ALF in Children: Etiology and Management

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ALF in children

- Definitions
- Etiology of ALF
- Management

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Acute Liver Failure

Massive liver necrosis with encephalopathy developing within 8 weeks from the first signs of illness in a patient without underlying chronic liver disease

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Acute Liver Failure in Children

Multisystem disorder in which severe acute impairment of liver function with or without encephalopathy occurs in association with hepatocellular necrosis in a patient with no recognised underlying chronic liver disease

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Practical problem

- Patient Hepatitis A
- Jaundice 350 micromol
- AST >1000

Should be we call it Acute hepatitis or ALF

Hepatitis

ALF

The Paediatric Acute Liver Failure (PALF) study group

(i) Hepatic-based coagulopathy defined as a prothrombin time (PT) ≥ 15 seconds or international normalized ratio (INR) ≥ 1.5 not corrected by Vitamin K in the presence of clinical HE or a PT ≥20 seconds or INR ≥2.0 regardless of the presence or absence of clinical HE,

(ii) Biochemical evidence of acute liver injury,

(iii) No known evidence of chronic liver disease

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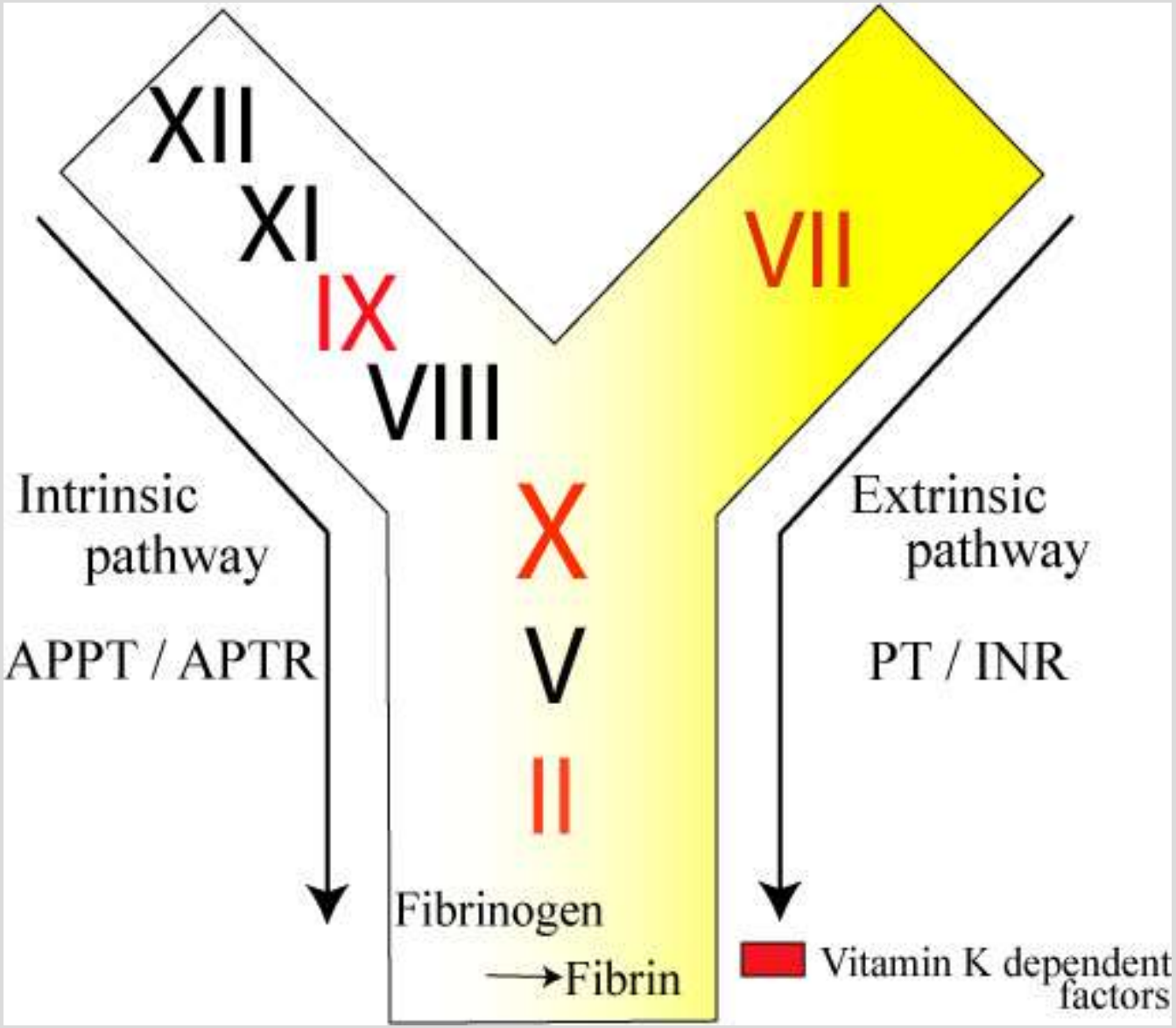
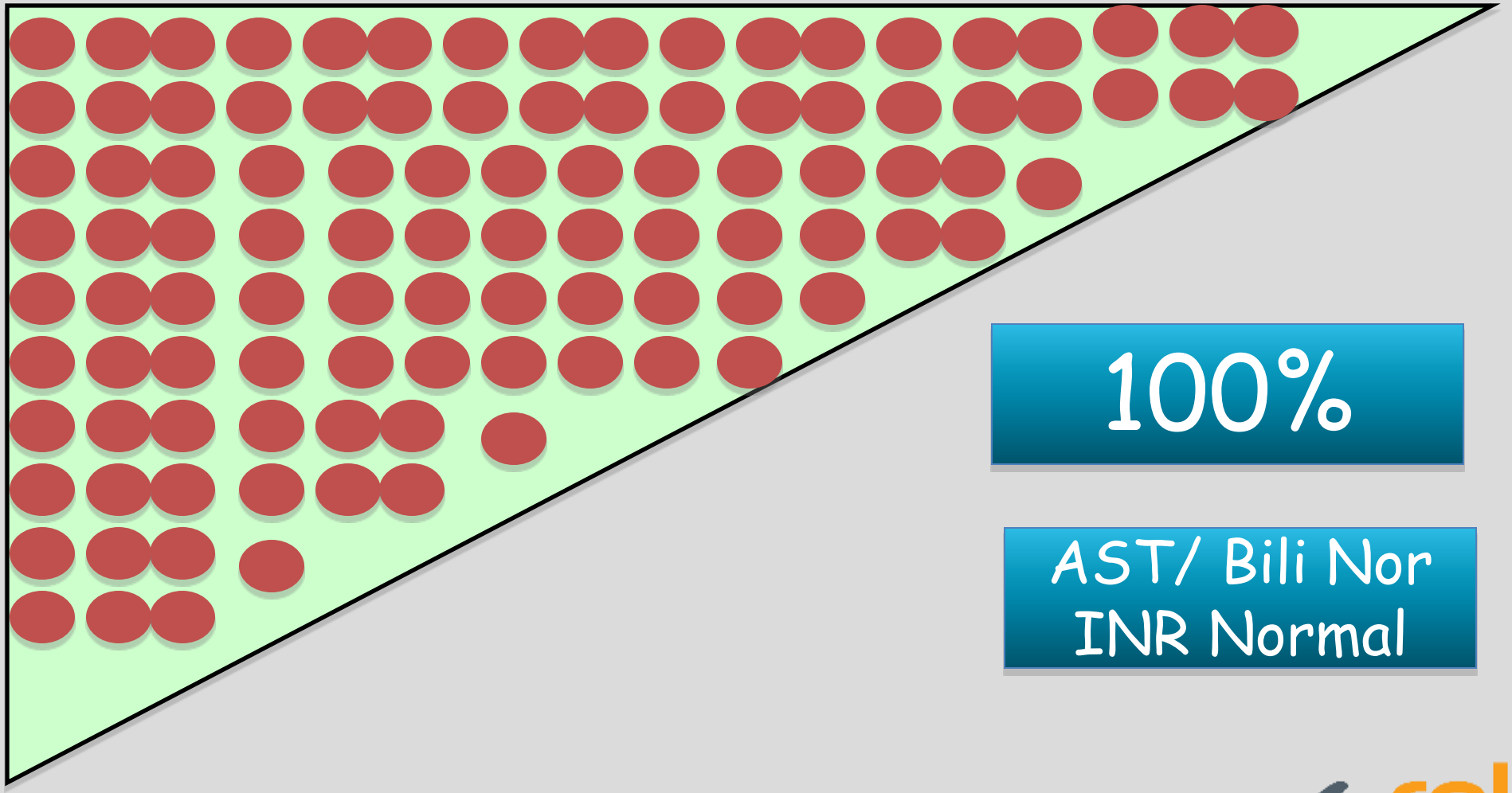

XII
XI
IX
VIII
VII
X
V
II
Intrinsic pathway
APPT / APTR
Extrinsic pathway
PT / INR
Fibrinogen
Fibrin
Vitamin K dependent factors

