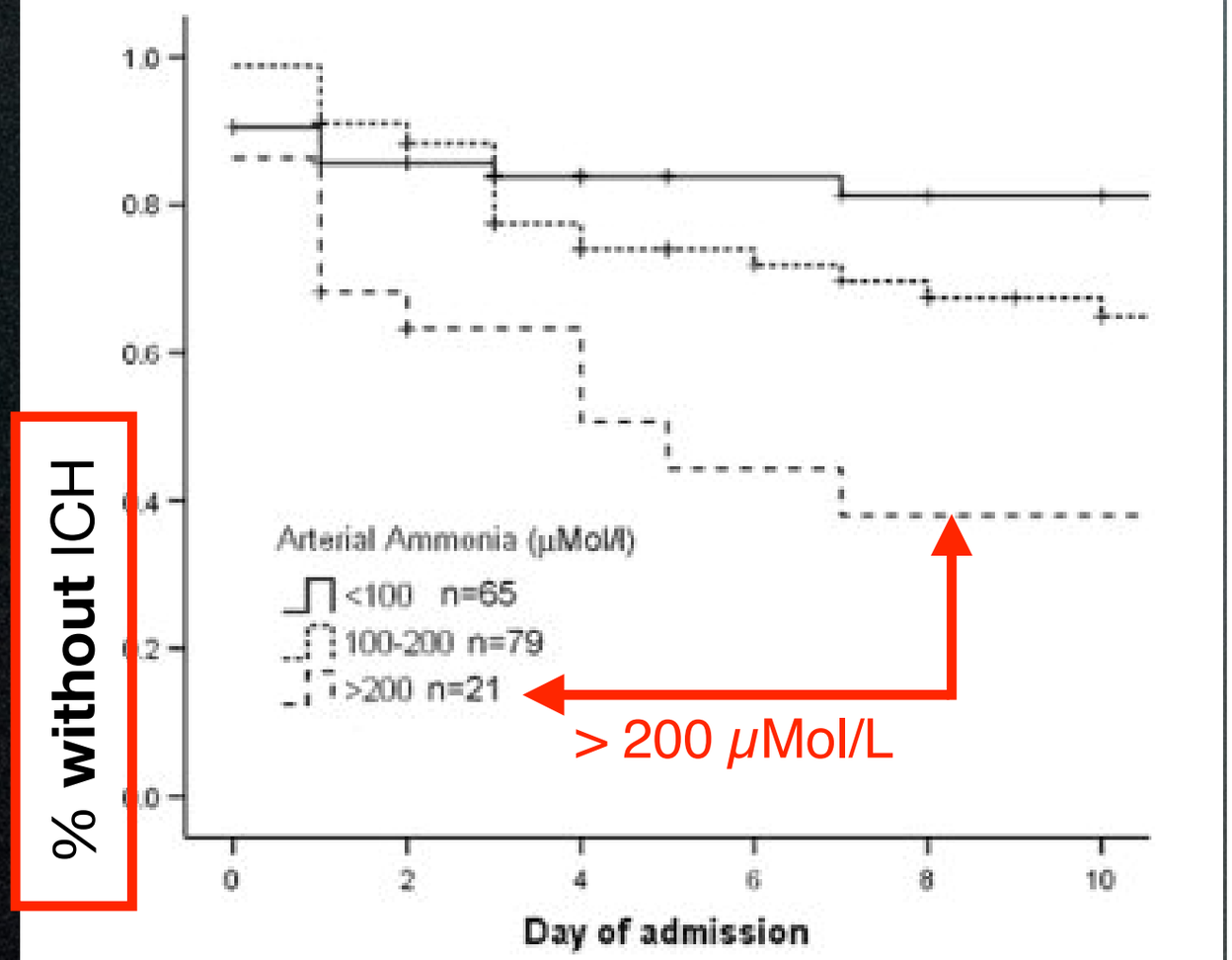
Arterial ammonia correlates with cerebral glutamine



