Abdominal Trauma

Aetiology

1. blunt trauma
   - i. MVA's cause ~ 75%
     - associated splenic damage ~ 46%
       hepatic damage ~ 33%
       mesenteric damage ~ 10%
   - ii. direct blows ~ 14%
     - some associated with CPR
   - iii. falls ~ 10%
2. penetrating trauma
   - majority are stabbings or gunshot wounds
   - simultaneous involvement of the thoracic cavity **~ 25%**

Investigation

1. FBE, Hct
2. XRays
   - major trauma → CXR, Cx spine, SXR, AXR, Tx spine, pelvis
3. peritoneal lavage
   - accuracy **~ 95%**
   - complication rate ~ 1%
4. CT scan
   - ideally should be performed ***prior*** to peritoneal lavage, so that interpretation is not obscured by introduced fluid/air
   - requires the patient to be haemodynamically stable prior to transport
   - allows diagnosis of organ damage prior to laparotomy
   - may provide additional diagnostic information → chest, Cx spine, Tx spine, etc.
5. ultrasound
6. nuclear scan
7. contrast studies
   - i. ***gastrograffin***
     - 250 ml and right lateral position may confirm gastric/duodenal perforation
   - ii. angiography
     - useful for continuous haemorrhage **> 2 ml/min**
     - allows selective embolisation of the bleeding vessel
8. laparoscopy
9. diagnostic laparotomy

- ***Management***

1. ABC / resuscitation
2. laparotomy
   - < 20% of gunshot wounds ***are not*** associated with visceral injury

   i. splenic injury
      - risks of overwhelming sepsis post-splenectomy, ∴***do not*** remove routinely
      - non-operative management of splenic trauma has a failure rate ~ 70%
      - success rate for conservative management in children is higher
      - operation with ***splenic conservation*** → R_X of choice
      - if repair not possible then require polyvalent ***pneumococcal vaccine***
      - common infecting organisms
        - *Pneumococcus*
        - *Meningococcus*
        - *Haemophilus influenzae*

   ii. hepatic injury
      - usually do not require operative repair
      - however, high incidence of associated injury and often require exploratory laparotomy to exclude other pathology

   iii. renal injury
      - usually presents with ***haematuria***
      - usually do not require operative repair
      - check IVP, cystogram

   iv. hollow visceral injuries
      - more commonly follow penetrating trauma
      - require operative correction

Peritoneal Lavage

a. sensitivity ~ 95%

b. specificity ~ 85%

c. complications ~ 1% *operator dependent

d. positive result

i. ***aspiration***

- fresh blood ≥ 10 ml
- faecal soiling or vegetable material
- bile

ii. ***lavage***

- appearance of lavage fluid in intercostal or urinary catheters

iii. ***analysis***

- RBC count > 100,000/µl
  > 50,000/µl ≡[t] eqivocal
  > 5,000/µl ≡[t] penetrating injuries
- WCC > 500/µl
  > 200/µl ≡[t] eqivocal
- ALP[§] > 3 IU/ml
- amylase[§] > 20 IU/ml

NB: [§]specificity for these is lacking → now rarely performed

- causes of ***false positives*** **~ 15%**

a. traumatic lavage

b. retroperitoneal haemorrhage

c. pelvic haematoma - 2° fractures

- causes of ***false negatives*** **~ 5%**

a. incorrectly performed

b. diaphragmatic rupture

c. retroperitoneal injuries - haemorrhage
- duodenum, pancreas
- renal injury

d. isolated hollow viscus perforation

- ***Indications***

a. multiple trauma patient in whom abdominal examination is,
   i. equivocal
   ii. unreliable - CHI, intoxication, cord injury
   iii. impractical - prolonged XRays, angiography
   - requiring GA

b. unexplained fluid requirements in resuscitation

c. penetrating injuries - including lower thoracic

d. gunshot wounds

- ***Contraindications***

a. full bladder

b. pregnancy

c. recent abdominal surgery

d. obvious signs of intraperitoneal haemorrhage/infection

NB: ie., any indication for immediate laparotomy

- ***Complications***

a. haemorrhage

b. intestinal perforation

c. bladder perforation

d. infection

- ***Technique***

a. empty baldder, sterile technique, IV access

b. dialysis catheter introduced into pelvis via sub-umbilical incision

c. aspiration for frank blood | peritoneal fluid

d. 1000 ml of normal saline introduced over 5 minutes + ballotment

e. fluid drained sent for,
   i. red & white blood cell counts
   ii. urgent gram stain & culture
   iii. amylase
   iv. ? cytology

Acute Abdomen in ICU - Differential Diagnosis

a.	adynamic ileus	- paralytic ileus, acute gastric dilatation - intestinal pseudo-obstruction - toxic megacolon
b.	acalculous cholecystitis	
c.	pancreatitis	
d.	postoperative	- anastomotic leak - abscess formation
e.	peritonitis	
	i. secondary	- bacterial, chemical
	ii. primary	- *Pneumococcal, Streptococcal, Enterobacteriaciae*
f.	trauma	- visceral perforation - laceration - haemorrhage, haematoma - post-CPR
g.	splanchnic hypoperfusion	- mesenteric ischaemia
h.	coincidental disease	- appendicitis, cholecystitis - peptic ulcer - volvulus - diverticulitis - carcinoma - strangulated hernia
i.	thoracic spinal trauma	

- ***Medical Causes of the "Acute Abdomen"***

a.	endocrine	- Addisonian crisis - diabetic ketoacidosis
b.	cardiac	- acute visceral congestion (CCF, tamponade, PE etc.) - lactic acidosis - mesenteric thromboembolism
c.	neurological	- tabes dorsalis - herpes zoster - porphyria - epilepsy
d.	autoimmune	- polyarteritis nodosa, SLE
e.	metabolic	- hypercalcaemia - uraemia
f.	respiratory	- lower lobe pneumonia - PTE

g.	other	- Familial Mediterranean fever - lead & other heavy metal poisoning - lactose intolerance - haemolytic crisis - Henoch-Schönlein purpura.
h.	allergy	- food allergy - hereditary angioneurotic oedema

- ***Investigation - Acute Abdomen***

a.	history of illness	
b.	physical examination	- incl. temp., PR and PV
c.	white cell count	- nonspecific
d.	AXR	- supine & lateral decubitus
e.	ultrasound	
f.	abdominal CT scan	- with IV and enteral contrast
g.	peritoneal lavage	
h.	diagnostic laparotomy	

NB: untreated abdominal sepsis has a high mortality,
whereas mortality is ***unchanged*** by a negative laparotomy

Acalculous Cholecystitis

- acute ***necrotising*** cholecystitis which may occur spontaneously in any critically ill patient
- multifactorial aetiology,

1.	reduced cystic artery perfusion	
2.	↑ bile viscosity 2° dehydration	
3.	bile stasis	- TPN, use of octreotide
4.	antibiotic precipitation	- eg Ca^{++}-salt of ceftriaxone

- may present as a tender RUQ mass, or as progressive jaundice with "sepsis"
- ***ultrasound*** may show an enlarged, oedematous gall-bladder, or may be ***normal***
- ie. a normal gallbladder and biliary tree ultrasound ***does not*** exclude the diagnosis
- high false positive rate for HIDA scans in ICU patients
- management is,

1. ***cholecystectomy***
2. cholecystotomy, or
3. radiological tube drainage

Intestinal Pseudo-Obstruction

- cause of acute abdominal distension and acute abdomen in the ICU patient
- ? due to alteration in neuromuscular function of the bowel

- ***Usual Presentation***

  a. dilated loops of large ***and*** small bowel
  b. absence of signs of a site of mechanical obstruction
  c. may become grossly distended

- ***Complications***

  a. splinting of diaphragms, respiratory embarrassment
  b. raised intra-abdominal pressure - adverse renal, respiratory, and CVS effects
  c. "toxic megacolon" and rupture > 6 cm diameter
  d. septicaemia
  e. pain and distension
  f. intolerance of enteral feed

- ***Aetiology *Multifactorial***

a.	autonomic neuropathy	- any cause
b.	drugs	- opiates - β-agonists, antihypertensives - anticholinergics, tricyclics, phenothiazines - purgatives, barium, aluminium - iron supplements
c.	electrolyte abnormalities	- hypo-K^+ / Ca^{++} / $HPO_4^=$
d.	neuromuscular	- Parkinson's disease - myotonic dystrophy - M.S.
e.	endocrinopathies	- myxoedema / hypothyroidism - diabetes mellitus - porphyria - hypoparathyroidism - amyloidosis
f.	autoimmune	- SLE, polyarteritis nodosa - scleroderma, dermatomyositis
g.	? IPPV causing reduced splanchnic blood flow	

- ***Treatment***

a.	reverse potential causes	- eg. cease narcotics
b.	colonoscopy & decompression	- may need to be repeated daily ± flatus tube
c.	operative decompression	- caecostomy
d.	prokinetic agents	? cisapride

- ***Differential Diagnosis***

a. adynamic / paralytic ileus
b. toxic megacolon
c. bowel obstruction- hernia, volvulus, adhesion, tumour
d. ischaemic bowel

- ***Adynamic Ileus***

Def'n: any non-surgical impairment of the distal propulsion of intestinal contents

• traditional belief that all abdominal operations are followed by ~ 48 hr period of ileus
• SI is largely ***unaffected*** by laparotomy and may accommodate enteral feeding almost immediately
• however, other factors delaying function

a.	gastric emptying impaired	~ 24 hrs
b.	colonic activity impaired	~ 48 hrs

• therefore, postoperative ileus is predominantly a ***colonic*** problem
• with prolonged ileus, mechanical obstruction (faecal impaction) must be excluded
• propulsion may be aided by,

a.	cisapride	- 5-10 mg q8h
b.	metoclopramide	- 10 mg q6h
c.	domperidone	- 10 mg q8h

■ ***Metoclopramide***

• structurally related to procainamide, but ***no*** LA activity

a. CNS
- effects due to ***dopaminergic blockade*** →

i. antiemesis

ii. hyperprolactinaemia
- galactorrhoea, breast tenderness
- menstrual irregularity in females
- used to promote milk production post-partum