Liver failure model



100%

AST/ Bili Nor
INR Normal

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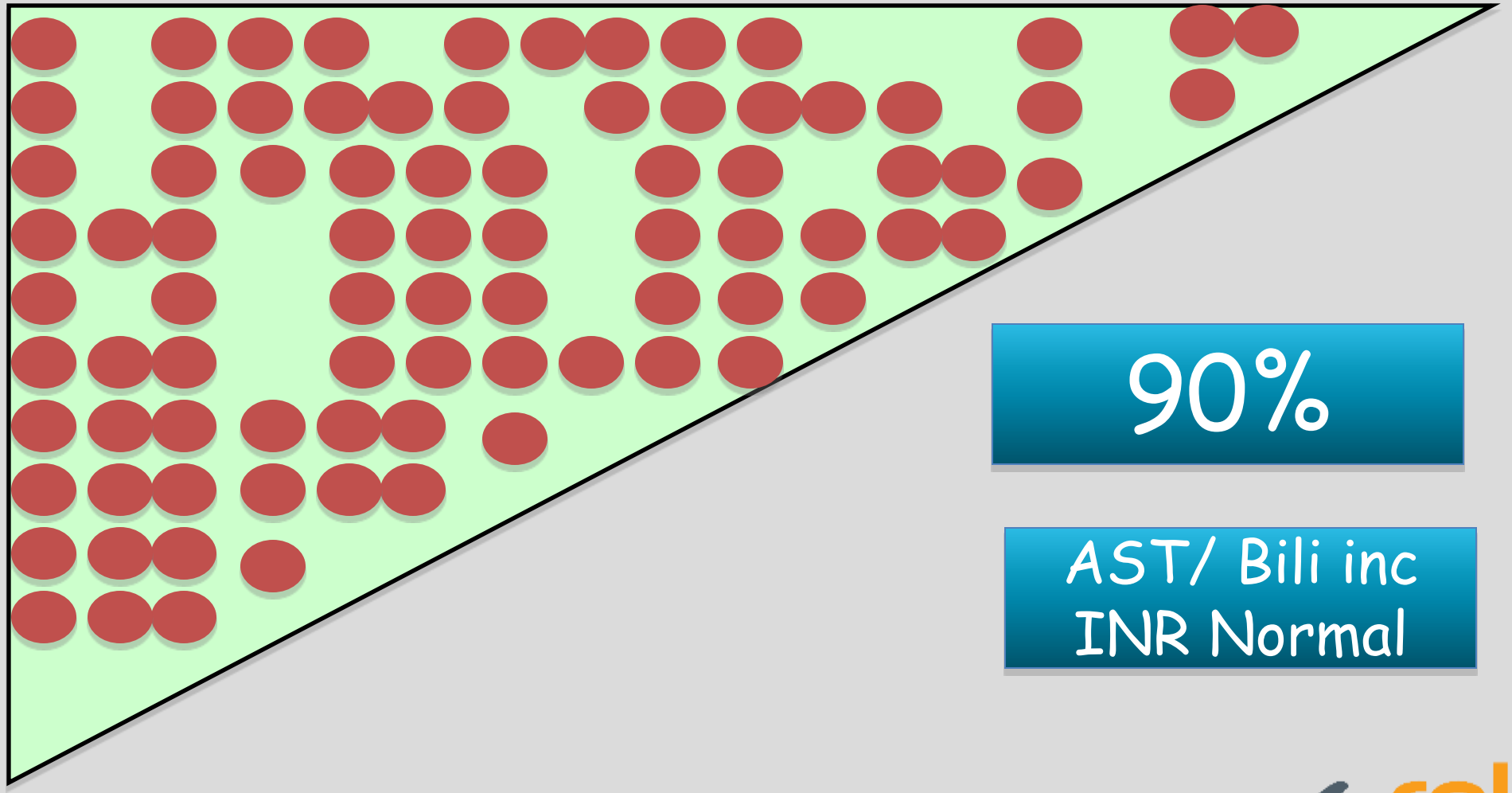
Liver failure model



90%

AST/ Bili inc
INR Normal

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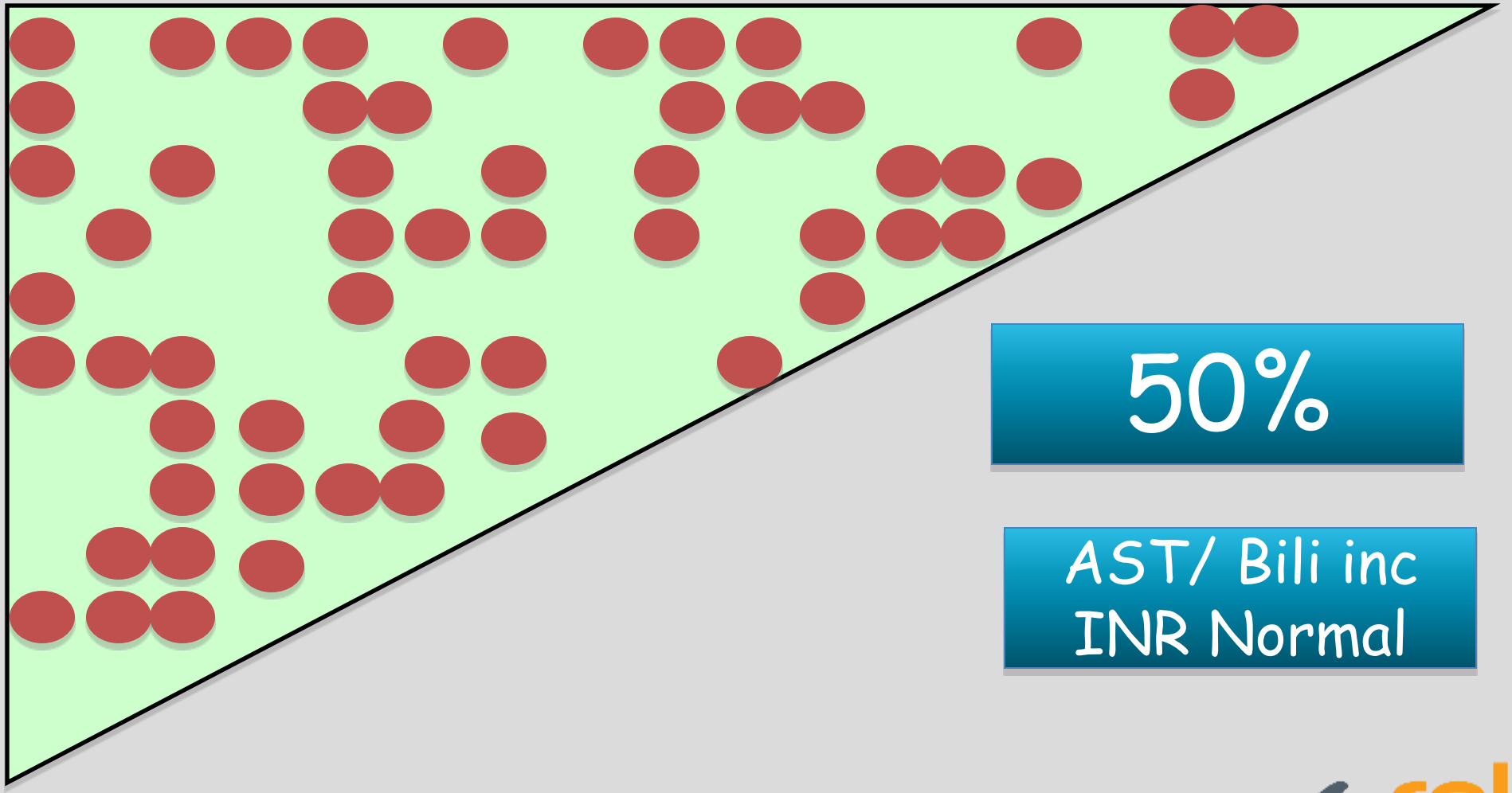
Liver failure model



50%

AST/ Bili inc
INR Normal

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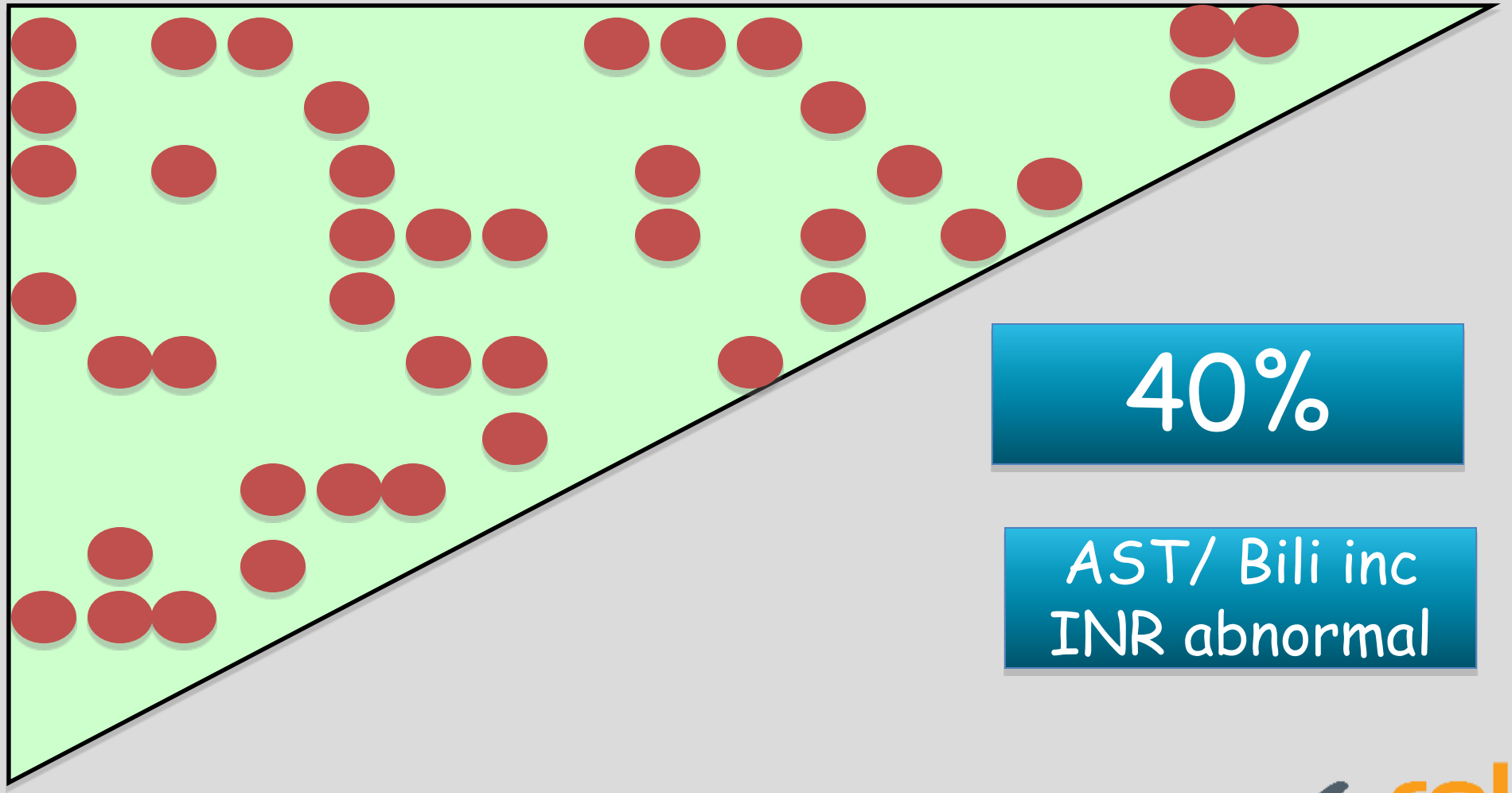
Liver failure model