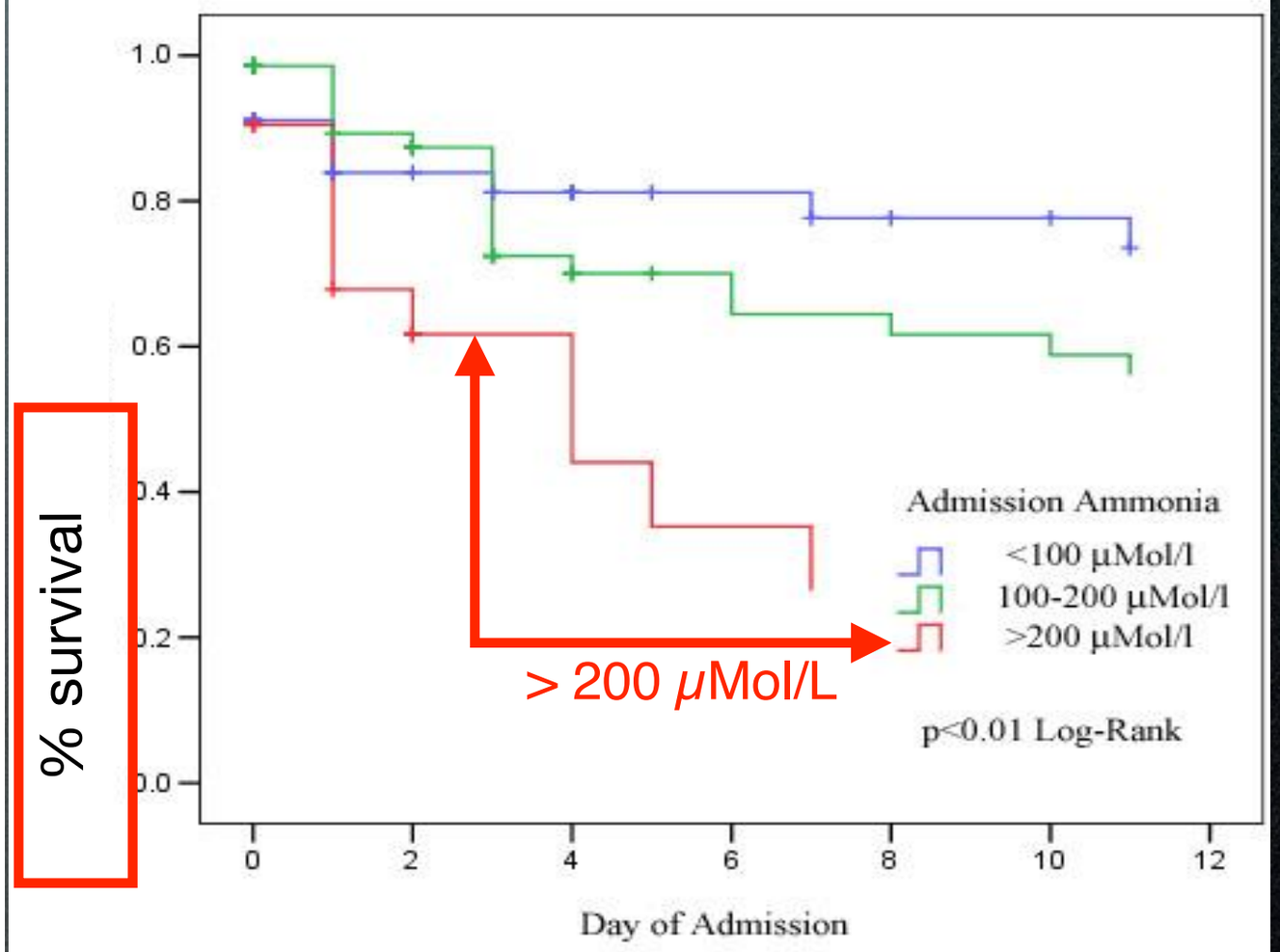
Journal of Cerebral Blood Flow & Metabolism (2006) 26, 21–27