- ***no*** antipsychotic activity
- may produce significant ***extrapyramidal*** symptoms
  Rx benztropine, diphenhydramine

b. GIT
- ↑ smooth muscle activity, mainly stomach & proximal SI
- ↑ LOS tone & ↓ pyloric tone
- ***no effect*** on colonic activity or gastric acid secretion
- mechanism of action not fully understood,

i. predominantly DA_2 receptor blockade

ii. ? stimulates release of ACh as 2° agonist
- GIT effects blocked by ***atropine***

■ ***Domperidone***

• both ***prokinetic*** and ***antiemetic***
• also a dopaminergic blocking agent
• effects on GIT →

a. same spectrum of activity cf. metoclopramide
- but ***not*** blocked by atropine
- efficacy for gastric motility equivalent

b. doesn't cross the BBB, ∴CNS effects are supposedly less

c. less antiemetic activity

■ ***Cisapride***

• effects on GIT ≡ metoclopramide | domperidone
• however, also increases ***colonic motility***
• mechanism poorly understood
• like metoclopramide activity is blocked by atropine, ∴partially due to myenteric ACh

Body Fluids

Body Fluids							
	Vol/day	Na^+	K^+	Cl^-	HCO_3^-	IVT	+ KCl
Plasma		136-144	3.5-5.0	95-110	25		
Gastric	1-5 l	30-120	10-15	140	pH ~ 1.5	N.Sal	~20-50
Bile	< 1000ml	145	5	100	35-70	Hart	20
Pancreas	< 1000ml	140	5	60	90	Hart	20
SI	1-3 l	120	5-10	105	25	Hart	20
LI	100-500ml	< 80	20-40	< 50	< 45	Hart	20-50
Sweat	~ 400ml	50	5-10	45		D_4W-N/5 N/2 Sal.	20

Diarrhoea

Def'n: ³ **3** watery bowel actions per day

- a common problem, occurring in **~ 25%** of enterally fed patients
- often independent of feeding regimen, often culture/toxin negative
- common aetiology of diarrhoea in ICU patients,

a. part of primary illness

b. drug induced

c. recovery from ileus

d. acquired hypoalbuminaemic "protein losing enteropathy"

e. change in bowel flora - bacterial overgrowth

f. hypo or hyper-osmotic feeds

- ***Diarrhoea - Classification***

a. ***infective***

i.	viral	- rotavirus, enteroviruses - Hepatitis A & B, CMV
ii.	bacterial ***toxins***	- enterotoxigenic *E. coli* - *Klebsiella sp.* - *Enterobacter* - *Staph. aureus* - *Bacillus cereus* - *Vibrio cholerae* - *Cl. perfringens* - *Cl. difficile* (pseudomembranous colitis) - *Cl. botulinum*
iii.	bacterial ***invasion***	- enteropathogenic *E. coli* - *Campylobacter sp.* - *Vibrio parahaemolyticus* - Salmonella - Shigella - Staphylococci
iv.	fungal	- Candidiasis
v.	protozoal	- Giardiasis - *Entamoeba histolyticum*

b. ***non-infective***

i.	drugs	- antibiotics - Mylanta and other antacids - osmotic agents, cathartics - cholinergics - antimetabolites - chemotherapy - common non-specific side effect
ii.	bowel disease	- diverticulitis - ulcerative colitis - Crohn's disease - enterocolic fistula - ischaemic colitis - pelvic abscess - villous adenoma - carcinoma - faecal impaction + overflow incontinence
iii.	malabsorption	- lactose intolerance - hypoalbuminaemia (acquired "protein losing enteropathy") - tropical sprue - pancreatic insufficiency - enteral feeds
iv.	post-GIT surgery	- short bowel - blind loop - post-gastrectomy - recovery from paralytic ileus, or obstruction
v.	endocrine / metabolic	- thyrotoxicosis - diabetes - hypoparathyroidism - carcinoid - hypoadrenalism - autonomic neuropathy - heatstroke

- ***Causes of Antibiotic-Induced Diarrhoea***

a.	direct irritation, decreased transit time	
b.	altered microflora	- decreased anaerobes - increased gram (-)'ves
c.	resistant organisms	- Candidiasis - Staphylcoccal overgrowth
d.	pseudomembranous colitis	- *Cl. difficile*

- ***Diagnosis***

a. history - medical/surgical problems, drugs

b. examination - fluid status, nature of feeding
- abdominal signs, PR, sigmoidoscopy

c. serum electrolytes and albumin

d. feces for microbiology - M,C & S
- ova & paracytes
- *Cl. difficile* toxin

e. AXR - erect and supine

f. sigmoidoscopy / colonoscopy

Short Bowel Syndrome

- SI resection,

a. ≤ 50% is usually tolerated without impairment

b. ≥ 75% usually results in malabsorption of nutrients

c. with remaining bowel 15-20% (60-80 cm), refeeding should be progressive, with a view to attaining a normal dietary intake

- clinical sequelae & management,

1. diarrhoea - loperamide, codeine, H_2-blockers, cholestyramine, octreotide
2. malabsorption
   - calcium - calcium salts, $1,25(OH)_2$-D_3
   - magnesium, zinc, other trace elements
   - folate, B_{12}, iron
   - fat soluble vitamins
3. nephrolithiasis / hyperoxaluria- cholestyramine
   - hyperoxaluria 2° ↑ colonic absorption with extensive ileal loss
4. gastric acid hypersecretion - H_2-blockers, omeprazole, octreotide, ketanserin
   - peptic ulceration
   - diarrhoea
5. metabolic acidosis
   - SI bacterial overgrowth
     → ***d-lactic acidosis*** - metronidazole, vancomycin
   - HCO_3 losing diarrhoea - sodium citrate / acetate
6. gall stones
   - ↓ bile salt pool & ↑ lithogenicity of bile

UPPER GASTROINTESTINAL HAEMORRHAGE

- ***Aetiology***

1. oesophageal
   i. varices
   ii. Mallory-Weiss syndrome
   iii. oesophagitis
2. gastric & duodenal
   i. peptic ulceration / acute stress ulceration
   ii. gastritis
   iii. hiatus hernia
   iv. tumours - benign, malignant
   v. AV malformation, telangectasia
3. aorto-enteric fistula
4. coagulation disorders

- ***Investigation***

1. laboratory investigation
   i. FBE/Coags - [Hb], platelets, INR/APTT
   ii. EC&U, LFT, CaP, BSL, Mg
      - ***urea:creat. ratio*** **> 100** in 87% with upper GI bleeding
        < 100 in 95% with lower GI bleeding
2. ***endoscopy***
   - potential bleeding site identified ~ **90%**
   - multiple potential bleeding sites ~ **33%**
   - performed within 12 hrs, active bleeding ~ 45%
3. contrast studies
   - less sensitive / specific cf. endoscopy
   - Gastrografin / barium swallow will only detect bleeding site in ~ 50%
4. angiography
   - may be of value with continued bleeding > 0.5-**2 ml/min**

- ***Management***

1. ABC / resuscitation → priority
2. **85%** will stop bleeding ***spontaneously***
3. specific management per lesion

Stress Ulceration

- distinguish stress erosions (75-100%), stress ulcers and stress haemorrhage (~ 5%)
- stress ulcers occur within minutes to hours → sign of ***splanchnic ischaemia***
- incidence in the 1970's,

a.	erosions	~ 75-100%		
b.	ulcers	~ 50%		
c.	macroscopic bleeding	~ 25%		
d.	***serious bleed***	**~ 5%**	→	~ 50-70% mortality
e.	perforation rare			

NB: markedly reduced with antacids / H_2 blockers → universal use

- ***overt bleeding*** occurred with,

a.	placebo	~ 15%
b.	antacids	~ 3.3%
c.	H_2 blockers	~ 2.7%

- the incidence in the 1980's,

a.	erosions	~ 40-50%			
b.	ulcers	~ 5%	∝	10x	↓ incidence
c.	macroscopic bleeding	~ 5%	∝	5x	↓ incidence
d.	serious bleed	→	rare but still a ***high mortality***		

NB: Reusser *et al.* CCM 1990
RCT of endoscopically detected stress ulceration in neurosurgical patients (n = 40)
prophylaxis and non-prophylaxis groups → ***no significant difference***
therefore queried whether antacids / H_2 blockers are still necessary !!

- ***Risk Factors***

a. previous ulcer disease
b. coagulopathy
c. mechanical ventilation > 48 hrs
d. previous factors → now questioned
   i. head injury, multiple trauma
   ii. severe burns
   iii. sepsis / SIRS
   iv. hypotension, hypovolaemia
   v. renal failure
   vi. hepatic failure

■ ***Prophylaxis***

• proven measures,

a. gastric pH control → antacids > H_2-blockers

b. cytoprotective drugs → sucralfate $\equiv^{T}$ antacids / PG-analogues

c. nutrition → enteral > TPN

• the reduced incidence is also probably due to,

a. better ICU management

b. better O_2 & fluid management

c. early NG feeding

d. improved analgesia

e. R_X of coagulopathy

f. ? dopamine → improved gut blood flow

■ ***Pathology***

• the site is usually the ***fundus*** and body
• rarely in the antrum, duodenum, or oesophagus

1. mucosal ulceration
   • superficial, eroding through to the muscularis mucosae only
   → results in little bleeding & heals rapidly
2. acute peptic ulceration
   • deep, through the muscular layer where the larger arteries reside
   → greater bleeding and slower to heal

• damage to mucosal defences is caused by,

a. alcohol

b. aspirin, NSAID's

c. vasoconstrictors

d. steroids

• factors which increase the risk of haemorrhage,

a. aspirin, NSAID's

b. anticoagulants

c. dextrans

d. antibiotics → vit K deficiency, platelet defect

• local defence mechanisms include,

a. the mucus barrier

b. surfactants & HCO_3^- - secreted by mucosal cells

c. H^+ reabsorbed by the mucosa is neutralised by blood derived HCO_3^- and washed away by rich mucosal blood flow

• ***shock states*** result in,

a. mucosal ischaemia
   - ***TNF*** results in thrombosis within gastric mucosal vessels
   - sympathetic redistribution of blood flow away from the splanchnic bed

b. H^+ / pepsin / bile seep in and damage intracellular components

c. mucosal necrosis → ulcer formation

• ***pepsin*** is still active unless pH > 7

1. pH ~ 5-7 → pepsin still ***dissolves*** clot, and
2. pH < 5.4 → pepsin ***prevents clot formation***