40%

AST/ Bili inc
INR abnormal

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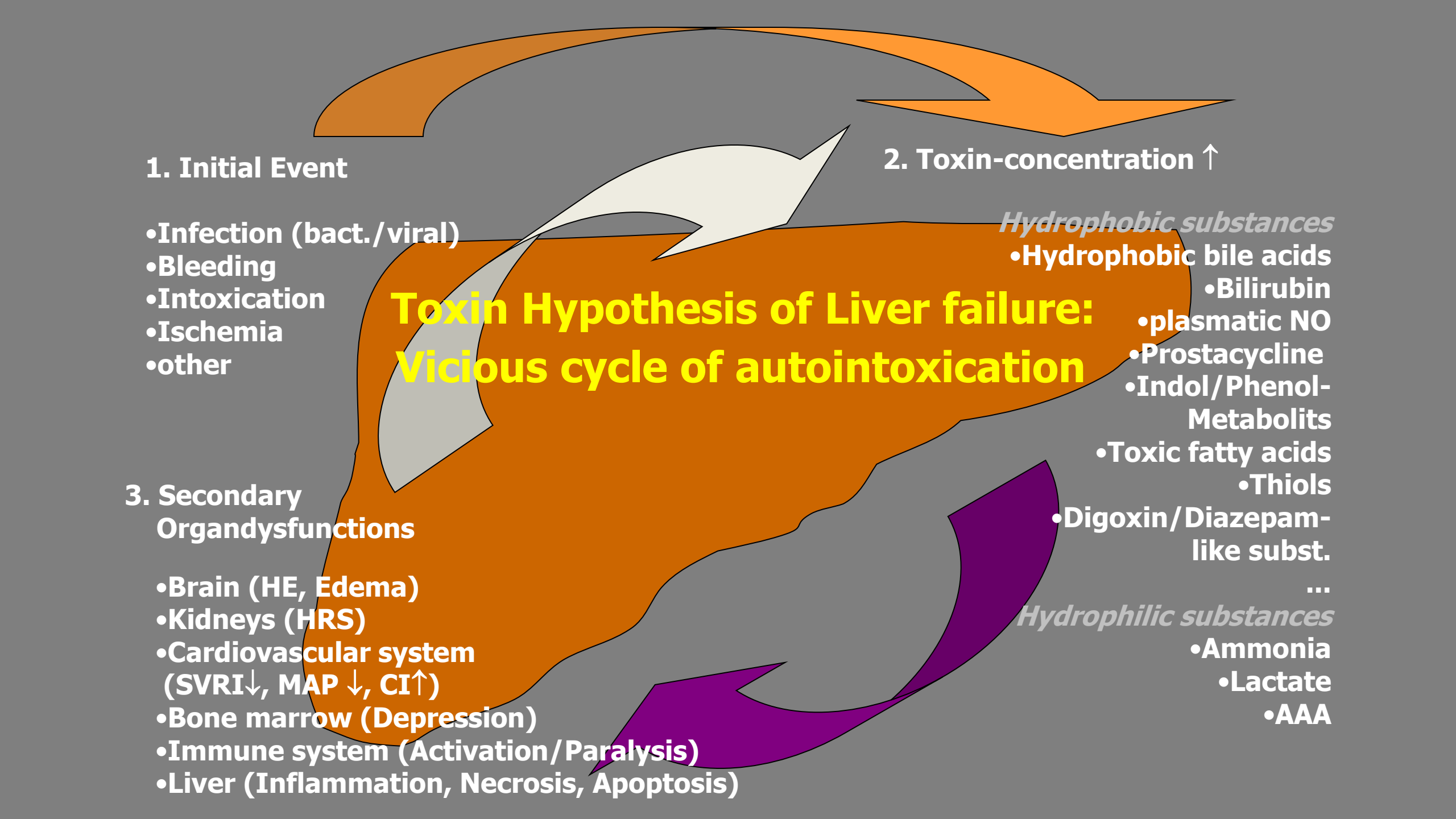
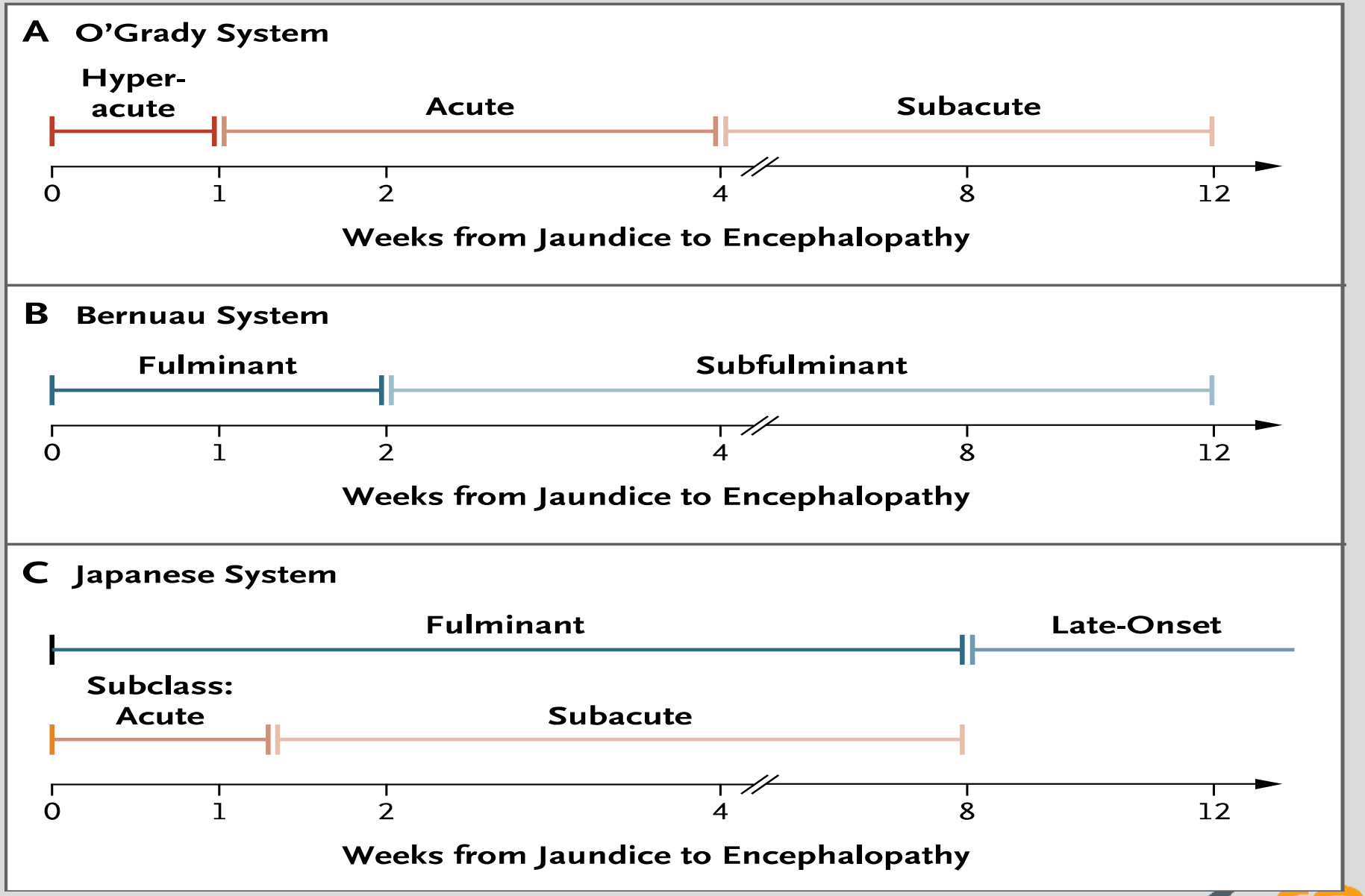

1. Initial Event
•Infection (bact./viral)
•Bleeding
•Intoxication
•Ischemia
•other
2. Toxin-concentration ↑
Hydrophobic substances
•Hydrophobic bile acids
•Bilirubin
•plasmatic NO
•Prostacycline
•Indol/Phenol-Metabolits
•Toxic fatty acids
•Thiols
•Digoxin/Diazepam-like subst.
...
Hydrophilic substances
•Ammonia
•Lactate
•AAA
Toxin Hypothesis of Liver failure:
Vicious cycle of autointoxication
3. Secondary Organdysfunctions
•Brain (HE, Edema)
•Kidneys (HRS)
•Cardiovascular system (SVRI↓, MAP ↓, CI↑)
•Bone marrow (Depression)
•Immune system (Activation/Paralysis)
•Liver (Inflammation, Necrosis, Apoptosis)