Ammonia, ICH and survival

Intracranial hypertension

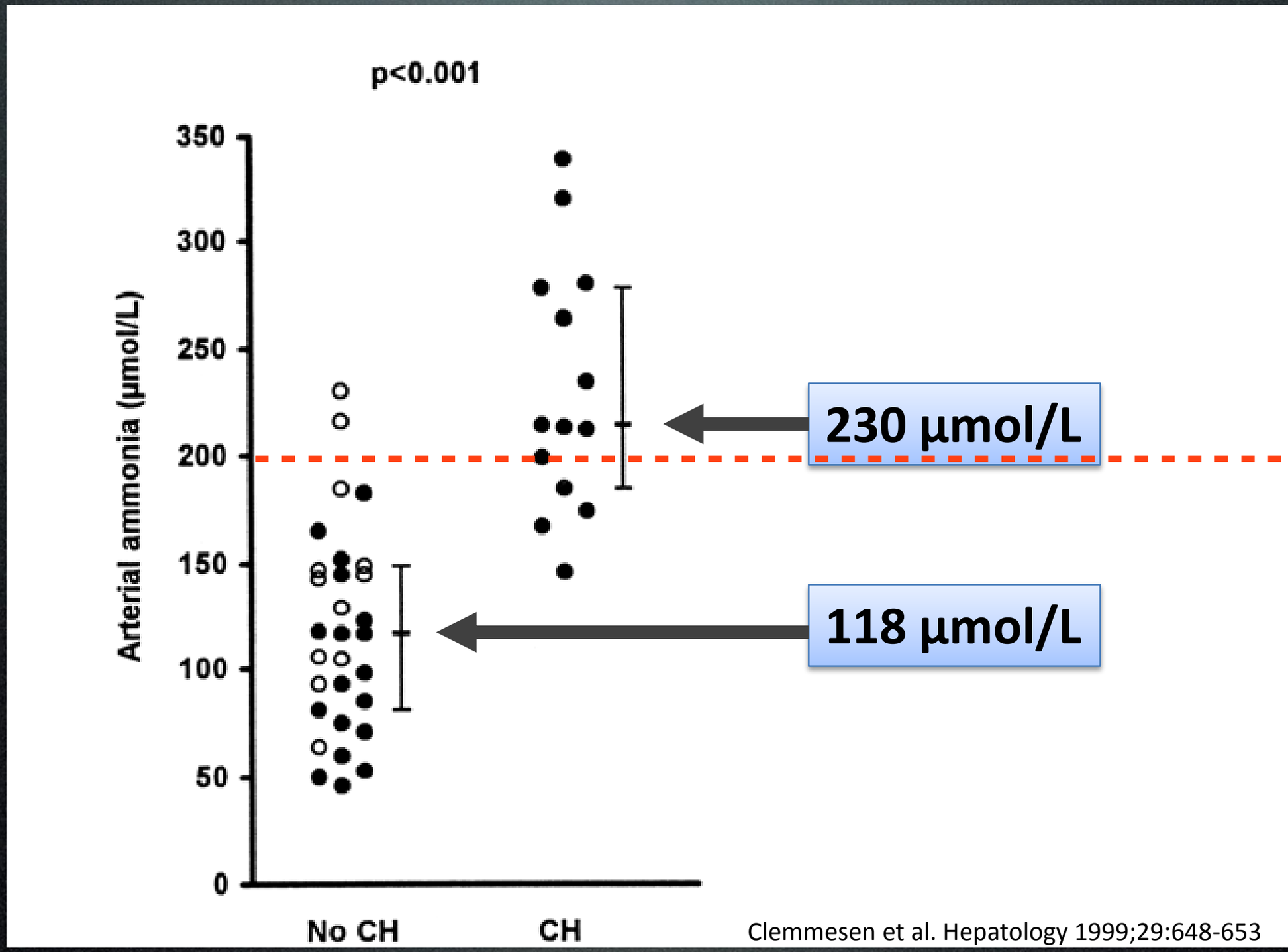


Cumulative survival



Bernal et al Hepatology 2007; 46: 1844-1852

Ammonia and cerebral herniation



Clemmesen et al. Hepatology 1999;29:648-653

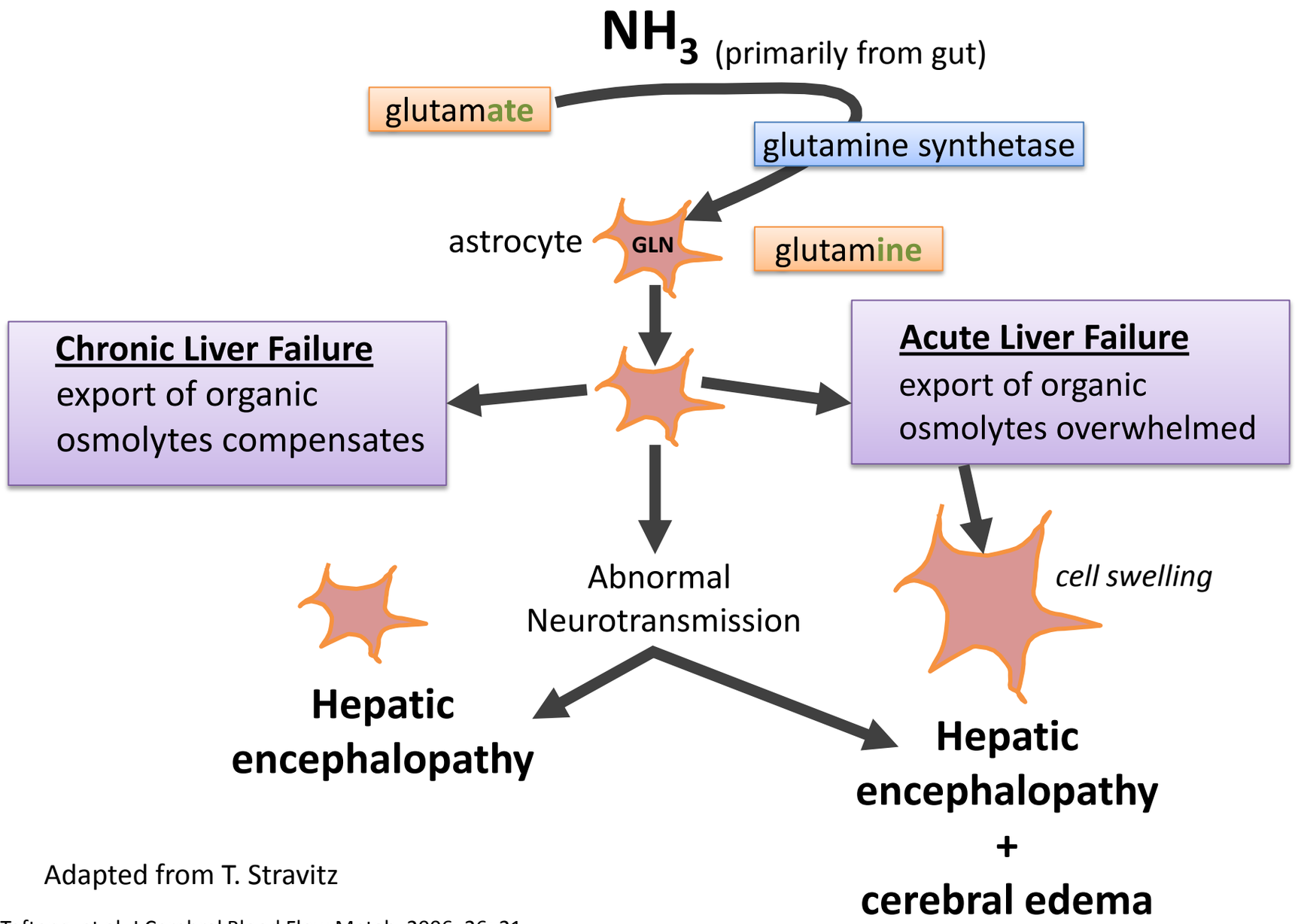
Clemmesen et al Hepatology 1999; 29:648-653