NB: but alkaline gastric contents are ***not*** necessary for prevention, and there is ***no evidence*** that hypersecretion *per se* is responsible for erosions

• ***intracellular pH*** is probably more important than intra-gastric pH
• ***prostaglandins*** result in,

a. ↑ blood flow

b. ↑ mucus production, and ? mucus secretion

c. ↓ ulcer incidence and promotion of healing

• ***bile salt*** disruption of the mucosal barrier occurs, and prevention of duodenal reflux is associated with a significant reduction in gastric ulceration

Acid/Pepsin Production ***reduced*** by	Mucosal Resistance ***increased*** by
• enteral feeds • prostaglandins • antacids • H_2 blockers	• enteral feeds • ? prostaglandins • sucralfate

- ***Prevention***

a. treat stress factors → improve gut O_2 delivery
   - normovolaemia, adequate O_2 / ventilation
   - maximise cardiac output & GIT perfusion pressure

b. NG feeds ASAP
   - especially high risk groups
     - head injury, major trauma, burns
     - prolonged IPPV
     - renal failure, hepatic failure
     - sepsis

c. sucralfate | H_2-blockers where
   - NG aspiration of blood / "coffee grounds"
   - no NGT and "at risk"
   - previous peptic ulcer disease

d. omeprazole
   - clinical bleed on H_2-blockers
   - endoscopically proven ulceration not healing with H_2-blockers

- ***Treatment: Mild Bleed***

a. maximise coagulation status / remove precipitants
   i. vit K
   ii. stop heparin, NSAID's etc
   iii. blood transfusion, FFP, platelets etc
   iv. DDAVP for patients on aspirin, or with liver or renal failure

b. antacids - pH > 3.5 (ideally > 7)

c. sucralfate

d. H_2-blockers
   - cimetidine, ***ranitidine*** and famotidine are ***competitive*** antagonists
   - ↑ GI gram negative colonisation ***does not*** increase nosocomial pneumonia ??

e. ***omeprazole***
   - absorbed in SI, short plasma $t_{½\beta}$ but effective for 24 hrs
   - binds ***irreversibly*** to fundic parietal cell H^+/K^+-ATPase
   - 20 mg → 65% inhibition at 4-6 hrs
     25% inhibition at 24 hrs
   - 40 mg → 100% inhibition of mean 24 hr gastric acid secretion
   - results in ***hypergastrinaemia*** & potential enterochromafin hyperplasia

f. prostaglandins - $PGE_{1\text{-}2\text{-}3}$

g. ***aminocaproic acid*** - 5g stat & 1 g/hr for 24 hrs IV
   - ~ 20-30% reduction in rebleeding
   - ~ 40% reduction in mortality

h. ***endoscopy*** for assessment

NB: if ***major bleed*** then proceed with,

1. octreotide infusion ~ 100 µg stat, then 12.5-25 µg/hr
   - some data now to say 50 µg stat, then 50 µg/hr equally effective to ***sclerotherapy***
2. pitressin infusion *questionable benefit
3. endoscopic haemostasis - laser coagulation, electrocoagulation
   *questionable benefit in stress ulceration
4. surgery
   - partial or total gastrectomy in the setting of uncontrolled GI haemorrhage

   → ***mortality*** **~ 70%**

▪ ***Cushing's Ulcer***

- lesions in the oesophagus, stomach & duodenum, initially described by Cushing in association with ***coma*** from any cause
- now accepted as acute peptic ulceration in association with severe ***head injury*** and raised ICP
- results from increased vagally mediated gastric acid secretion & responds to H_2-blockade

▪ ***Curling's Ulcer***

- circumscribed (≤ 2 cm) duodenal ulcer in patients with ≥ 35% ***burns***
- also results from gastric acid hypersecretion & responds to H_2-blockade

Ulcer Prophylaxis

- early 1970's R_X → hourly gastric pH, plus mylanta 30 ml/hr to keep pH > 5
- this resulted in a large reduction in GIT bleeding
- problems with high dose Mylanta included,

1. diarrhoea / constipation
2. electrolyte abnormalities → hypo-$PO_4^{=}$
   hyper-Mg^{++} / hyper-Al^{-}
3. ↓ drug absorption
4. bowel obstruction

- following the introduction of H_2-blockers, R_X →

1. hourly gastric pH
2. if pH < 5 add antacids

- problems of H_2-blockers (***cimetidine***),

1. CNS side effects
2. drug interactions - P_{450} inhibition
3. thrombocytopaenia, leukopaenia
4. bradycardia, hypotension
5. jaundice, renal failure
6. GIT side effects
7. rash / fever
8. endocrine effects

NB: cimetidine >> ranitidine, famotidine

- very few proper studies comparing the efficacy of ***antacids*** vs ***H_2 blockers***
- faecal occult blood test useless,

a. cimetidine → false (+)'ve
b. antacids → false (-)'ve

- problems of antacids and H_2 blockers,

1. diarrhoea
2. drug interactions
3. microaspiration ? gram (-)'ve pneumonia
4. sepsis

■ ***Sucralfate***

• Sucrose-Al(OH_3)-sulphate, with added H^+ → paste formation which results in,

a. coating of cells

b. ↓ ***back-diffusion*** of H^+

c. ↑ ***prostaglandin*** secretion

• therefore, must avoid simultaneous use of antacids and ***H_2-blockers***
• ***problems*** of Sucralfate include,

1. blockage of NG tube
2. nausea, vomiting, constipation - rarely obstruction with high dose
3. hypo-$PO_4^=$ and increase Al^-
4. prevents drug absorption
5. overt bleeding - same incidence as antacids and H_2-blockers
6. nosocomial pneumonia - cf H_2 blockers
   i. German → 10% vs 34%
   ii. Boston → 9% vs 23%

NB: ***enteral feeds*** partially buffer gastric acid, the increased energy supply to the mucosa improves defences, ∴ sucralfate is not necessary

■ ***Cook et al. JAMA 1996***

• ***metanalysis*** of 63 PRCT's assessing efficacy of sucralfate, H_2-antagonists and antacids in the ***prevention*** of,

1. overt bleeding
   - H_2-antagonists → significant ↓ cf. placebo | no therapy | antacids
   - sucralfate → significant ↓ cf. no therapy
   - ***no evidence*** for differential efficacy of sucralfate versus antacids | H_2-antagonists
2. clinically significant bleeding
   - H_2-antagonists → significant ↓ cf. placebo | no therapy
   - sucralfate no difference from antacids | H_2-antagonists
3. pneumonia *diagnostic criteria variable & suspect
   - sucralfate was associated with a ***trend*** toward lower incidence cf. H_2-antagonists
4. mortality
   - ***sucralfate*** was associated with ***reduced mortality*** cf. antacids | H_2-antagonists
   - OR = 0.73 (CI: 0.54-0.97)

Peptic Ulceration

▪ ***Duodenal Ulceration***

• 95% occur in 1st part
• chronic and recurrent disease
• approximately 2x the normal ***parietal cell*** mass & secrete ≤ 40 mmol/hr of H^+
• seen with increased frequency in,

a. smoking
b. NSAID use
c. chronic renal failure / renal transplantation
d. alcoholic cirrhosis
e. hyperparathyroidism
f. COPD

• *Helicobacter pylori* (GN spiral bacterium) produces a ***urease***, which splits urea producing ***ammonia*** which neutralises H^+ in the stomach, blocking the negative feedback on the antral production of ***gastrin***
• colonisation has been reported in up to 100% of DU patients

• all H_2-blocking agents are equally efficacious,

a. 75% healed at 4 weeks
b. 90% at 8 weeks
c. high 12 month recurrence rate → ~ 33% without symptoms
d. ∴all should receive 12 months maintenance therapy - 150 mg ranitidine nocte

• ***omeprazole*** 20 mg/day is efficacious in 5-10% of DU patients not responsive to H_2-blockers
• if not healed at 8 weeks, then 2-4 weeks of omeprazole 40 mg/day
• while more efficacious, omeprazole induced ***hypergastrinaemia*** results in

1. hypertrophy of enterochromafin-like cells
2. carcinoid tumours in animals

• levels of gastrin are generally less than those found in ***pernicious anaemia***
• however, therapy is generally limited to 4-8 weeks, followed by maintenance ranitidine

• ***pirenzipine*** is a selective M_1-antagonist → ↓ acid secretion ~ 50-60%
• minimal anticholinergic side-effects (blurred vision, dry mouth, constipation, urinary retention)
• equally effective to H_2-blockers in healing, but slower resolution of ulcer pain

• ***sucralfate*** shows similar rates of ulcer healing to H_2-blockers

- ***colloidal bismuth subcitrate*** promotes healing as a cytoprotective agent, cf sucralfate
- also inhibits *H. pylori* and has a lesser relapse rate cf. H_2-blockers & sucralfate

- ***surgery*** is indicate for,

    1. patients > 60 years of age
    2. bleeding ulcer not controlled by medical therapy

    NB: truncal vagotomy & oversew of ulcer ± pyloroplasty

Gastric Ulceration

- peak incidence ~ 60 years, cf. DU at 40-50 years
- requires endoscopy & ***biopsy*** to exclude carcinoma
- other therapy is cf. DU

Oesophageal Varices

- systemic / splanchnic anastomoses occur at,
    1. gastro-oesophageal junction
    2. retroperitoneal space, between kidneys & spleen
    3. mesenteric / gonadal veins
    4. diaphragm
    5. umbilicus
    6. rectum

- portal venous pressure,
    a. normal ~ 5-10 mmHg
    b. ***portal hypertension*** > 12 mmHg
    c. bleeding varices ~ 12-40 mmHg

- of patients with ***cirrhosis***,
    a. 60% develop oesophageal varices
    b. 66% of these bleed → **~ 40%** of cirrhotics develop bleeding varices

- ***Poor Prognostic Factors***

    a. severity of liver disease ≥ Child's grade C
    - ascites, encephalopathy

    b. severity of haemorrhage ≥ 2000 ml, or ≥ 5^{U} transfusion
    - continuing / recurrent haemorrhage

    c. age > 60

    d. associated disease - IHD, respiratory or renal disease
    - coagulopathy
    - malignancy