Bernal W and Wendon J. NEJM 2013

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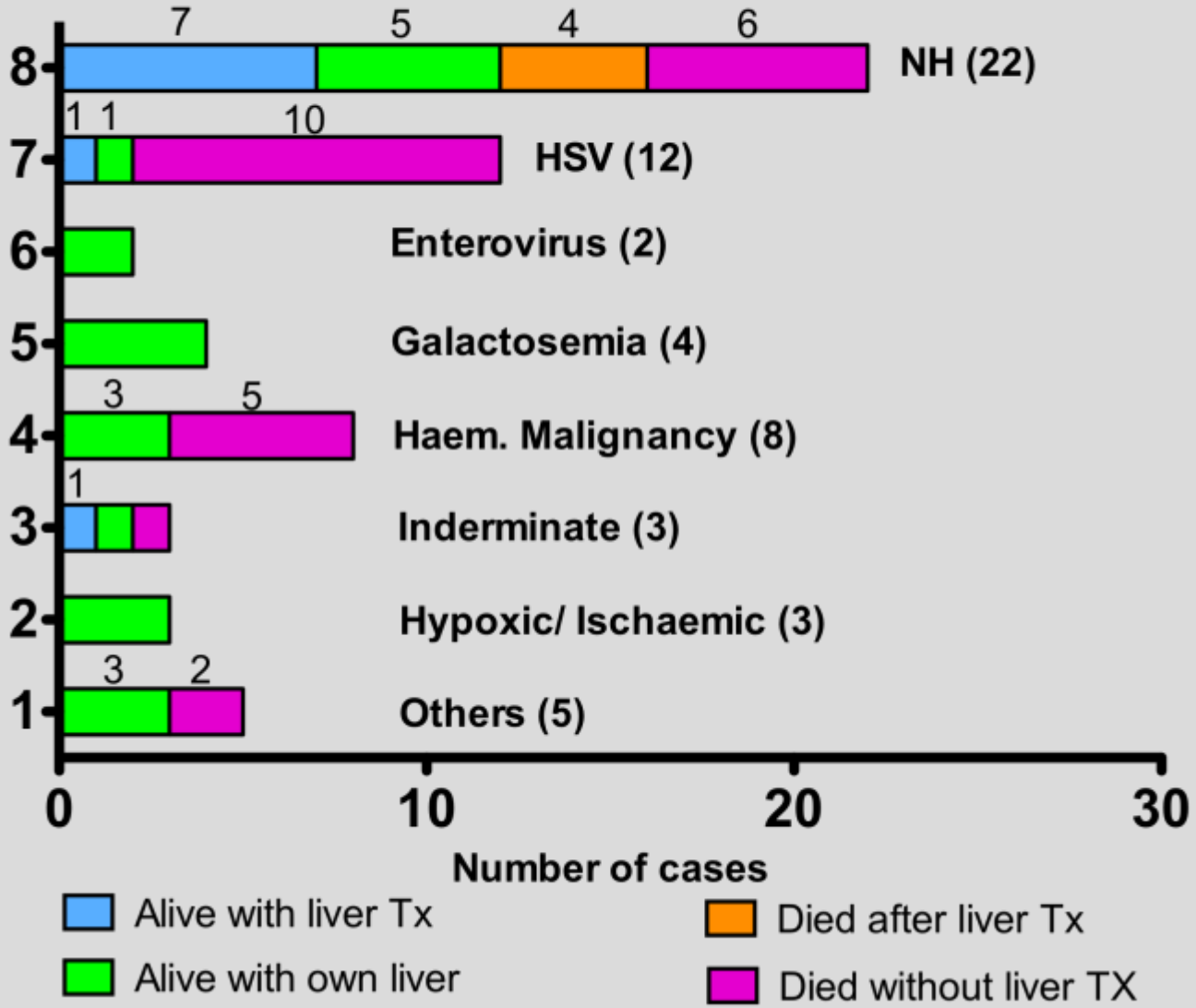
Aetiology

Table 1 Aetiology of acute liver failure (n=215) according to age group, at King's College Hospital, London (1990–2003)

Aetiology	Age category				Total
	Neonate (≤28 days)	Infant (29 days to 1 year)	Child (1.1–12 years)	Adolescent (12.1–18 years)	
Autoimmune	0	0	9	4	13
Indeterminate	2	8	41	17	68
Wilson's	0	0	6	4	10
Drug	1	6	19	25	51
NH	17	0	0	0	17
Metabolic	5	3	6	1	15
Viral	10	4	8	1	23
Haem Malig	6	1	1	0	8
Misc	1	1	5	3	10
Total	42	23	95	55	215

Aetiology and outcome of NLF at King's College Hospital (1990-2007)



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Metabolic

Galactosemia –

GAL-1-PUT deficiency

Tyrosinemia type 1

Defect in fumaryl acetoacetate hydrolase

urine Succinyl acetone diagnostic

High AFP

NTBC – best with in first m of life

Urea cycle disorders

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Neonatal Haemochromatosis

- NH is a syndrome in which severe liver disease associated with deposition of stainable iron in extrahepatic sites
- Supporting diagnostic features:
  - Presentation at birth
  - 80% Day 1
  - 93% Week 1
  - Jaundice (conjugated BR)
  - Moderately elevated alanine aminotransferase
  - ascites, edema, low albumin
  - coagulopathy
  - hypoglycaemia
  - Parenchymal iron deposition

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Neonatal Haemochromatosis

- Alloimmune process
- 32 kd foetal liver antigen in the maternal blood
- demonstration of extra hepatic iron deposits sparing the reticuloendothelial system
- IVIG given at a dose of 1 gm/kg bodyweight weekly from the 18th week until the end of gestation
- Gestational Alloimmune liver disease (GALD)