Standard ITU management

Strategies to reduce ammonia

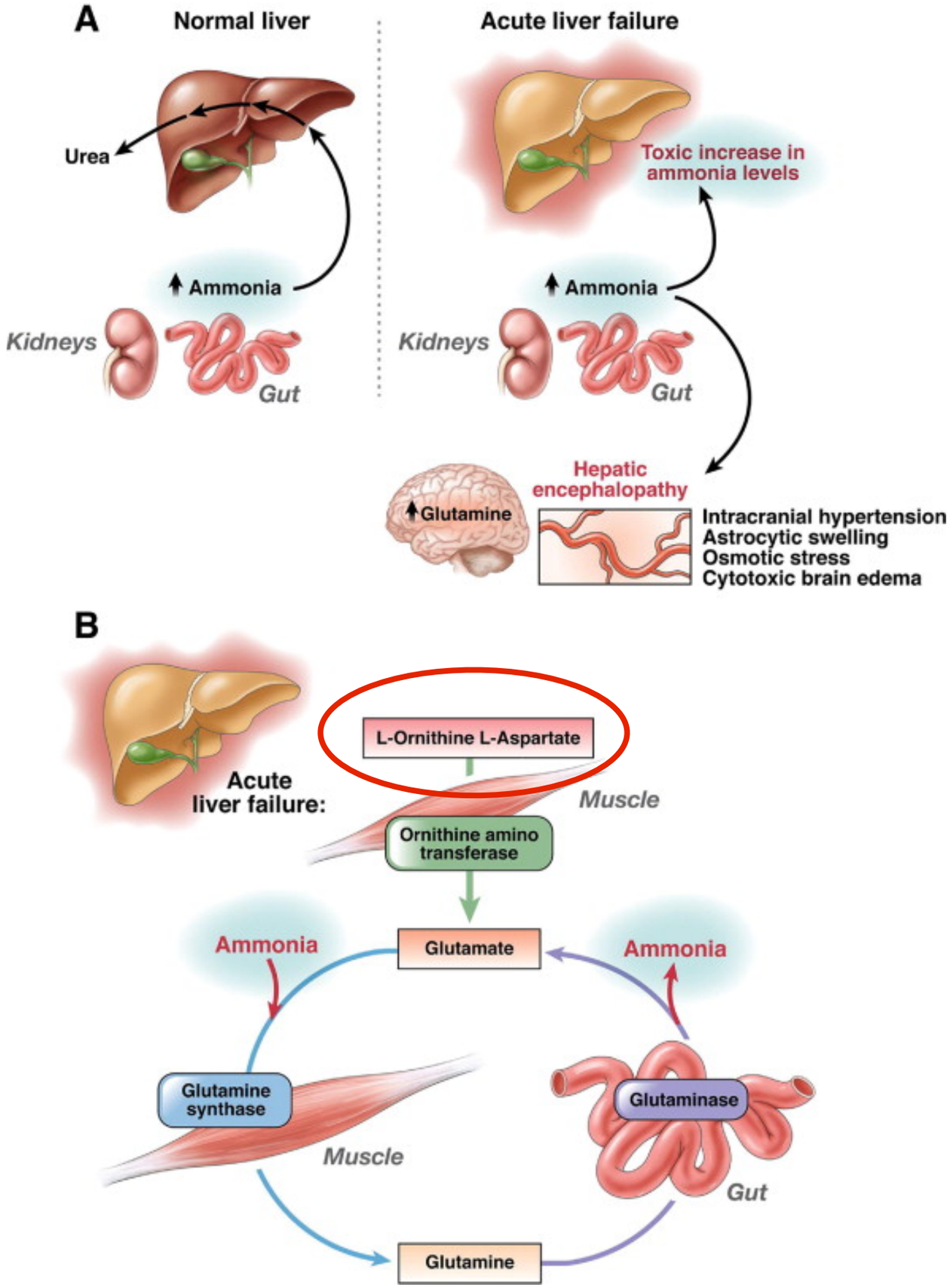
- LOLA
- LOPA
- CVVH (high dose)
- Hypothermia
- Sedation

Ammonia metabolism in ALF



Adapted from T. Stravitz

Tofteng, et al. J Cerebral Blood Flow Metab. 2006; 26: 21.



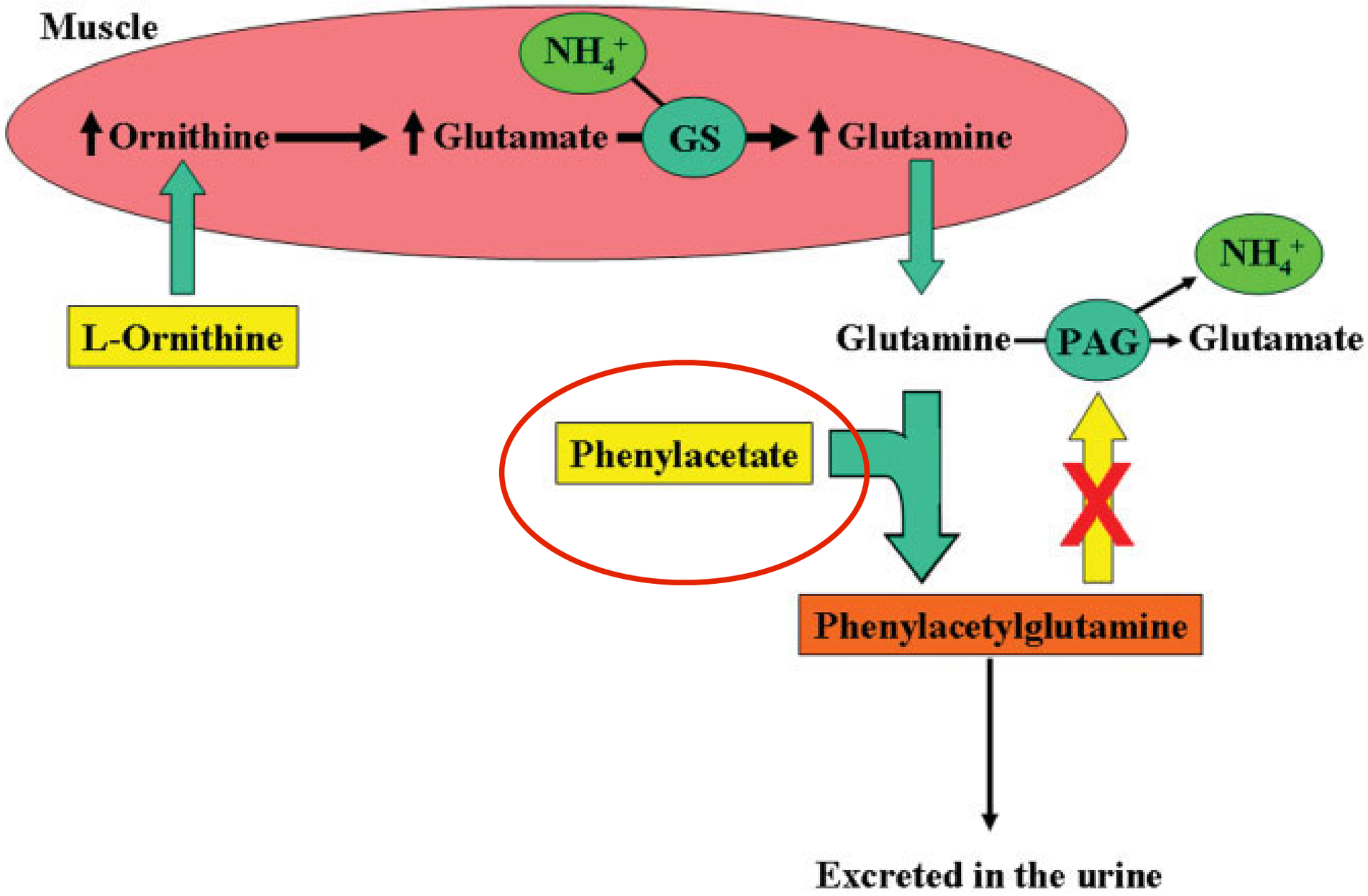
Severe liver dysfunction--> impaired urea synthesis.