- ***Treatment Aims***

    1. resuscitation
    2. control of haemorrhage
    3. prevention of encephalopathy
    4. correction of complications

- ***Therapy Options***

a. endoscopic ***variceal sclerosis***
- R_X of choice for acute haemorrhage and control of rebleeding
- greater efficacy **~ 80-90% *control*** of haemorrhage
  cf. ~ 60% for balloon tamponade
- better survival ~ 84% at 6 months
  cf. ~ 45% for balloon tamponade
- gastric varices also regress following eradication of oesophageal varices
- ***prophylactic*** sclerotherapy, in those who have not bled,
  is of ***no value*** and is associated with ***increased mortality***
- complications - retrosternal pain, strictures, dysphagia
  - fever, bacteraemia, mediastinitis, empyema
  - aspiration, pneumonia, ARDS

b. variceal banding
- some suggest more effective than sclerotherapy, ∴ procedure of choice if experienced operator

c. Vasopressin - 0.2-0.8 U/min
- reduces portal pressure and temporary control of bleeding
- efficacy → $\equiv^T$ placebo ~ 30-50% controlled
- ± GTN for systemic effects ~ 20% side effects, 3% mortality
  - hypertension, coronary & bowel ischaemia
  - diarrhoea, colic

d. ***Somatostatin*** - 250-500 µg/hr
- controlled trial vs vasopressin showed ***more effective*** & less complications Jenkins *et al.* BMJ 1985
- no trials with ***octreotide*** (12.5-25 µg/hr) but probably equally effective

e. ***balloon tamponade*** ~ 80-90% control of haemorrhage
→ but **50% *rebleed***
- reserved for acute haemorrhage not controlled by sclerotherapy

i. Linton-Nachlas - single gastric lumen

ii. Sengstaken-Blakemore - oesophageal & gastric balloons, gastric suction

iii. ***Minnesota*** - 4 lumens, 2 balloons, gastric & oesophageal suction
- intubate if required, tube may be inserted nasally or orally to 60 cm
- inflate gastric balloon with 250-500 ml of air & apply traction (≤ 1kg)
- seldom necessary to inflate oesophageal balloon if gastric correctly placed
- continuously aspirate stomach to assess bleeding control
- if required, inflate oesophageal balloon with air to a pressure ≤ 40 mmHg
- check position on CXR

f. TIPS transjugular intrahepatic porta-systemic shunt
- successful in reducing portal presssure → < 12 mmHg
- likely to become procedure of choice, irrespective of patient's Child's classification

g. porta-systemic shunt ~ **90%** control
~ 20-40% mortality
- 4 RCT's showing PSS reduces rebleeding, but ***no decrease*** long-term ***mortality***
- high incidence ***encephalopathy***

h. distal / selective shunts - spleno-renal (Warren)
- effectively divides the splanchnic circulation into portomesenteric and gastrosplenic
- incidence of post-shunt encephalopathy is greatly reduced
- does not prevent later liver transplantation
- ***no difference*** in mortality cf central shunts

i. transhepatic embolisation

j. oesophageal transection

k. orthoptic liver transplantation

- ***Current Recommendations***

1. resuscitate
2. early endoscopy, if ongoing bleeding, then
   i. Minnesota tube ~ 150-200 ml air in gastric balloon
   ~ 0.75-1.0 kg traction
   ± 30-40 mmHg in oesophageal balloon
   ii. variceal sclerosant ± variceal banding
3. octreotide infusion
4. TIPS

- β-blockade in ***contraindicated*** in the acutely bleeding patient
- however, does reduce portal pressure and rebleeding once bleeding is controlled

HEPATIC DISORDERS

▪ *Functional Anatomy*

1. hepatic lobule - central hepatic venule | sinusoids | peripheral portal triad
   - traditional unit
2. ***hepatic acinus***
   - i. zone 1 - portal vein & hepatic artery supplying sinusoids
   - ii. zone 2 - follows sequentially
   - iii. zone 3 - drains to hepatic venule
   - arrangement produces gradient of all nutrients, etc from zone 1 to 3
   - zone 3 is most susceptible to ***hypoxic injury***
3. blood flow ~ 1500 ml/min
   - i. hepatic artery ~ 33% of flow & ~ 60% of DO_2
   - ii. portal vein ~ 66% of flow & ~ 40% of DO_2

▪ *Liver Functions*

1. ***bile production*** ~ 500 ml/day secreted
   → - fat digestion & excretion of drugs, toxins and bilirubin
   - bile salts, lecithen, cholesterol, bilirubin & electrolytes
   - i. bile salts
     - Na^+/K^+-salts of cholic & chenodeoxycholic acids
     - ~ 95% reabsorbed in terminal ileum
     - daily synthesis ~ 0.2-0.4g of total pool of ~ 3.5g
     - absence results in ~ 25% fat malabsorption & ADEK deficiency
   - ii. bilirubin
     - ~ 7.5g of Hb are catabolised per day → 250 mg (440µmol)/day
     - ~ 80% old RBCs, remainder from young RBCs, myoglobin, enzymes
     - liver capacity ~ 15g Hb/day
     - conjugated in microsomes in 2-step process
     - normal excretion → ~ 85% diglucuronide / 15% glucuronide
       - energy dependent and ***rate limiting*** step
2. ***protein synthesis***
   - albumin, some globulins
   - coagulation & fibrinolytic factors
   - prekallikrein, kininogen
   - serum proenzymes / enzymes
   - carrier proteins
   - ***acute phase reactants*** - C-reactive protein, complement, coagulation
     - haptoglobins, plasminogen
     - α_1-antitrypsin, α_2-macroglobulin, caeruloplasmin

3. ***CHO and intermediary metabolism***
   - i. amino acids - protein synthesis
     - gluconeogenesis
     - transamination
   - ii. glucose - production and storage
     - conversion to fat, AA's
     - glucuronidation
     - energy source
     - NADPH production
   - iii. fat - metabolism
     - lipoprotein for transport
     - cholesterol, ketones
4. ***hormone synthesis & metabolism***
5. ***biotransformation***
   - i. ammonia & ***urea cycle***
   - ii. drugs & toxins
6. ***storage***
   - i. glycogen ~ 80-100g
   - ii. fat ≤ hepatic weight
   - iii. Fe^{++}, B_{12}, folate, Cu
7. ***immune defence*** - against agents entering the portal circulation

Post-operative Jaundice *Aetiology*

a. ***increased bilirubin load***
   - i. haemolysis
   - ii. haematoma - reabsorption
   - iii. transfusion - old cells, incompatibility, sepsis

b. ***hepatocellular dysfunction***
   - i. congenital
     - Gilbert's disease - ***ligandin*** deficiency → ↓ uptake
     - Crigler-Najjar Type I & II - low or absent ***glucuronyl transferase***
     - Rotor's & Dubin-Johnson - low biliary excretion
   - ii. acquired **see hepatitis*
     - hepatitis - hypoxia/ischaemia, infective, sepsis, drugs, trauma, etc
     - cholestasis - hypoxia/ischaemia, drug-induced, TPN, pregnancy

c. ***obstructive***
   - i. bile duct trauma, oedema, ligation
   - ii. cholangitis
   - iii. cholelithiasis

Hyperbilirubinaemia

- ***Predominantly Unconjugated***

1. ***overproduction***
   - i. haemolysis
   - ii. reabsorption of haematoma
   - iii. ineffective erythropoeisis
2. decreased hepatic ***uptake***
   - i. sepsis
   - ii. prolonged fasting
   - iii. RV failure
   - iv. drugs - rifampicin, probenecid
3. decreased ***conjugation***
   - i. hepatocellular disease - hepatitis, cirrhosis
   - ii. sepsis
   - iii. drugs - chloramphenicol
   - iv. inherited glucuronyl transferase deficiency
     - Gilbert's syndrome - actually ***ligandin*** deficiency
     - Crigler-Najjar - types II & I

- ***Predominantly Conjugated***

1. impaired hepatic ***excretion***
   - i. sepsis
   - ii. post-operative state
   - iii. hepatocellular disease
     - hepatitis - viral, ischaemic, drug-induced
     - cirrhosis
   - iv. drug-induced cholestasis - OCP, methyltestosterone
   - v. inherited disorders - Dubin-Johnson, Rotor syndrome
     - benign familial recurrent cholestasis
   - vi. cholestasis of pregnancy
2. biliary ***obstruction***
   - i. biliary cirrhosis - primary | secondary
   - ii. sclerosing cholangitis
   - iii. extrahepatic obstruction - stone, tumour, stricture

Intrahepatic Cholestasis

Def'n: severe form ~ "ICU liver"
mild form ~ "benign postoperative intrahepatic cholestasis"

- common after major, abdominal, or emergency surgery
- especially if associated with ***hypotension & hypoxia***

- ***Pathogenesis***

a. liver hypoxia / ischaemia
b. sepsis
c. inflammatory mediators - endotoxin, TNF, IL-1, free radicals
d. ↑ bilirubin load - haematoma, transfusion
e. TPN induced hepatic ***steatosis***
f. ↓ renal excretion
g. drugs
   - flucloxacillin, rifampicin, erythromycin estolate
   - chlorpromazine, phenytoin, carbamazepine, valproate
   - steroids, OCP

- ***hyperbilirubinaemia*** (≥ 100 µmol/l) disproportionate to enzyme levels, common at 2-14th day
- usually > 80% ***conjugated*** and may rise as high as 600 µmol/l
- mild ALP elevation 3-10x increase → "obstructive jaundice" pattern (ie. biliary stasis)
- this is often delayed 5-10 days after the rise in bilirubin
- mild increase in AST/ALT
- prolonged form also has severe ***hypoalbuminaemia*** → INR ≥ 1.4
- associated reduction in protein synthesis, reduced AA clearance, & low redox potential
- differential diagnosis,

1. acalculous cholecystitis
2. calculous colecystitis
3. hepatic abscess
4. drug induced cholestasis