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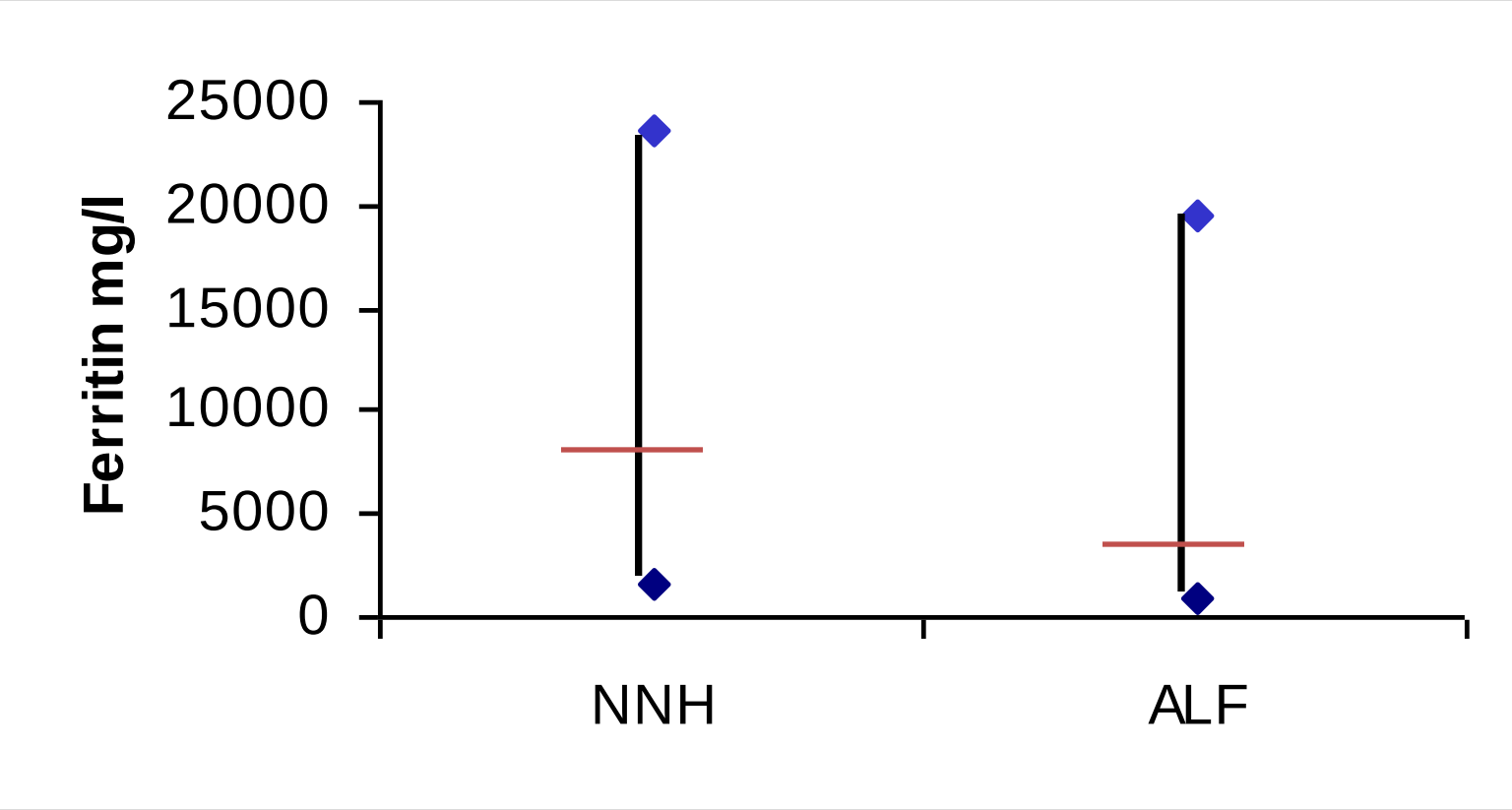
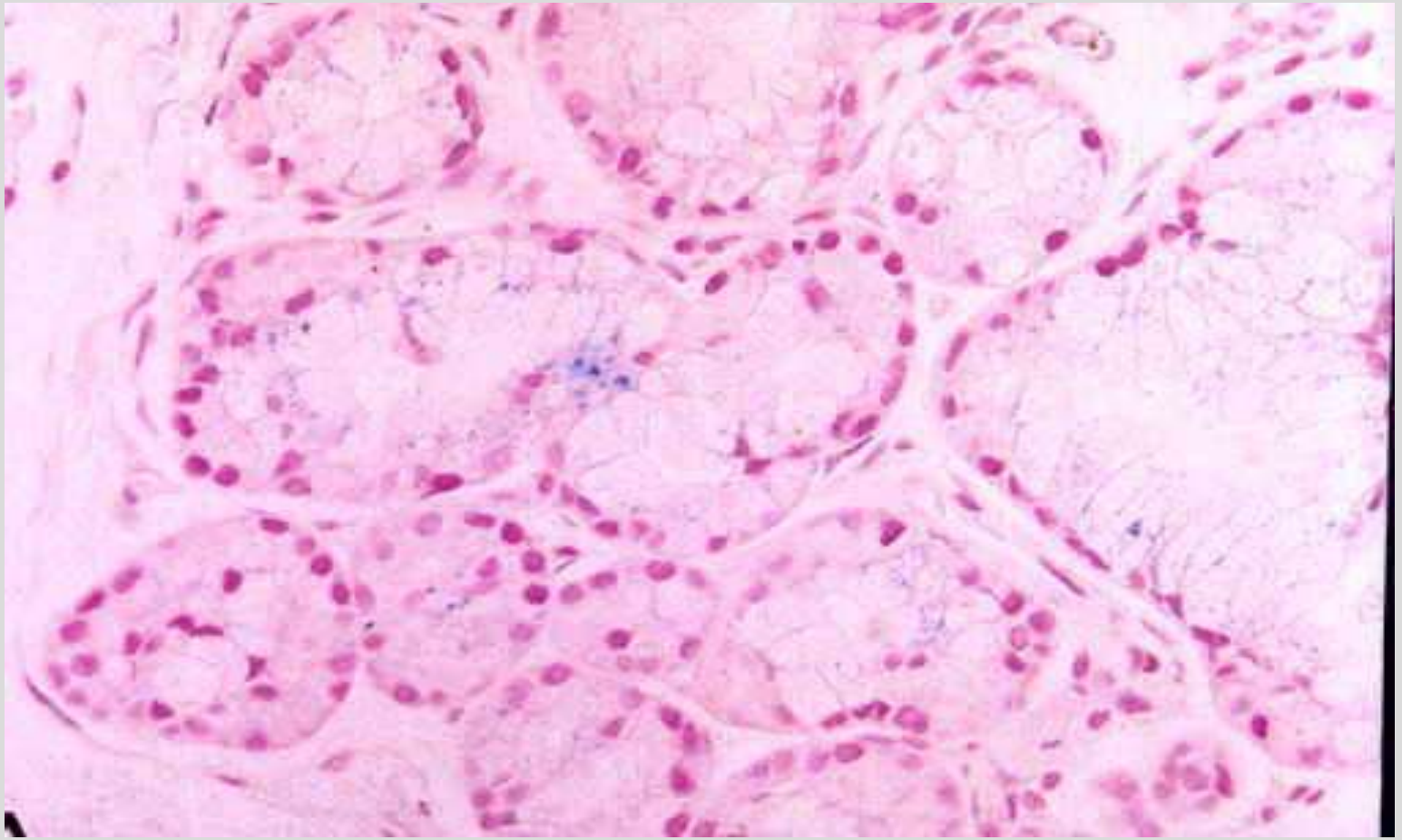
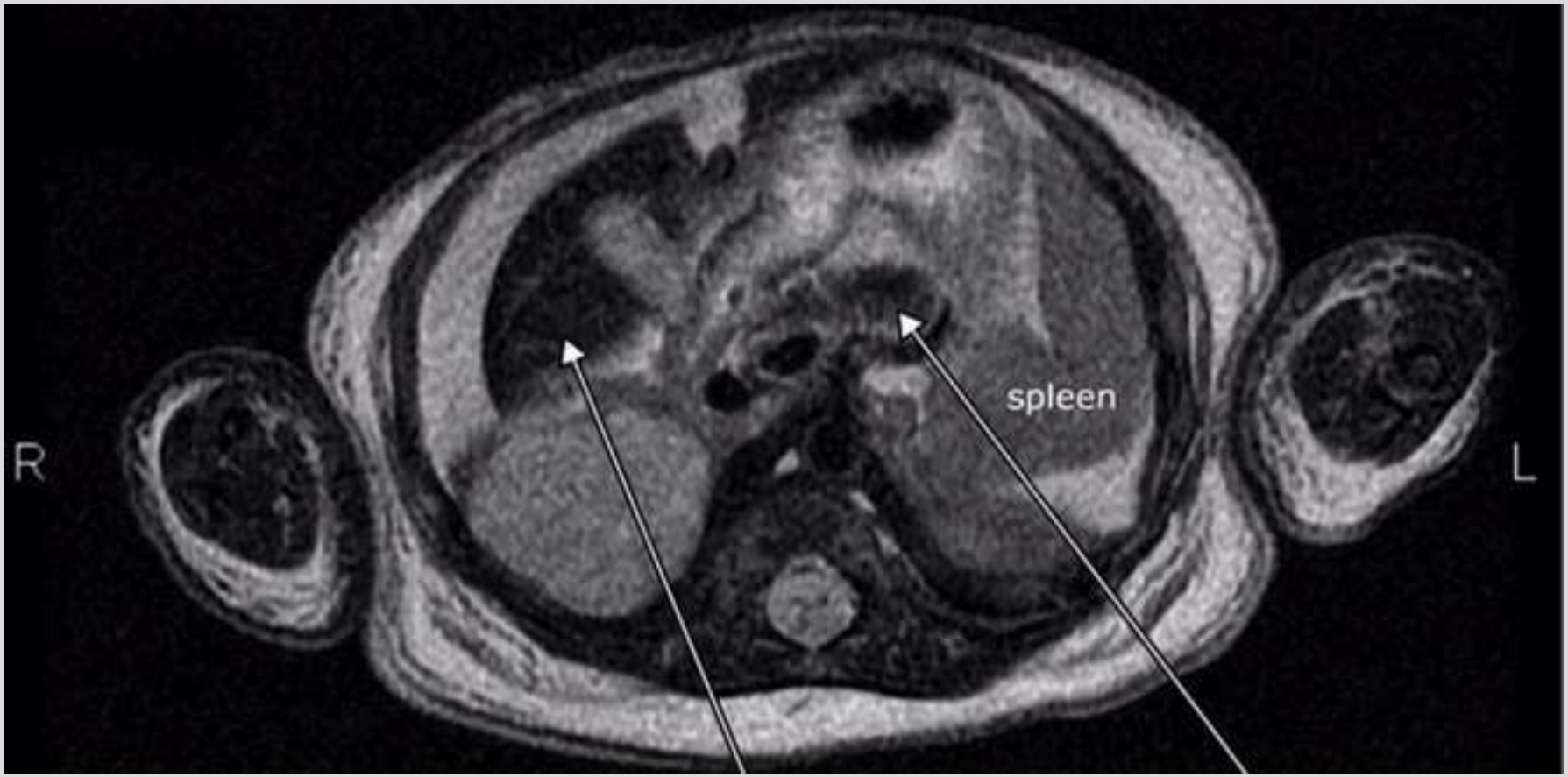
Ferritin levels in neonatal liver failure due to neonatal haemachromatosis and other causes (Median and range)



Siderosis in buccal minor salivary glands



MRI



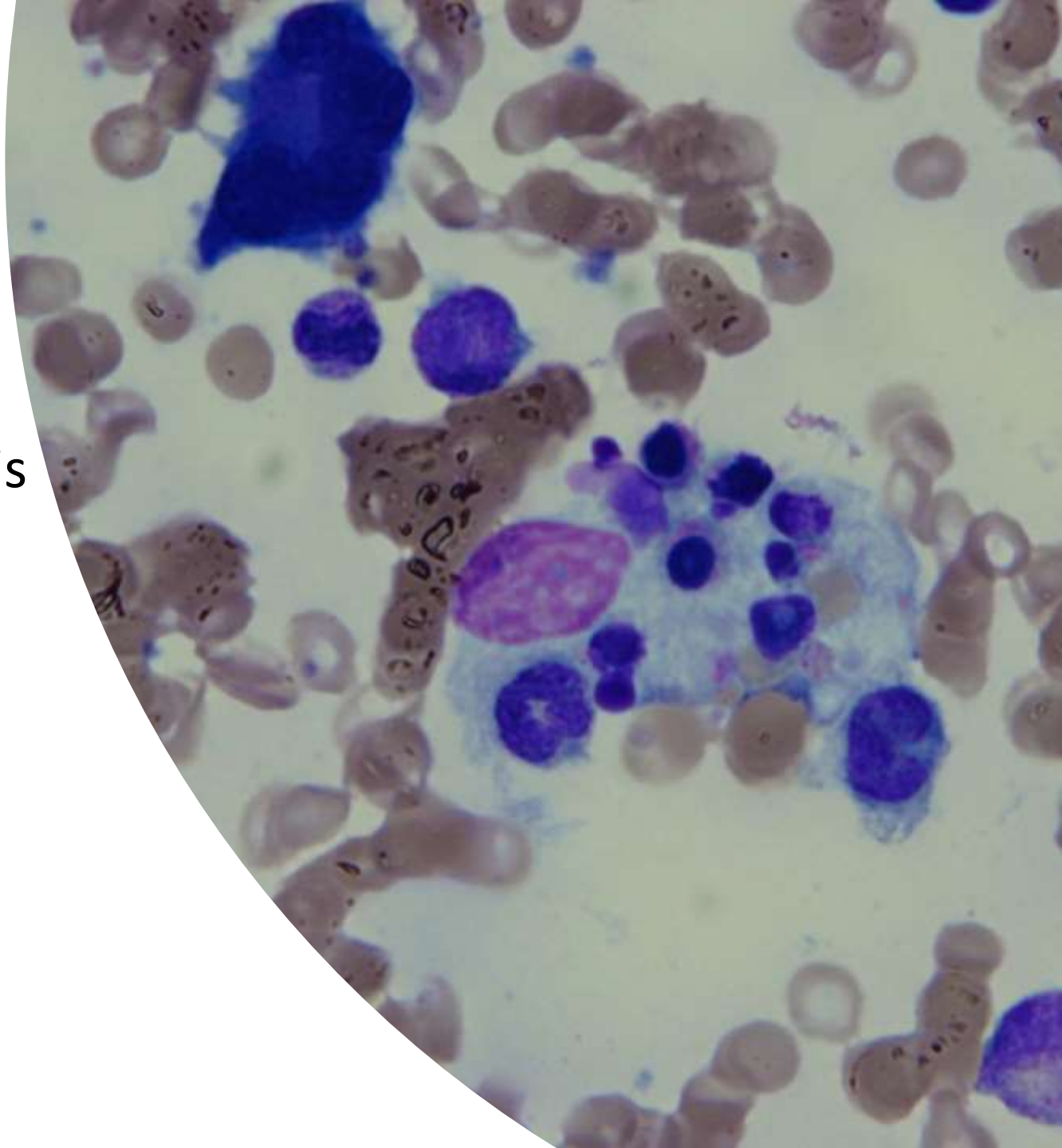
Treatment

- Antioxidant cocktail ✗

- IV immunoglobulin ✔
- exchange transfusion ✔

Infiltrative

- Hemophagocytic Lymphohistiocytosis
- Inappropriate activation of T lymphocytes and macrophages