Ammonia + glutamate --> glutamine (major **alternative** ammonia detoxification pathway)

If it occurs in **astrocytes** --> brain swelling.

LOLA acts to stimulate glutamine synthesis in **muscle** --> ammonia detoxification.
But rebound seen as glutamine metabolised in gut to ammonia.....

“LOPA” - L-Ornithine Phenylacetate



Giving **LOPA** with **LOLA** may **stop ammonia rebound** by stopping from glutamine being metabolized in the gut to ammonia. Phenylacetate lowers ammonia by binding glutamine to form phenylacetylglutamine instead of ammonia.

HEPATOLOGY, Vol. 50, No. 1, 2009

Standard ITU management

Specific therapy

Specific therapy

Treatable	
paracetamol, ? non paracet.	NAC
amanita phalloides	Penicillin G, silymarin
pregnancy related (HELLP, PET)	delivery
herpes	acyclovir
autoimmune	steroids
Budd Chiari	heparin/TIPS

Evidence base is poor as it is a **rare** condition

Transplant **only hope**

Wilson's disease

Transplant **contra-indicated**

infiltrating cancer

NAC in non-paracetamol ALF

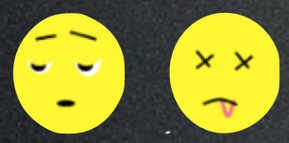
Antioxidant properties

Improves oxygen delivery

Multi-center, placebo controlled study

Transplant free survival at 3 weeks

- All patients: 40% (NAC) v 27% (placebo) *
- Grade **I - II** HE: 52% (NAC) v 30% (placebo) ***
- Grade III - IV: 9% (NAC) v 22% (placebo) **NS**



Lee WM, et al Hepatology 46:268A (2007)

Liver transplant

To transplant or not to transplant... that is the question !