Liver Function Tests

1. albumin
   - spectophotometric absorption of bromocresol green at pH = 4.2
   - BCG also bound to acute phase reactants, ∴ Alb actefactually elevated (up to 10g/l)
   - ~ 50% resides in intravascular space
2. globulins
   - usually not measured, but calculated from total protein - albumin
   - increases either,

   i. polyclonal - cirrhosis, infection, autoimmune diseases

   ii. monoclonal - myeloma, lymphomas
   - decreased with malignancy, malnutrition, plasmapheresis
3. gamma-glutamyl transferase
   - resides in cells of the bile canaliculi, responsible for AA transport
   - also present in the pancreas and brush border of renal tubules
   - ***nonspecific*** indicator of hepatic dysfunction
   - levels usually highest with ***obstructive*** disorders
   - most common causes for elevation - chronic ethanol abuse
     - antieplieptic medication
4. alkaline phosphatase
   - originates from liver, bone, placenta, and intestine (? brain)
   - occasionally from malignancies - indistinguishable from placental isoenzyme
   - normal plasma ALP ~ 80% liver / 20% GIT
   - in children/adolescents, major source is growing bone (osteoblasts)
   - resides on luminal surface of bile canalicular cells
   - elevated in obstructive/cholestatic disorders
   - however ~ 20% of patients with a cholestatic disorder → < 250 IU/l

   i. hepatic - cholestatic disorders

   ii. bone - physiological
     - Paget's disease
     - recent fracture(s)
     - carcinoma, primary / secondary
     - hyperparathyroidism, 1°, 2°, 3°
     - osteomalacia, 2° calcium/phosphorus deficiency
       → Vit.D, malabsorption, RTA

   iii. placenta - 3rd trimester pregnancy

5. lactic acid dehydrogenase
   - exists as 5 isoenzymes - LDH_{1-2} → haemolysis, myocardial damage
     - LDH_{3-4-5} → hepatic, skeletal muscle
   - also produced by lung (LDH_{2-3}) and kidney (LDH_{1-2}) but these are rare causes
   - normal LDH_1:LDH_2 < 1 → > 1 in - myocardial infarction
     - renal infarction
     - haemolysis
6. transaminases
   i. aspartate amino-transferase
      - AST, cytosolic & mitochondrial - also called SGOT
      - liver, kidney, cardiac & skeletal muscle

   ii. alanine amino-transferase
      - ALT, cytosolic - also called SGPT
      - predominantly liver, some skeletal m., brain & pancreas
   - both elevated in hepatocellular disorders **see hepatitis*
   - degree of elevation ***does not*** correlate well with the degree of liver damage
     → ie. they have no predictive value
   - infective / toxic hepatitis → ↑ lasting weeks
     → ↑ AST:ALT ~ 1.5:1
   - ischaemic hepatitis → ↑ lasting days
     → ↑ AST:ALT ~ 1.5:1
   - alcoholic hepatitis → ↑ AST:ALT > 2:1 (rarely > 500 IU/l)
   - false lowering of the AST may occur with azotaemia
7. prothrombin
8. ammonia < 30 mmol/l normal
   - absolute elevation correlates poorly with encephalopathy, but may be used as a guide to therapy response in an individual patient
9. ***urobilinogen***
   - formed by intestinal bacteria acting on conjugated bilirubin
   - 80% excreted in feces, 20% reabsorbed in terminal ileum
   - 90% of reabsorbed urobilinogen re-excreted in bile, 10% → urine (~ 2%)
   - complete absence in urine suggests absence of intestinal bilirubin & obstruction
   - ↑ urinary urobilinogen - liver in unable to excrete absorbed urobilinogen
     - increased excretion of bilirubin, haemolysis
10. urinary bilirubin
    - normally absent
    - excretion occurs in conjugated hyperbilirubinaemia

Liver Function Tests		
Test	Hepatocellular injury	Obstruction
Aspartate transaminase[1] **AST** / SGOT Alanine transaminase **ALT** / SGPT	↑ to ↑↑↑	↑
Alkaline Phosphatase[2] **ALP**	↑	↑↑↑
Gamma-glutamyl transpeptidase **GGT**	N to ↑↑↑	↑↑↑
5-Nucleotidase	N to ↑	↑ to ↑↑↑
Albumin	↓ to ↓↓↓	N
Prothrombin time	↑ to ↑↑↑[3]	N to ↑[4]
Bilirubin	N to ↑↑↑	N to ↑↑↑

[1] **AST** also in heart, rbc's, muscle **ALT** is more specific for liver,
enzyme rise reflects extent & acuteness of cellular injury, but ***does not*** correlate with ***prognosis***

[2] origins of **ALP** include: liver, bone, intestine, placenta & lung

[3] increase does have worse ***prognosis***
shorter half-life & more rapid change cf. albumin

[4] correctable with vitamin K

- ***Sequelae of Liver Dysfunction***

a.	hypoalbuminaemia	- low COP, increased tendency to ***oedema*** formation
b.	coagulopathy	- ↓ vit K dependent factors * may bleed or have thromboses
c.	septicaemia	- immune dysfunction
d.	toxaemia	- metabolites, bacteria, toxins
e.	amino-acid imbalance	- low branched-chain / high aromatic
f.	drugs	- altered pharmacodynamics & kinetics, ↑ $t_{½\beta}$
g.	hyperammonia	- not cleared
h.	severe ***hypoglycaemia***	- impaired glucose & AA metabolism
i.	citrate toxicity	- impaired metabolism with large volume transfusions - especially the anhepatic phase of transplantation - R_X $CaCl_2$

Hepatitis

1. ***infective*** - Hepatitis A, B, C, Delta, E, NANBNC
   - EBV, CMV, HSV, Coxsackie, Yellow fever
2. ***drugs***
   - i. cholestasis
     - alcohol
     - chlorpromazine, chloramphenicol, chlorpropamide
     - tetracyclines, erythromycin, rifampicin
     - oestrogens, OCP, androgens
   - ii. hepatitis
     - α-methyl-dopa → 5% abnormal LFT's; 1% hepatitis; 0.15% CAH
     - paracetamol, phenytoin, isoniazid, rifampicin
     - ***halothane***, enflurane, & ? isoflurane
3. ***toxins***
   - CCl_4, vinyl chloride, chloroform
   - *Amanita phalloides* (mushroom)
4. ***cardiovascular***
   - i. ischaemic
     - hypovolaemic shock, ischaemia
   - ii. congestive
     - cor pulmonale, RV failure, CCF
     - Budd-Chiari syndrome
5. ***metabolic***
   - alcohol
   - parenteral nutrition
   - Wilson's disease (hepatolenticular degeneration)
   - Haemochromatosis
   - α_1-antitrypsin deficiency
6. ***autoimmune***
   - chronic active hepatitis
   - drug induced
   - vasculitis, SLE, UC, PN
   - 1° biliary cirrhosis
7. pregnancy
   - acute fatty liver of pregnancy
8. hyperthermia

▪ *Ischaemic Hepatitis*

• centrilobular necrosis (acinar zone 3) secondary to liver ischaemia, hypotension, hypoxia, sepsis, MODS, pancreatitis, etc.

a. mild to moderate hyperbilirubinaemia

b. ↑ liver enzymes → ratio **AST:ALT < 1.5:1**
   - cf. ETOH hepatitis, AST:ALT > 2:1
   - often rapid rise to high levels (10x) followed by dramatic fall with recovery

NB: DD_X viral hepatitis (Hepatitis A/B/C, CMV, EBV)
drug induced hepatitis

Hepatitis C Infection

- positive stranded RNA virus of classified within the *Flaviviridae* family (heterogeneous group)
- the most widely used nomenclature comprises ***six*** major genetic groups and a number of recognised subtypes that are more closely related
- numbered from 1 and the subtypes a, b, and c in order of discovery
- possibility that different genotypes may respond differently to ***interferon alfa***

▪ ***Diagnosis***

- no tests for HCV-Ag
- diagnosed by HCV-Ab based immunoassay
- HCV-IgM antibody doesn't differentiate persistent viraemia from an episode of resolved viraemia
- supplemental tests → recombinant immunoblot assay
- confirmatory tests are invariably positive in HCV-Ab positive patients with chronic hepatitis

a. serum ALT

b. HCV antibody tests

c. HCV RNA, genotypes, and HCV RNA concentrations

- infection is usually monitored by serum ALT, but nonspecific
- young patients without evidence of cirrhosis have a generally indolent course of the infection
- with development of ***cirrhosis*** → frequently complicated course
- older patients may present with complications of cirrhosis or ***hepatocellular carcinoma***

- there is evidence that ***alcohol*** and HCV may synergistically aggravate hepatic injury
- there are ***no vaccines*** available
- sexual transmission has been described but is a comparatively infrequent
- mother to infant transmission of HCV has been recorded but seems to be unusual
- transmission of HCV from infected surgeons to patients has been verified by molecular epidemiological evidence

- ***Interferon Alfa***

1. acute HCV
   - acute icteric HCV has become comparatively rare
   - HCV infection is clinically mild and ***subclinical*** disease is common
   - only 25% of cases are icteric, and the peak serum ALT activities are less than those in acute hepatitis A or B
   - the mean incubation period of HCV is 6-12 weeks
   - diagnosis in these cases requires confirmation by HCV RNA testing
   - severe or fulminant HCV is rare but may occur, especially in immunosuppressed
2. chronic HCV
   i. advantages
      - inhibits HCV replication in some patients with chronic disease
      - sustained response in some patients
      - important component of combined antiviral treatment
      - can improve histological hepatitis

   ii. disadvantages
      - given by injection
      - low sustained response rates in many patients with type 1 hepatitis and higher levels of viraemia
      - high relapse rates
      - side effects
      - neutralising antibodies in some patients
      - relative expense
3. ***ribavirin*** and combination antiviral therapy

- several therapeutic trials of interferon alfa for acute HCV have been completed
- most indicate that amelioration of the severity of the chronic hepatitis lesion or even a reduction in the rate of chronic disease is possible with at least ***six months*** of treatment