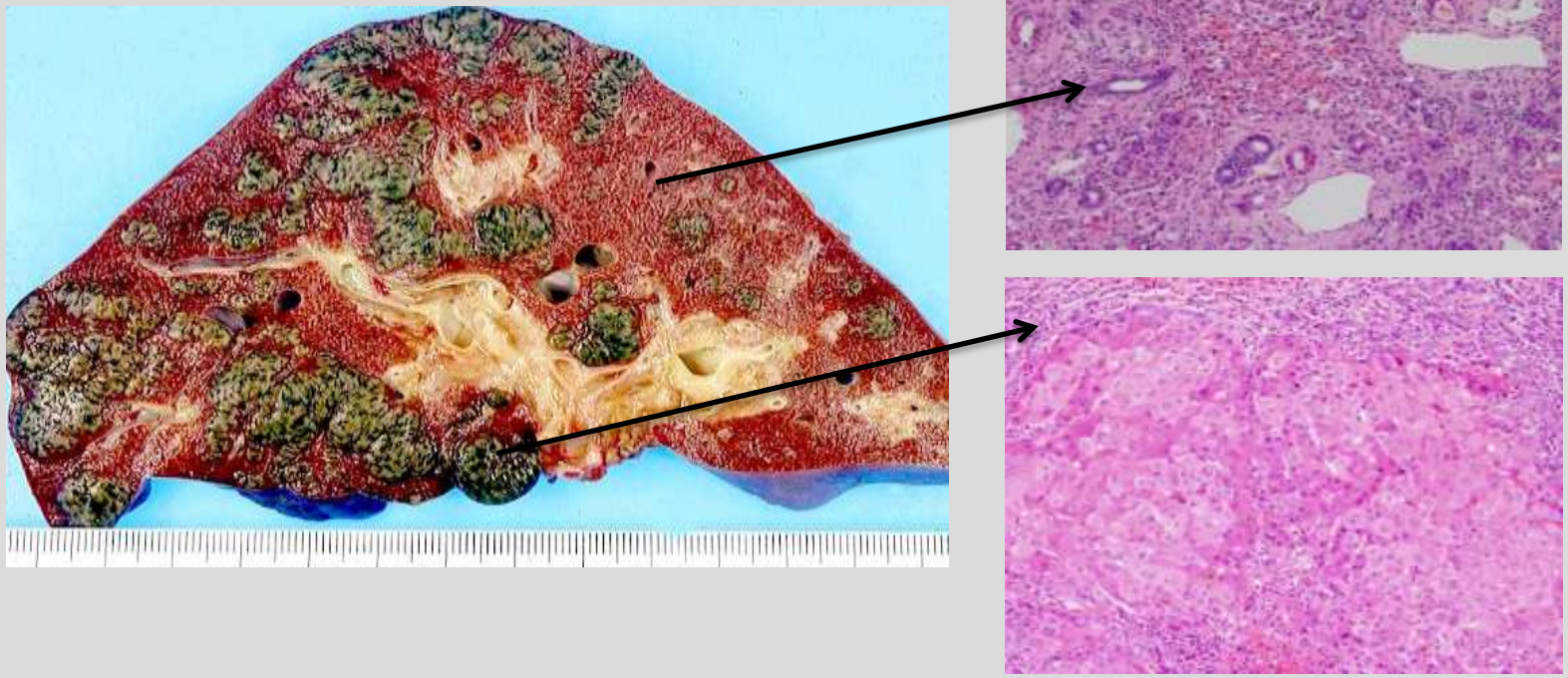


Wilson disease

- Autosomal recessive disorder,
- Coombs-negative hemolytic anaemia,
- Low ceruloplasmin
- low alkaline phosphatase.
- Antibodies might be positive
- Biopsy might not be possible

Is it worth squeezing the juice ?

Value of liver biopsy



ALF Management

- General measures
- Aetiology related treatment
- Management of specific complications
- Indications for Transplantation

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General Measures

- Nurse in quite environment
- Avoid sedation
- Nutrition (1 gm/kg of protein) NG feeds / PN

Management

- Ventilation- Protect airway
- Fluids – Hypoglycemia/ 4 to 6 mg/kg/min of G
- Infection

  Bacterial -82%/ Fungal -34%in Grade ¾ encephalopathy not on prophylaxis. Add acyclovir in infants

Coagulopathy

- Vitamin K: Daily dose
- Platelets if <10,000/mm3
- For procedure 50 – 70,000 is adequete
- Cryo if fibrinogen < 100
- Recombinant activated factor VII/ FFP: give only for invasive procedures or active bleeding

Which Pressor?

- Norepinephrine
  - increase BP, CPP
  - little effect on ICP
- Vasopressin analouge
  - increase CPP
- Adrenaline - Concerns Regarding Splanchnic Perfusion
- Hydrocortisone

Larsen *J. Hepatol* 1995;23:212

Encephalopathy

Ammonia lowering agents

Protein elemination

Lactulose

Gut decontamination

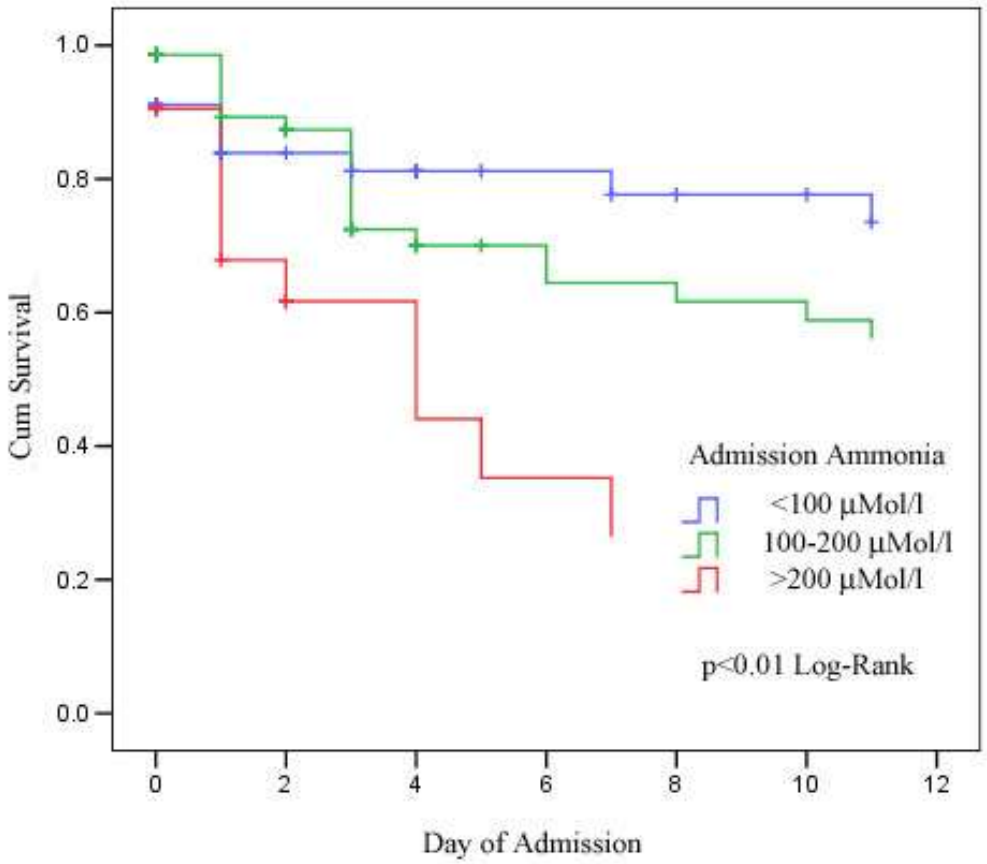
Not helpful in acute /hyperacute setting

No role of prophylactic HS/ Mannitol/ steroids

Raised ICP

Neurologic Support; Arterial Ammonia and Risk of Cerebral Oedema

- Arterial ammonia correlates with raised ICP
- Risk of cerebral oedema high in younger age group
- Signs of raised ICP - mannitol / HS
- No role of prophylactic HV/ HS/ Mannitol/ steroids



BERNAL W, ET AL. *HEPATOLOGY* 2007; 46:1844-52

Aetiology related treatment

• NH	IV IG
• Autoimmune	Steroids
• Tyrosinemia	NTBC
• Galactosemia	Galactose free diet
• Herpes infection	Aciclovir
• Paracetamol	NAC

NAC in non-paracentamol ALF

- NAC did not improve 1-year survival in non-APAP PALF.
- 1-year LTx-free survival was significantly lower with NAC, particularly among those < 2 years old
- These results do not support broad use of NAC in non-APAP PALF

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High volume plasma exchange in ALF