Transplant

>80% 1 yr survival

>50% 20 yr survival

Lifelong immunosuppression

No Transplant

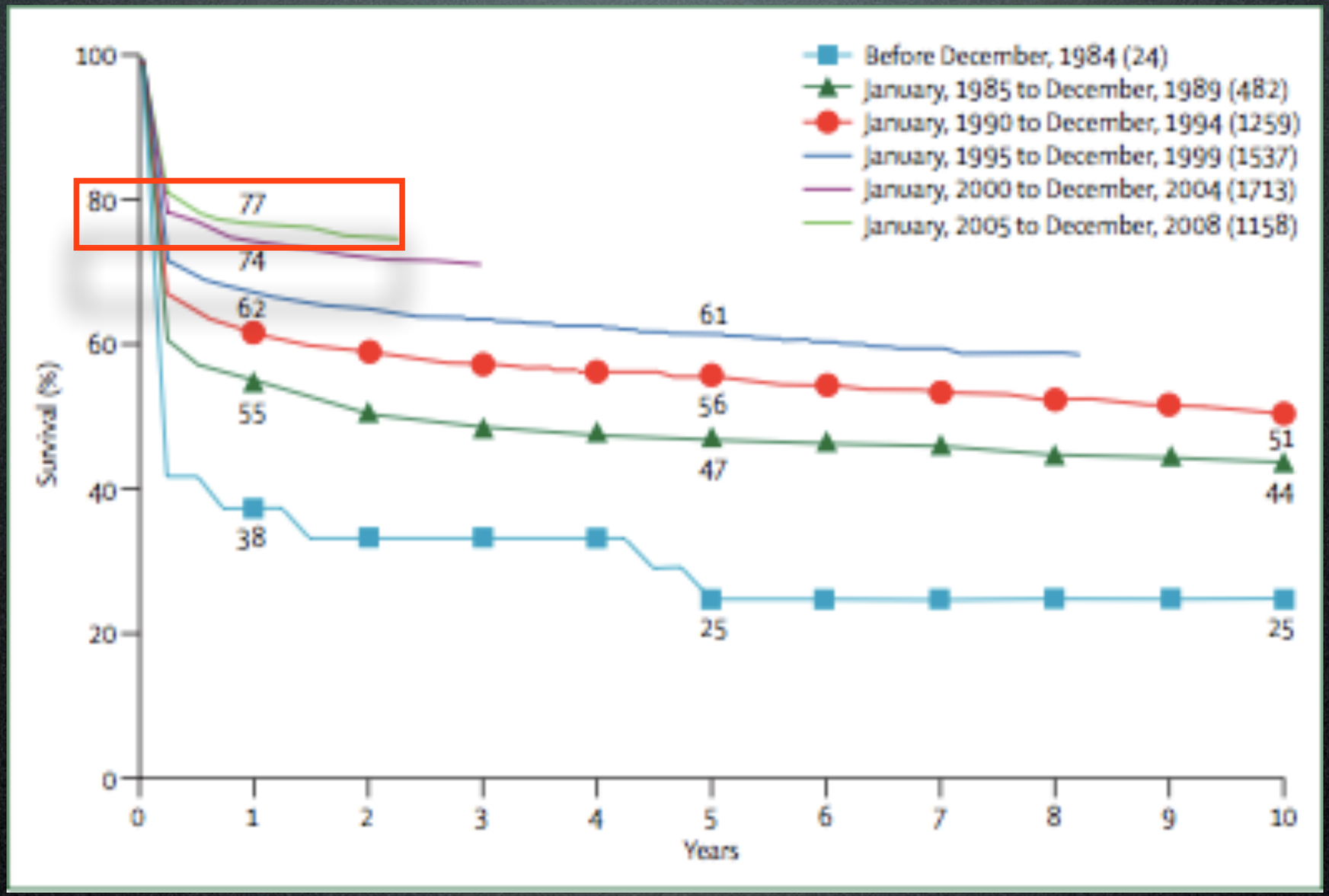
40%-50% spontaneous survival

Varies by aetiology

Most survivors recover completely

Liver transplant

2013 - Emergency transplant
1 yr survival >80%



Lancet 2010; 376: 190–201

Liver transplant

1/3rd with severe ALF **survive without** transplantation
(depending on cause)

Patients meeting certain criteria based on :

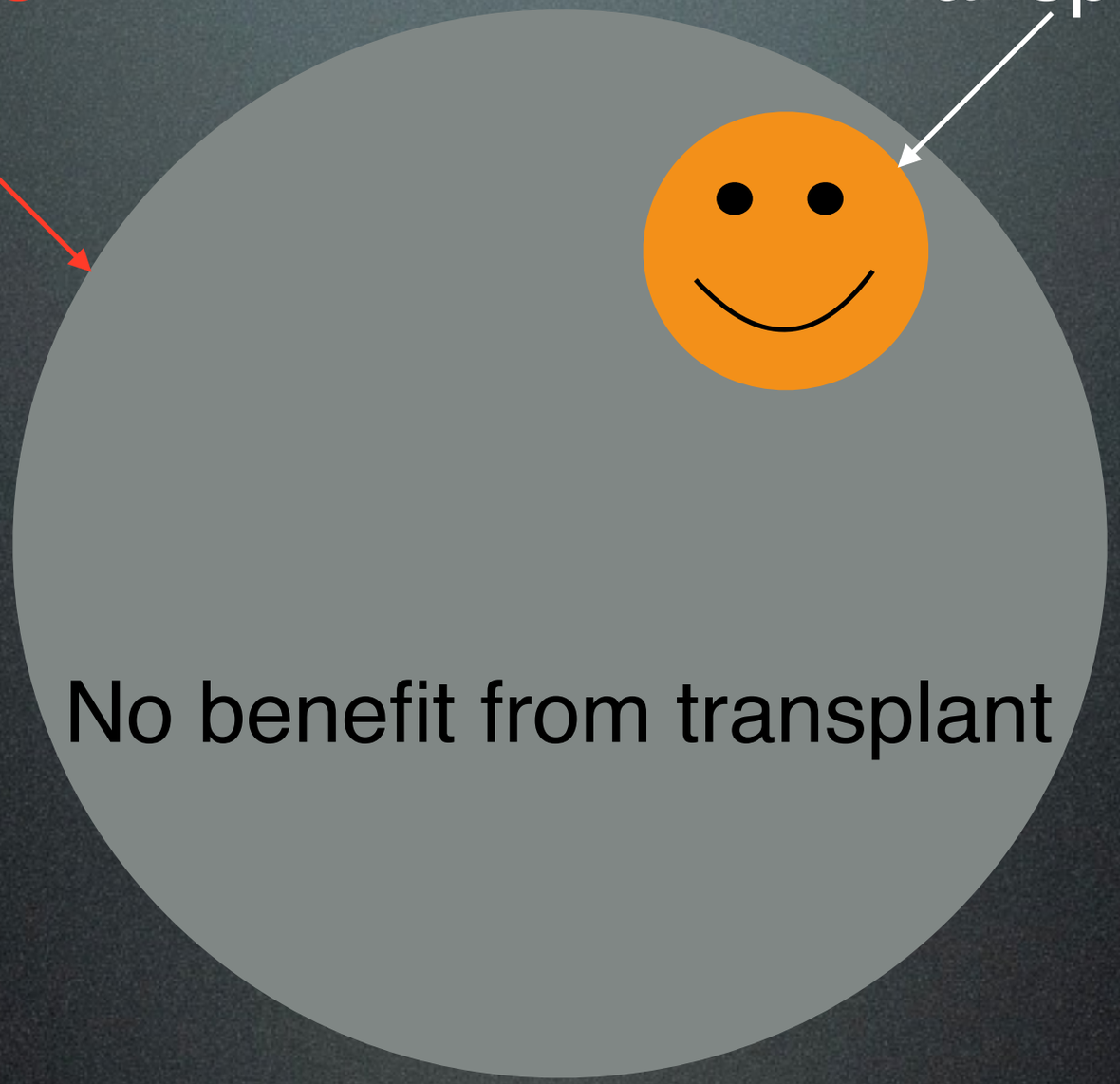
- Aetiology of liver failure
- Severity of encephalopathy
- Severity of coagulopathy
- Extra-hepatic organ dysfunction

if higher risk of death, survival advantage from LT

Liver transplant

All ALF patients

Transplant



No benefit from transplant

How to decide?