- require HCV confirmation and exclusion of other causes $\rightarrow$ $\uparrow$ ALT,

a. obesity
b. alcoholism, drug induced hepatotoxicity
c. biliary tract disease
d. ***autoimmune hepatitis*** *treated differently, $\therefore$ test autoantibodies
   - dividing line between this and chronic HCV is not always clear
   - a high proportion of HCV patients have low titres of anti-Sm & ANA

e. thyroid disease must be excluded $\rightarrow$ $T_{3/4}$, TSH, and antithyroid antibodies
f. inborn errors of metabolism

- ***Side Effects of Interferon Alfa***

1. early
   i. flu-like illness, chills, fever, malaise, muscle aches, headache
   ii. poor appetite
2. later - common
   i. weight loss
   ii. increased need for sleep
   iii. psychological side effects - irritability, anxiety, depression
   iv. hair loss
   v. thrombocytopenia,leucopenia
3. unusual or severe
   i. seizures
   ii. acute psychosis
   iii. bacterial infections
   iv. autoimmune reactions
   v. hyperthyroidism or hypothyroidism or transient thyroiditis
4. rare
   i. proteinuria
   ii. myocardiopathy
   iii. rashes
   iv. interstitial lung disease
   v. retinal changes
   vi. ototoxicity

- ***Summary Points***

1. the natural course of chronic HCV is not fully defined
2. a range of disease exists
   - from mild asymptomatic infection to serious disease with dire sequelae
3. assessment of viral load and genotype/serotype may help in predicting response
4. difficult to indicate the prognosis for younger patients with mild disease
   - they may need to be considered for treatment, so that the opportunity to avoid later disease is not forfeited
5. it is not yet clear whether patients who are more responsive to interferon have a better prognosis

HEPATIC FAILURE

Def'n: ***fulminant hepatic failure***, is a clinical syndrome resulting from massive hepatic necrosis, in an individual with previously normal liver function, characterised by,

1. severe progressive ***encephalopathy***
2. ***jaundice***, hepatic foetor, asterixis
3. ***hypotension***, tachycardia, oliguria
4. coagulopathy, hypoglycaemia
5. high mortality ~ 80% with grade 4 coma

- ***Classification King's***

1.	hyperacute	- encephalopathy within ***7 days*** of the onset of jaundice
2.	acute hepatic failure	- 8-28 days from jaundice to encephalopathy
3.	subacute hepatic failure	- 29-72 days from jaundice to encephalopathy

- ***Causes***

a.	viral hepatitis*	- Hepatitis A, B, C, D, E - CMV, EBV, HSV, ? HIV - yellow fever virus, echovirus
b.	drugs	- paracetamol* - anti-TB drugs, rifampicin, isoniazid - MAOI, α-methyl dopa - halothane ± enflurane
c.	chemicals	- carbon tetrachloride, vinyl chloride - hydrocarbons, chloroform, phosphorus - mushroom poisoning (*Amanita*)
d.	acute steatosis syndromes	- fatty liver of pregnancy - tetracyclines - Reye's syndrome
e.	ischaemic liver necrosis	- Budd-Chiari, CCF - hypoxia, shock, sepsis syndrome, MODS*
f.	massive infiltration	- lymphorecticular tumours | acute leukaemia - transplant rejection

NB: ****commonest causes***

note differences cf. chronic liver failure / cirrhosis later

- ***Acute-on-Chronic Liver Disease***

a. alcoholic cirrhosis
b. primary biliary cirrhosis
c. chronic active hepatitis
d. chronic persistent hepatitis
e. Wilson's disease
f. haemochromatosis
g. α_1-antitrypsin deficiency

Child's Classification[1]
Severity of Chronic Liver Disease

Class	A	B	C
• albumin	> 35 g/l	> 30 g/l	< 30 g/l
• total bilirubin	< 35 µmol/l	35-60 µmol/l	> 60 µmol/l
• ascites	absent	controlled	uncontrolled
• encephalopathy	absent	absent	present
• nutrition	good	fair	poor
surgical risk	**5%**	**10%**	**50%**
prothrombin time[2]	+ 1 1-4 s	+ 2 4-6 s	+ 3 > 6 s

[1] Child *et al.* 1964 surgical cohort undergoing ***portasystemic shunting***

[2] Pugh *et al.* 1973 increased risk for ***each*** group, according to ↑ PT

- ***Prognostic Factors***

1. age
2. severity of 1° illness
3. underlying cause
4. complications
   i. sepsis
   ii. cerebral oedema
   iii. renal failure
   iv. ARDS
5. duration and severity of ***coma***

- ***Shellman CCM 1988***

1.	Child's classification	- severity
2.	mechanical ventilation	- respiratory failure
3.	high creatinine	- renal failure
4.	other significant factors	- coagulopathy - hypo/hyper-Na^+ - sepsis

- Bihari, 1987, ***tissue hypoxia*** important
- Gazzard, 1975, causes of death,

a.	neurological (***cerebral oedema***)	**~ 67%**
b.	GIT haemorrhage	~ 13%
c.	haemodynamic (shock)	~ 8%
d.	respiratory failure	
e.	renal failure	

Organ System Involvement

- ***Liver***

a.	hypoalbuminaemia	- low COP, increased tendency to oedema formation
b.	coagulopathy	- ↓ vit K dependent factors
c.	septicaemia	- immune dysfunction
d.	toxaemia	- metabolites, bacteria, toxins
e.	amino-acid imbalance	- low branched-chain / high aromatic
f.	drugs	- prolonged effect
g.	hyperammonia	- not cleared
h.	severe ***hypoglycaemia***	- impaired glucose metabolism

- ***Central Nervous System***

Def'n: ***hepatic encephalopathy:*** a neuropsychiatric syndrome in a patient with advanced liver disease or porta-systemic shunting, characterised by,

1. early frontal area impairment (behaviour/motor/sensory) with ***brainstem sparing***
2. followed by varying degrees of ***coma***, with brainstem dysfunction resulting in
   i. respiratory failure
   ii. vasomotor imbalance - vasodilatation, arrhythmias
3. Wernicke-Korsakoff syndrome
4. ↑ muscle tone early
5. very high sensitivity to - sedatives, narcotics, general anaesthetics
6. EEG
   - slowing of rhythm
   - low frequency theta rhythm
   - high amplitude delta waves (deep coma)
7. ***asterixis***
   - flapping tremor usually found in grade 2-3 coma
   - nonspecific finding, also seen in
     - hypercarbia, hypokalaemia
     - severe CCF, polycythaemia
8. ***cerebral oedema*** often without clinical or CT signs
   - NB: CT is ***unreliable*** for diagnosis, ∴ require pressure monitoring
   - predominantly ***cytotoxic*** and responds to mannitol & STP
   - recent work suggests also a vasogenic component 2° endothelial dysfunction

- ***Renal / Electrolytes***

NB: hyponatraemia, hypokalaemia,
hypophosphataemia, hypomagnesaemia & hypoglycaemia

a. 2° hyperaldosteronism - hypokalaemia
* ***hypo***natraemia cf. expected hypernatraemia

b. renal failure - hypotension / hypovolaemia, haemorrhage
- sepsis
- hepatorenal syndrome

c. respiratory alkalosis - central hyperventilation

d. later metabolic alkalosis - renal 2° aldosterone, vomiting

e. metabolic acidosis with hypoxia, hypoglycaemia

- ***Respiratory System***

a. foetor hepaticus ∝ ***methylmercaptan*** and present in all grades of coma

b. central hyperventilation → respiratory alkalosis

c. vasodilatation / ↓ HPV → ↑ ***shunt fraction*** & hypoxaemia / cyanosis

d. aspiration, infection

e. intra-abdominal hypertension due to ascites
   i. ↓ chest wall compliance
   ii. ↓ FRC / TV
   iii. may result in pleural effusion

f. central respiratory failure occurs late

g. rarely ***hepatopulmonary syndrome***

- ***Cardiovascular System***

a. initially high cardiac output with ***peripheral vasodilatation***

b. central ***vasomotor depression*** *low HR, CO and SVR

c. arrhythmias - hypo-K^+, hypoxia
- cerebral oedema

- ***Coagulation Disorders***

  a. fall in production of coagulation factors
     i. ***VII*** - shortest $t_{½}$ ~
     ii. vit K dependent factors - II, VII, IX, X
     iii. low ***factor* V** implies liver impairment ***other*** than vit K lack
     iv. fibrinogen falls last * ↓ FI → probably DIC
  b. also fall in coagulation inhibitors - protein C & S
  c. ***DIC*** is usually secondary to sepsis, severe hypovolaemia and rarely to the liver failure

- ***Gastrointestinal Tract***

  a. gastric erosions ~ 50%
  b. oesophageal, gastric or duodenal haemorrhage
  c. bacterial breakdown of protein → ↑ encephalopathy
  d. enteric bacteria are (? maybe) a source of septicaemia
  e. spontaneous bacterial peritonitis

- ***Reticuloendothelial***

  a. pneumonia
  b. spontaneous gram negative septicaemia
  c. often associated with hypothermia, low WCC, hypodynamic circulation

Treatment Principles

a. remove precipitating cause where possible
b. manage / prevent infection
c. manage / prevent respiratory failure
d. normalise vasomotor instability
e. maintain urine output * central hypovolaemia / arterial underfilling
f. minimise and treat cerebral oedema
g. prevent hypoglycaemia
h. identify high risk patients early → liver transplantation

- ***Treatment Hepatic Encephalopathy***

a. minimise protein load
   i. dietary protein restriction
   ii. avoid GIT bleeding
   iii. ***lactulose*** ~ 30 mg q8h
      - synthetic nonabsorbable disaccharide → large bowel
      - metabolised by GI bacteria → lactate, formate, acetate & CO_2
      - ↓ GIT pH → inhibits gram (-)'ve bacteria (proteolytic)
        favours the growth of ***lactobacilli***,
        traps $\boldsymbol{NH_3}$ in the gut, and cathartic
   iv. neomycin ~ 1 g q6h
      - additive effect with lactulose
      - may be absorbed in patients with chronic encephalopathy, ∴not used
        → nephrotoxic & ototoxic effects
      - FMC use enteral ***gentamicin*** & claim added efficacy to lactulose
   v. $MgSO_4$ enema
b. treat and prevent electrolyte disturbances
   i. Na^+, K^+, osmolality
   ii. pH, especially alkalosis
c. avoid narcotics, sedatives, etc.
d. experimental
   i. alter amino-acid balance in favour of ***branched-chain*** amino-acids
   ii. infusion of neurotransmitter precursors (L-dopa)
   iii. charcoal haemoperfusion / haemofiltration * no survival benefit
   iv. flumazenil
      - improves EEG & clinical markers of encephalopathy, but effects are short-lived & has no effect in patients with cerebral oedema