N = 182

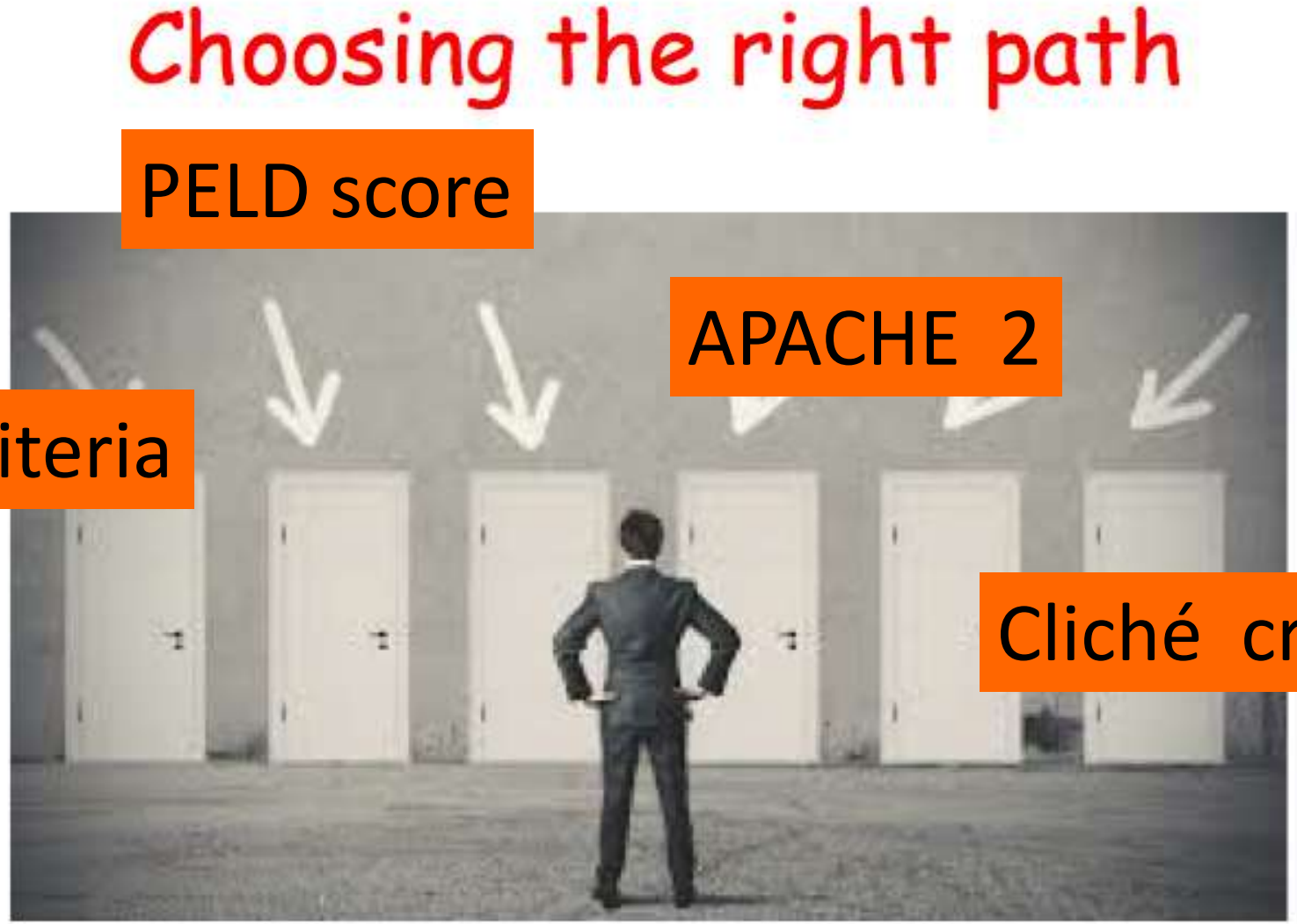
survival was 58.7% (HVP) *vs. 47.8% (Control)(p = 0.0083).*

severe adverse events was similar in the two groups.

SIRS and sequential organ failure assessment (SOFA) scores fell in the treated group compared to control group, over the study period (p <0.001).

High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial Fin Stolze LarsenCorrespondence information about the author Fin Stolze LarsenEmail the author Fin Stolze Larsen, Lars Ebbe Schmidt, Christine Bernsmeier, Allan Rasmussen, Helena Isoniemi, Vishal C. Patel, Evangelos Triantafyllou, William Bernal, Georg Auzinger, Debbie Shawcross, Martin Eefsen, Peter Nissen Bjerring, Jens Otto Clemmesen, Krister Hockerstedt, Hans-Jørgen Frederiksen, Bent Adel Hansen, Charalambos G. Antoniades†, Julia Wendon†

When to transplant??????



When to transplant

- INR > 4

or

- Factor V < 30%

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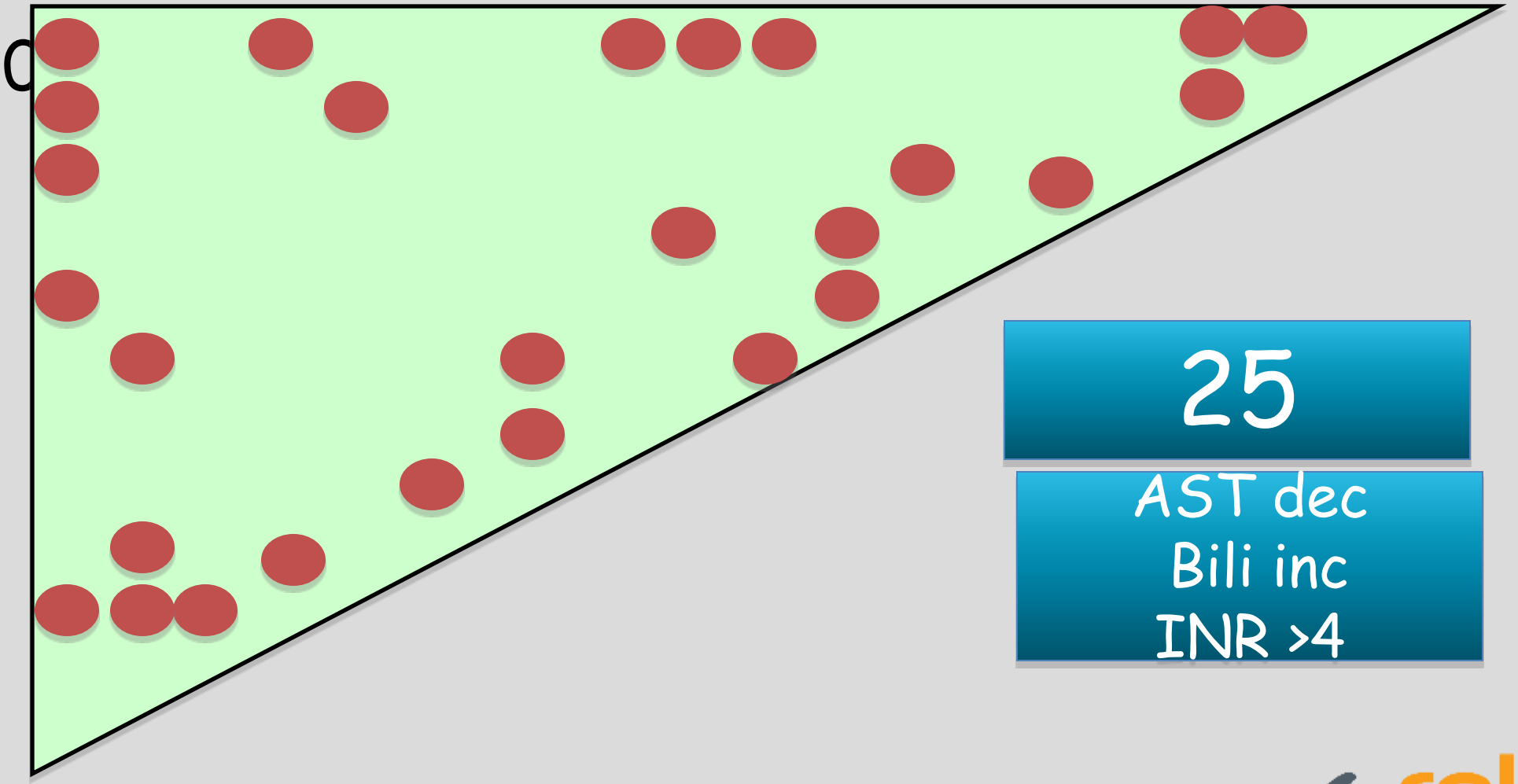
Liver failure model

- 100



25

AST dec
Bili inc
INR >4

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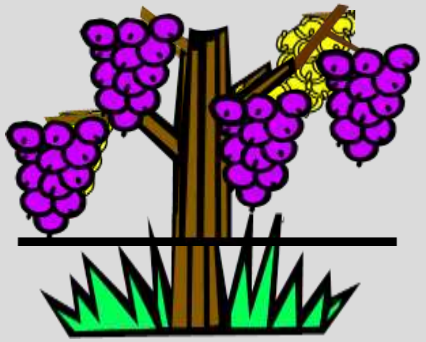
New Wilson's Index

Score	Bilirubin (μmol/l)	INR	AST (IU/l)	WCC (10^9/l)	Albumin (g/l)
0	0 - 100	0 - 1.29	0 - 100	0 - 6.7	>45
1	101 - 150	1.3 - 1.6	101 - 150	6.8 - 8.3	34 - 44
2	151 - 200	1.7 - 1.9	151 - 200	8.4 - 10.3	25 - 33
3	201 - 300	2.0 - 2.4	201 - 300	10.4 - 15.3	21 - 24
4	> 301	> 2.5	> 301	> 15.4	0 - 20