King's College criteria for selection of recipients of emergency liver transplants

Paracetamol

Arterial pH < 7.3 following fluids

or

All of the following:

encephalopathy (III or IV)

creatinine >300 µmol/L

INR > 6.5

PPV: 70-100%
NPV: 25-94%

All other causes

INR > 6.5 and encephalopathy

or

3 of the following:

INR > 3.5

age <10 or >40

bilirubin > 300 µmol/L

unfavorable cause

(drug induced injury, seronegative disease).

Inter-hospital transfer

<u>Deterioration</u> can occur <u>swiftly</u>

Ventilation

Intubate

Cardiovascular

Reserves of :

colloid/crystalloid

norepinephrine

Neurological

Monitor pupil size and response, if rising ICP, give **mannitol**

Metabolism

Beware of **<u>hypoglycaemia</u> !**

Acute on Chronic Liver Failure

Acute-on-chronic liver failure is:

background of **compensated cirrhosis :**

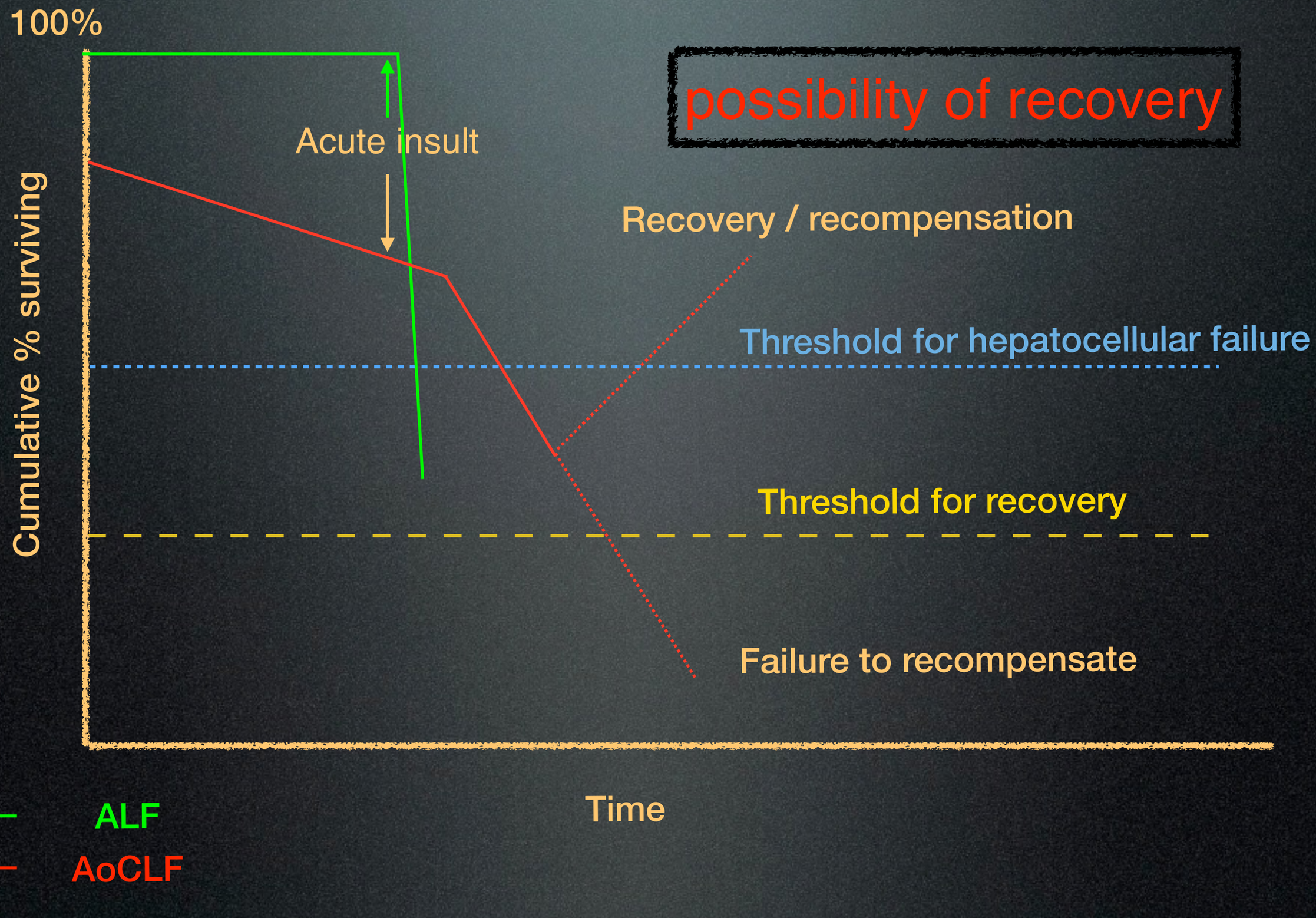
- **jaundice**
- **hyperdynamic circulation**
- **encephalopathy** (cerebral oedema rare)
- **hepatorenal** syndrome