- ***Treatment Cerebral Oedema***

a. regular neurological assessment

b. early institution of controlled ventilation to maximise P_{aO2} & lower P_{aCO2}

c. ICP monitoring * ***all*** patients with grade 4 coma
→ CPP > 50 mmHg

d. diuretics
   i. mannitol ~ 0.25 g/kg q2h
      • ICP > 25 mmHg for > 15 min
        > 30 mmHg for > 1 min
   ii. ± frusemide
   iii. fluid restriction - however, often intravascularly deplete
   iv. ultrafiltration - if in ARF and on CVVHD

e. ***thiopentone*** ~ 10 mg/kg over 30 mins
~ 5 mg/kg/hr for 5 hrs
~ 1 mg/kg/hr
   • may be used in cases of CSF hypertension refractory to all other therapy

f. ? cranial decompression for resistant cases

g. ? CVVHF to clear middle-molecules

h. high dose steroids of ***no benefit***

- ***Treatment Nutrition***

a. low total protein
   • with high ratio of branched-chain amino-acids ? no benefit

b. high glucose intake, no fats / intralipid

c. vitamin supplements
   i. Vit K ~ 15-20 mg/day
   ii. thiamine ~ 200 mg/day
   iii. folate ~ 1-2 mg/day ± ***folinic acid*** for coagulopathy
   iv. Vit C ~ 500 mg/day

- ***Treatment Liver***

a. maintain adequate oxygen and blood supply

b. minimise complications

c. ? insulin/glucagon infusion to stimulate hepatic regeneration

d. orthoptic liver transplantation

- ***Keays King's College J-Hepatol. 1993***

• 36 of 68 consecutive patients with FHF progressing to grade 4 encephalopathy

→ extradural ICP monitors inserted

• only minor complications were encountered,

1. local wound bleeding at the burrhole site in 4 patinets
2. a small cerebral hemorrhage in relation to the monitor in one patient
3. no significant long-term sequelae were related to the operative procedure

• monitoring identified rises in ICP unaccompanied by clinical signs and treatment was given to the monitored patients more often than the non-monitored group ($p < 0.01$)
• survival from the onset of grade 4 encephalopathy was significantly greater in the ICP monitored group (median 60 vs. 10 h, $p < 0.01$) although overall survival was unchanged
• monitoring also provided important prognostic information since the peak ICP was higher in non-survivors than in survivors (median 45 vs. 35 mmHg, $p = 0.051$)

- ***N-Acetylcysteine***

• will prevent paracetamol-induced FHF if given within 8 hrs in most cases
• lower efficacy at > 8 hrs, and generally ineffective if > 15 hrs
• however, even though it does not prevent FHF, it does improve the ***outcome*** of patients by reducing encephalopathy & renal failure associated with paracetamol FHF

- ***Forbes et al Hepatology 1989***

• FHF & intracranial hypertension in the presence of renal failure → mortality > 90%
• incremental IV thiopental in 13 patients until ICP (extradural) fell to within normal limits or adverse hemodynamic changes occurred
• 5 patients made a complete recovery, there were 3 deaths from intracranial hypertension

NB: "the response of otherwise intractable intracranial hypertension and the 38% survival rate was remarkable for a group of patients with such a poor prognosis"

Other Therapies

- therapies ***not*** altering mortality in FHF,
    1. heparin
    2. corticosteroids
    3. exchange transfusion / plasmapheresis
    4. BCAA
    5. bromocriptine
    6. charcoal haemoperfusion / polyacrylonitrile-membrane haemodialysis
    7. L-dopa
        - improves conscious level temporarily
        - however, both L-dopa & carbidopa are no better than placebo in PRCT

Orthoptic Liver Transplantation

- 1 year survival **~ 80%** in non-FHF cases
- grade 4 coma,
    1. medical therapy → ~ 20%
    2. OLT → **~ 60%** survival at 1 year

Hepatic Encephalopathy

Def'n: complex organic brain syndrome characterised by,

1. evidence of advanced hepatocellular failure
2. disturbance of CNS function - esp. mentation, awareness, memory
3. fluctuating neurological signs - tone, reflexes, extensor plantar response
   - occasionally seizures
4. EEG - symmetrical high-voltage, slow-wave (2-5Hz)

NB: ***exclusion*** of the differential causes below essential

- ***Differential Diagnosis***

a. acute alcoholic intoxication

b. other drug overdose - esp. sedatives, narcotics

c. Wernicke's encephalopathy
   - nystagmus, ataxic gait, confusion ± peripheral neuropathy
   - later cranial nerve III & VI paralysis, conjugate gaze abnormalities
   - seen in alcoholics & AIDS patients ∝ ↓ ***thiamine***
   - IV glucose prior to thiamine may ***worsen*** symptoms

d. Korsakoff's psychosis - defect of retentive memory
   * same disease process, stages of evolution

e. subdural haematoma

f. meningitis | sepsis

g. hypoglycaemia

h. respiratory failure - hypercapnia | hypoxaemia

i. uraemia

Hepatic Encephalopathy Grading

Grade	Asterixis	Foetor	Conscious state
1	rare	moderate	• minor lapses in attention • impaired coordination of fingers, hands • impaired arithmetic and complex functions
2	occasional	severe	• lethargy, disorientation • behaviour or irregular personality change
3	frequent	severe	• confused or very drowsy • respond to stimuli, or bizarre behaviour
4	continuous	severe	• coma, unresponsive to stimuli • decerebrate or decorticate posturing

- ***Summary of Coma Grades***

1. confused, speech alteration
2. drowsy
3. sleeps but rousable
4. coma with response to pain
5. deep coma without response to pain ~ 80-90% mortality
6. coma with flat EEG

- ***Investigations***

a. neurological examination - exclude focal lesion
b. serum chemistry
   i. glucose
   ii. E,C&U - exclude other metabolic disturbances
   iii. LFTs, CaP
   iv. blood gases
c. blood picture
   i. Hb - evidence of GIT bleeding
   ii. WCC - may be low with infection
   iii. platelets - ETOH associated thrombocytopaenia / hypersplenism
d. septic screen
   i. blood cultures
   ii. T/Aspirate ± BAL
   iii. ascitic culture
   iv. lumbar puncture * exclude raised ICP first
e. drug screen
f. CT head scan

- ***Precipitating Factors***

a. acute fulminating hepatic failure
b. GIT bleed
c. high protein load
d. sedatives, narcotics, general anaesthesia, alcoholic binge
e. acute infections / sepsis
f. electrolyte disturbance, esp. alkalosis

- ***Pathogenesis***

a. ***hyperammonaemia***
- ~ 40-50% from GIT organisms degrading protein/urea
- ~ 50-60% from deamination/deamidation of AA's
- urinary excretion ~ 460 mmol/d, 400 as urea, 40 as ammonia, 20 as other
- urinary ammonia excretion may increase up to 300 mmol/d in acidosis
- in CNS: $\alpha KG + NH_3 \rightarrow$ glutamate + $NH_3 \rightarrow$ glutamine
- results in CNS depletion of citric acid cycle intermediate αKG
- clinical picture of hyperammonaemia differs from hepatic encephalopathy
- also, *poor correlation with coma level ??
- FFAs and mercaptans enhance the encephalopathic effects of ammonia
- alkalosis & hypokalaemia $\rightarrow \uparrow [NH_3]_{ICF}$

b. α-ketoglutarate
- can 'mop up' excess NH_3
- may be toxic in its own right
- serum & CSF levels $\equiv^T$ coma level

c. ***glutamine*** ($\alpha KG + NH_3$)
- CSF levels high with encephalopathy
- degree of correlation reasonably good
- neurotoxic in animals

d. amino-acid imbalance — * aromatic > branched-chain
- ammonia liberates ***glucagon*** $\rightarrow \uparrow$ gluconeogenesis; $\uparrow$ skeletal muscle catabolism & plasma AA's
- hyperinsulinism $\rightarrow \uparrow$ uptake of BCAA by skeletal muscle
- common AA carrier, $\therefore \uparrow$ plasma aromatic:BCAA's $\rightarrow \uparrow$ CNS aromatic AA's
- $\uparrow$ CNS ***tyrosine & phenylalanine*** $\rightarrow \downarrow$ dopamine & noradrenaline
  $\uparrow$ CNS ***tryptophan*** $\rightarrow \uparrow$ serotonin (inhibitory)

e. tryptophan / serotonin
- CNS toxic
- CSF level $\equiv^T$ coma level

f. false neurotransmitters
- animal studies $\rightarrow$ - GABA, glycine, octopamine, 5HT
  - histamine, catechols, phenylethylamine

g. "GABA-like" substances
- synthesised by the GIT flora and are normally cleared by the liver
- an ***endogenous benzodiazepine*** has been postulated (GABA receptor facilitator)
- benzodiazepine-like immunoreactivity is increased in CSF in encephalopathy
- ***flumazenil*** $\rightarrow$ unpredictable $\uparrow$ CNS state

h. methionine (mercaptan) — - serum level $\equiv^T$ coma level

i. short-chain FA
- poor correlation
- displaces tryptophan

j. impaired BBB — - becomes 'leaky' with HE

- ***Management of Proven Benefit***

a. prevention

b. empty gut
   - lactulose → osmotic agent, cathartic, acidification, NH_3 trapping
   - and/or Neomycin/Gentamicin (oral or rectal)
   - $MgSO_4$ enema

c. protein restriction

d. α-keto-analogues of non-essential amino-acids

e. branched-chain AA's - effective nutrition, costly
   - ***no*** decrease in mortality

f. Bromocryptine, Levodopa - increase arousal but side effects

g. charcoal haemoperfusion / CVVHF
   - improves early haemodynamics, but ***no*** alteration in mortality

h. cross-circulation

i. minimise complications
   i. hypoglycaemia
   ii. hyper/hypo-Na^+, hypo-K^+
   iii. coagulopathy / haemorrhage
   iv. infection / sepsis
   v. renal failure - hepatorenal syndrome, ATN
   vi. sedatives / narcotics
   vii. alkalosis