Orthotopic or Whole liver Tx

Donor

Patient with liver failure



AUXILIARY ORTHOTOPIC LIVER TRANSPLANTATION

SUPRA-HEPATIC VEINS

NATIVE LIVER

GRAFTED LIVER SEGMENT

HEPATIC DUCT ANASTOMOSIS

HEPATIC ARTERY ANASTOMOSIS

PORTAL VEIN ANASTOMOSIS

ROUX-en-Y LOOP

HEPATIC DUCT

HEPATIC ARTERY

PORTAL VEIN

INFERIOR VENA CAVA

AORTA

ARTERY CONDUIT

Auxiliary Liver tx

Donor

Recipient

Successful liver regeneration

CASE REPORT

Auxiliary Liver Transplantation for Acute Liver Failure

NARESH P SHANMUGAM, *TAWFIQ AL-LAWATI, CHAYA KELGERI AND #MOHAMED RELA

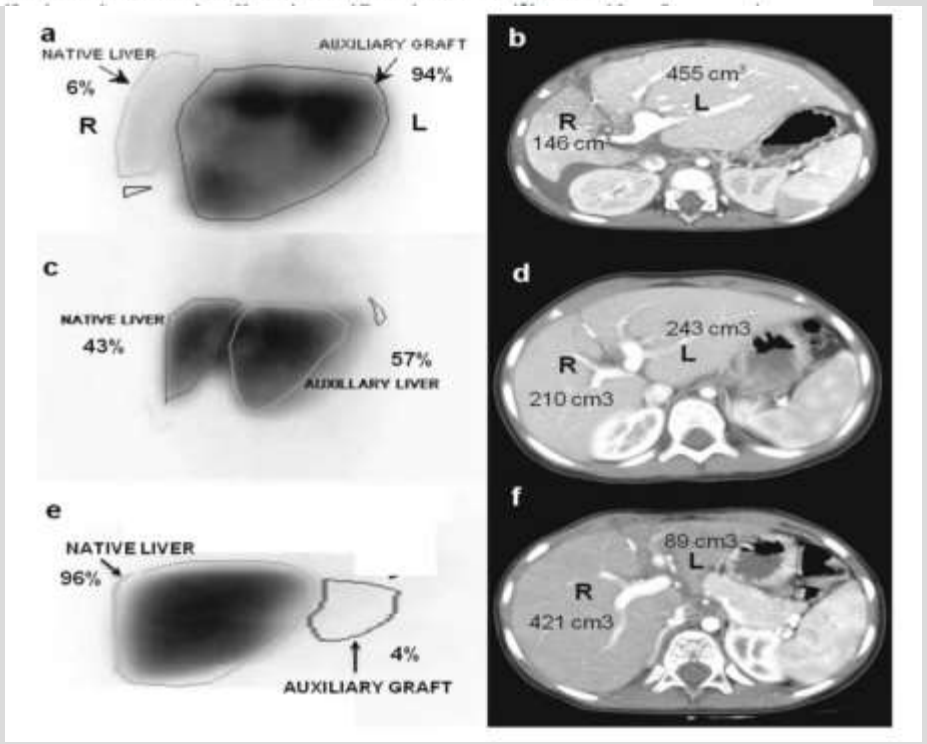


FIG.1 *Serial DISIDA scan at 1, 24 and 30 months after APOLT showing gradual recovery of native liver (right lobe) function (a,c,e); and corresponding CT images of gradual volumetric regeneration of native liver (right lobe) (b,d,f). L: left lobe (transplanted liver), R; right lobe (native liver).*

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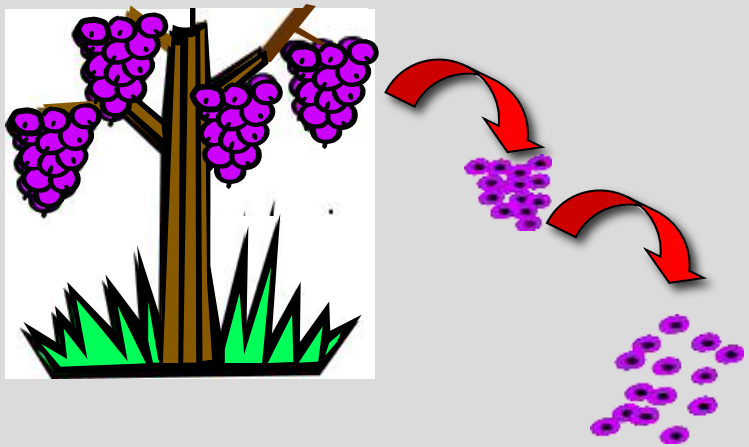
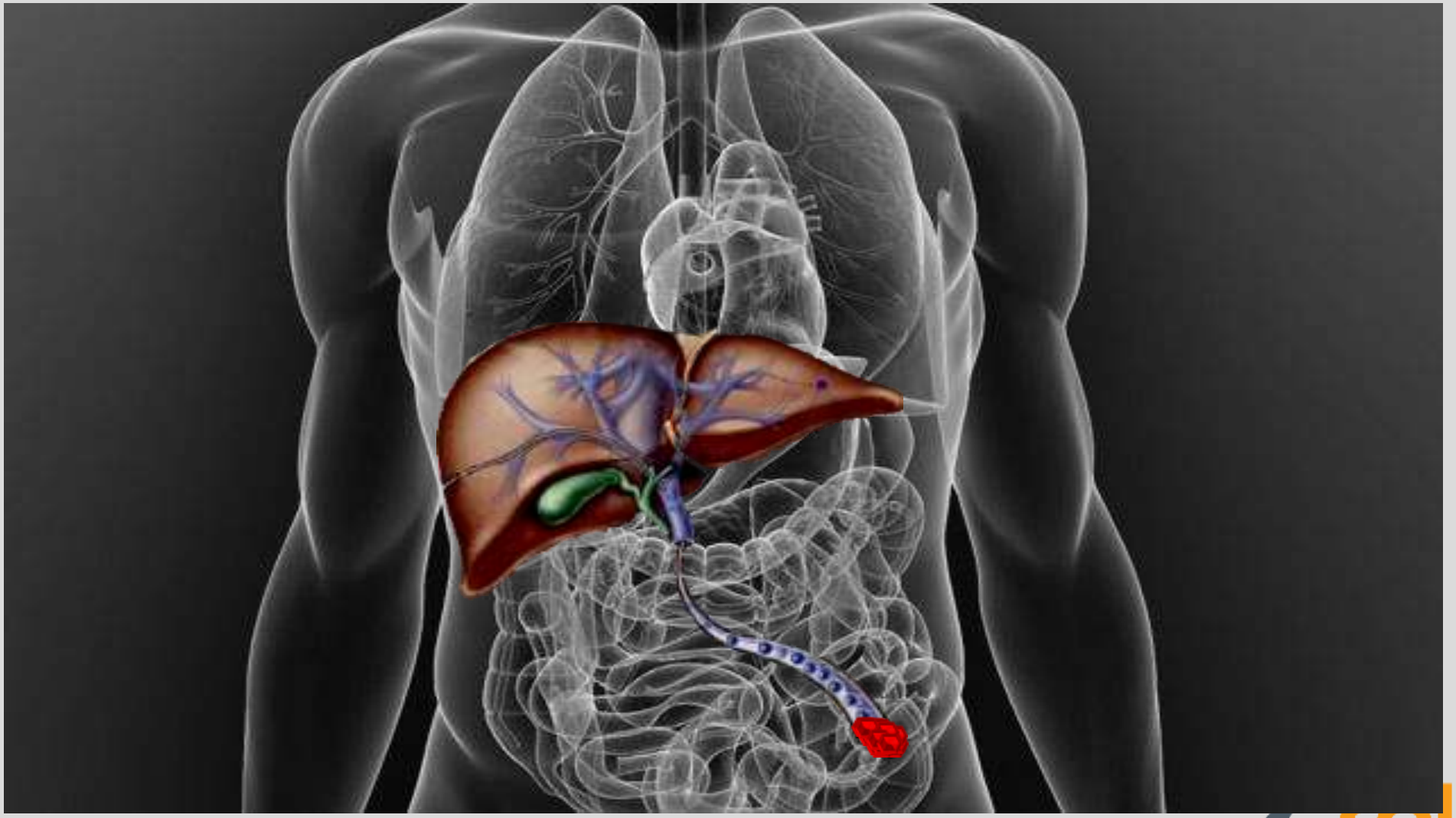
Hepatocyte tx

Donor

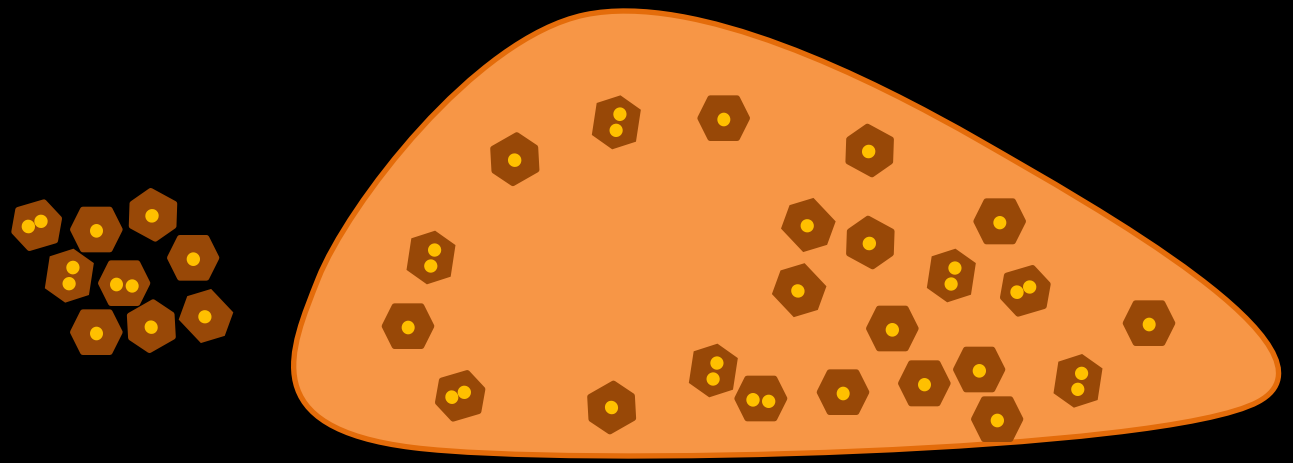


Recipient

Liver cell infusion



Repopulation!



Take home message

- New definition for ALF
- Neonatal Hemochromatosis is not metabolic condition
- ALF and transplant criteria are not same
- Supportive measures - essential
- Auxiliary transplant is new option
- Cell transplant and dialysis – still experimental

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Thank you

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