progresses to **organ failure / SIRS**

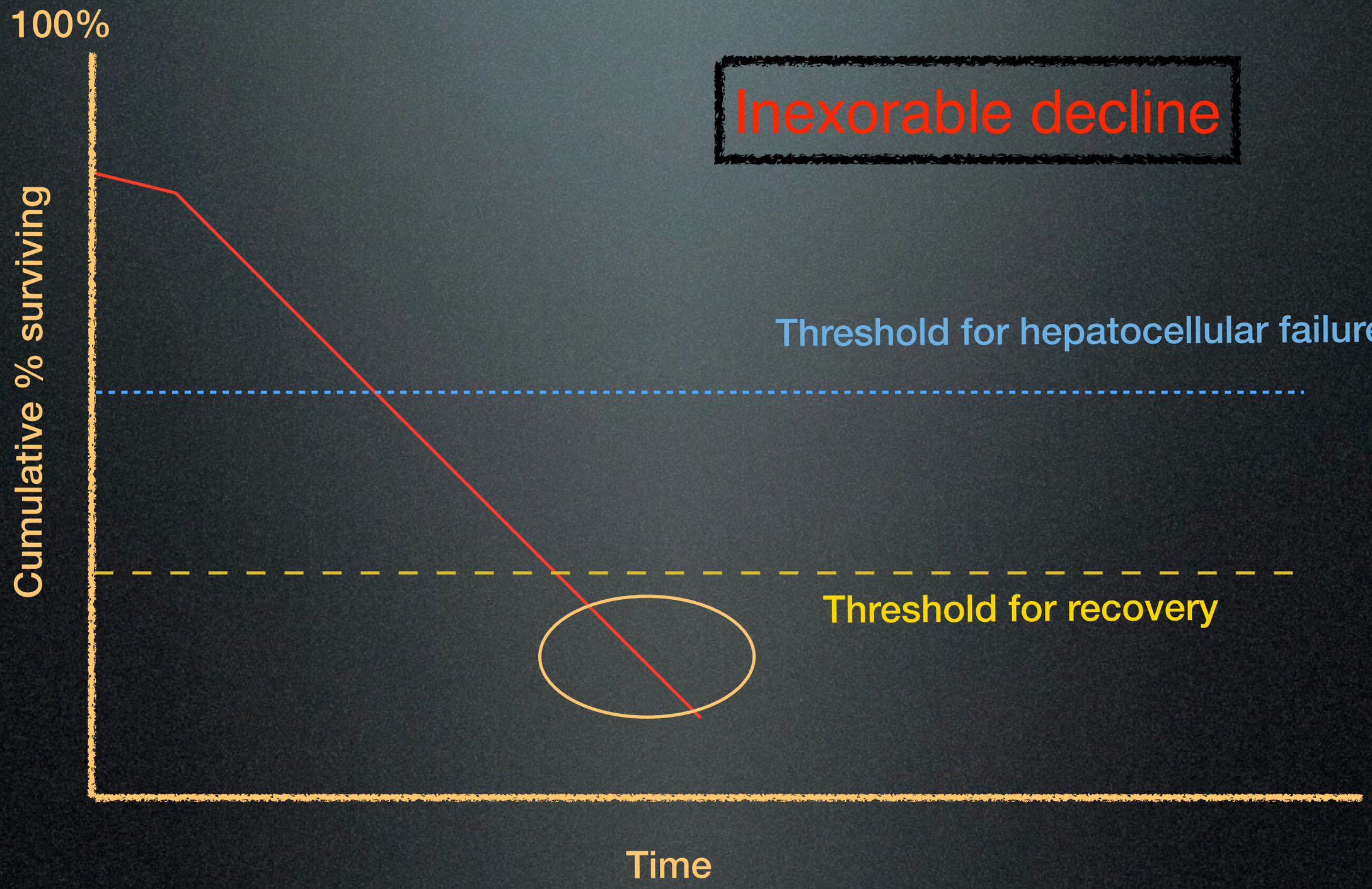
precipitated by **infection, bleed, alcohol**

→ **poor prognosis** (x15 RIP)

Acute on Chronic Liver Failure is acute decompensation of cirrhosis



Chronic Liver Failure



Typical cases of ALF vs AoCLF

	Acute Liver Failure	AoChLF
AST	**9450**	45
ALT	**7750**	40
ALP	250	120
Bil	41	**177**
Alb	35	**22**
INR	**5.5**	2.3
Complications	cerebral oedema, ARF, MOF, hypoglycaemia	ascites, portal hypertension, bleeding varices, SBP, encephalopathy, HRS, HPS, HCC (?)

How does cirrhosis predispose to ACLF

Cirrhosis → Altered gut permeability → Endotoxaemia → Priming → ACLF

Increased expression of TLR's 2 and 4 Liver, kidneys, brain

Insult

Shah et al. AASLD 2009

Pathogenesis of bacterial infections

Enteric bacteria

Non-enteric bacteria

Impaired hepatic RES function
Reduced systemic clearance
Portosystemic shunts

Bacterial translocation to lymphatics

Impaired mucocutaneous barriers.Instrumentation

Hemorrhage

Spontaneous bacteremia

Reduced antimicrobial activity of ascitic fluid

Spontaneous bacterial peritonitis

Pneumonia, secondary bacteremia, urinary infections

Acute Liver Failure - Recap

Think ALF !!!

if

- **Coagulopathy**
- **Encephalopathy**

- Rare
- Deadly
- Give NAC first, ask questions later
- Liver centre

Further reading

- Lancet Vol 376 July 17, 2010
- Gut 2006 55: 98-104
- Current Opinion in Critical Care 2008, 14:179– 188
- Best Practice & Research Clinical Gastroenterology 26 (2012) 3–16


THE LIVER
IS EVIL AND
MUST BE
PUNISHED
COLD
premiere
The liver need no longer be viewed as a black box

???

Download at :

http://www.jvsmedicscorner.com

Mallory/Everest2013