Ascites

Def'n: generalized swelling of abdomen, especially in the flanks, which gives a ***fluid thrill*** and ***shifting dullness***

- ***Aetiology***

a.	cirrhosis	± portal hypertension
b.	congestive cardiac failure	
c.	nephrotic syndrome	
d.	pancreatitis	± pseudocyst
e.	Budd-Chiari	- hepatic vein thrombosis
f.	infective	- pyogenic, TB (with or without AIDS)
g.	malignancy	- lymphoproliferative, metastatic, Kaposis sarcoma, DXRT
h.	rare causes	- lymphatic leiomyomatosis, vagotomy, sarcoidosis - Bechéts syndrome, trauma, retroperitoneal vascular surgery - lympatic cyst rupture, lymph node biopsy

NB: poor prognostic indicator **~ 40%** 24 month survival

- ***Pathophysiology Cirrhosis***

1. portal hypertension / raised sinusoidal pressure
2. hypoalbuminaemia
3. renal retention of salt & water *cause unknown (?? not hyperaldosteronism)
   ? peripheral arteriolar vasodilatation
   - studies have shown ***increased*** intravascular volumes in these patients
   - however, head-out water immersion still produces natriuresis
4. excess hepatic lymph formation - "overflow" phenomenon

- ***Investigation***

a.	history		- alcohol, IHD
b.	examination		
	i.	periphery	- chronic liver disease - CCF (JVP, heart size, oedema, etc.)
	ii.	abdominal	- liver/spleen, pelvic tumour, pancreatitis
	iii.	nephrotic syndrome	- kidney size, hypertension, urinalysis
c.	investigations		- ascitic tap - urinalysis - U+E's, LFT's, FBE, INR/APTT - CXR

- ***Management***

1. bed rest
2. fluid/salt restriction ~ 10-20 mmol of Na^+/day
3. spironolactone ~ 100-600 mg/day
   - urine **Na:K *ratio*** > 1 generally respond to smaller doses (100-150 mg)
     < 1 require higher doses (ie. ↑ plasma aldosterone)
4. frusemide
   - risks of volume depletion and renal failure
   - diuresis should be ≤ rate of absorption of abdominal lymph ~ 600-900 ml/d
   - weight-loss of ~ 0.5 kg/day is generally satisfactory
5. NSAIDs are ***contraindicated***
6. paracentesis & IV albumin replacement
7. peritoneovenous (LeVeen) shunt if intractable
   - shunt malfunction, peritonitis, endocarditis, DIC, SVC obstruction

Budd-Chiari Syndrome

Def'n: acute liver disease secondary to ***hepatic vein thrombosis***

- ***Clinical Features***

a. sudden or gradual onset
b. grossly enlarged liver
c. splenomegaly
d. portal hypertension
e. intractable ascites
f. ***absence*** of right heart failure

- ***Aetiology***

a. polycythaemia
b. hyperviscosity syndromes
c. renal carcinoma invading IVC
d. rarely congenital fibrous webs in hepatic veins
e. ? association with OCP in women

NB: biopsy → centrilobular congestion, necrosis & sinusoidal dilatation

Spontaneous Bacterial Peritonitis

- classically develops in patients with ***cirrhosis & ascites***
- may also occur in ascites with,
    1. nephrotic syndrome
    2. cardiac failure
    3. peritoneal carcinomatosis
    4. immunosuppression
- organisms,
    1. *E.coli, Klebsiella pneumoniae*
    2. other *Enterobacteriaciae*
    3. Pneumococcus
    4. Streptococci
- diagnosis,
    1. WCC > **500** / mm^3
       PMN > **250** / mm^3 → high suspicion of bacterial infection
       commence antibiotic therapy
    2. positive culture
    3. absence of a primary source of infection

    NB: WCC > 500/mm^3 & negative culture may →

        i. peritoneal carcinomatosis
        ii. pancreatitis
        iii. perforated ulcer
- mixed aerobic/anaerobic infections ***do not*** normally occur without visceral perforation
- initial antibiotic therapy,
    1. amoxicillin 1g tds IV
    2. gentamicin 3.5 mg/kg/d IV

Cirrhosis

Def'n: chronic disease of the liver, characterised by,

1. fibrosis
2. disorganisation of the lobar and vascular architecture
3. nodular regeneration of hepatocytes

- ***Aetiology***

a.	alcohol*	
b.	congestive cardiac failure*	* most common causes
c.	infection	- HBV*, HCV*, CMV - brucellosis - toxoplasmosis, schistosomiasis
d.	drugs / toxins	- pyrrolidizine alkaloids - α-methyldopa - isoniazid - halothane, enflurane
e.	autoimmune	- chronic active hepatitis - primary biliary cirrhosis - inflammatory bowel disease
f.	metabolic	- glycogen storage disease - α_1-antitrypsin deficiency - haemochromatosis - Wilson's disease - Fanconi syndrome
g.	cystic fibrosis	??
h.	familial	
i.	idiopathic	

NB: differences cf. acute hepatic necrosis

many ***idiopathic*** cases were probably HCV

- ***Clinical Signs***

NB: great variation in severity → from asymptomatic to fulminant hepatic failure
~ 10% diagnosed incidentally at laparotomy

a. jaundice
b. ascites
c. tender hepatomegaly, or a firm nodular liver
d. encephalopathy
e. splenomegaly
f. clubbing of the fingers
g. palmar erhythema
h. Dupuytren's contractures
i. spider naevi
j. parotid & lacrimal swelling
k. weight loss, generalised muscle wasting
l. peripheral oedema, thin skin
m. males - decreased body hair
- testicular atrophy
n. females - virilisation
- menstrual irregularities
o. signs of chronic renal insufficiency

Chronic Active vs. Chronic Persistent Hepatitis		
	CAH[1]	CPH[2]
PHx acute viral hepatitis	30%	70%
recurrent episodes	yes	no
other organs involved	yes	no
prognosis	variable	good
liver necrosis	yes	no
end-stage cirrhosis	yes	no
ALT increase	2-10x	≤ 2x
albumin	low	normal
autoimmune features	yes	no
autoantibodies		
• elevated IgG	~ 70%	normal
• anti-smooth muscle	~ 80%	
• anti-nuclear factor	~ 50%	
• anti-mitochondrial	~ 20%	

[1] Chronic active hepatitis ~ autoimmune hepatitis

[2] Chronic persistent hepatitis ~ prolonged viral hepatitis ≥ 6/12

- ***Complications of Hepatitis B***

a.	massive hepatic necrosis	± encephalopathy
b.	cirrhosis with portal hypertension	~ 15-30%
c.	carrier state (HBsAg / HBcAb)	~ 5%
d.	chronic active hepatitis	~ 3-5%
e.	hepatocellular carcinoma	
f.	immune complex syndromes	- serum sickness - polyarteritis - glomerulonephritis - urticaria

NB: many of the complication previously ascribed to HBV may well be due to ***concurrent*** HCV infection

LIVER TRANSPLANTATION

- first performed 1963 but limited survival
- current 5 year survival in USA ~ 60%
- ***fulminant hepatic failure*** is increasingly an indication for transplantation
- 1 year survival with medical R_X ~ 20-30%, cf. following transplantation **~ 65%**

▪ *Considerations Preoperative*

1. malnutrition
2. liver failure
   - i. coagulopathy
     - factor deficiency < 20% **V** → ↑ intraoperative haemorrhage
     - thrombocytopaenia ∝ splenomegaly | Ab's
     - splenectomy → ↑ portal vein thrombosis, \ ***not*** an option
     - ± ? relationship to transfusion requirements
   - ii. immunosuppression - spontaneous bacterial peritonitis
   - iii. metabolic derangement - hypoglycaemia, hyponatraemia, hypokalaemia
3. CNS failure - hepatic encephalopathy
   * acute cerebral oedema
4. respiratory insufficiency - ↑ shunt / ↓ compiance / central drive failure
   - infection, aspiration
5. cardiovascular insufficiency - ↓ effective blood volume despite ascites (????)
   - ↓ LV function masked by ↓ afterload
6. renal failure * hepatorenal syndrome

▪ *Intraoperative*

1. aspiration risk - RSI
2. cerebral oedema - ↑ ICP ∝ ↑ permeability of BBB & toxins
   - steroids ***not effective***
   - limit use of volatile agents, vasodilators
   ? ICP monitoring
3. high risk of VAE ? avoid using N_2O
   - monitoring
4. prolonged procedure ~ 8 hrs
5. massive transfusion ~ 25 units average
   - IV access & fluid warmers
   - monitoring: CVP/PAP, IABP, CUD, core T.
   - ***citrate*** toxicity & ↓ Ca^{++} when ***anhepatic***

6.	electrolyte disturbances		- ↓ Na^+, ↓ K^+, ↓ Mg^{++} * BSL usually OK - progressive ***metabolic acidosis*** ± $NaHCO_3$ ~ 50 mmol prior to unclamping
7.	coagulopathy		- INR, APTT, fibrinogen & platelets hourly
8.	***fibrinolysis***	∝	↑↑ tissue plasminogen activator - treat with Amicar (EACA) - monitor with ***thromboelastography***
9.	maintenance of renal perfusion		
10.	***venovenous bypass***		- used by some institutions - ↓ CVS compromise, inotropes & blood loss - ***no*** difference in morbidity / mortality
11.	unclamping		- H^+ & K^+ load, plus cold fluid - highest risk of VAE - arrhythmias (↓ HR), ↑ PAOP, ↓ CO - risk of PTE

- ***Postoperative Considerations***

1.	pain relief / sedation		
2.	fluid requirements		
3.	hypothermia		
4.	transfusion		- blood, FFP, platelets
5.	electrolyte changes		
	i. hyper-		- Na^+, osmolarity
	ii. hypo-		- Mg^{++}, K^+
	iii. glucose		- usually hyperglycaemic
	iv. uraemia		
	v. ***metabolic alkalosis***		
6.	pulmonary	→	- elective ventilation ± ARDS, pneumonia
7.	1° graft non-function		- small percentage, ? reperfusion injury
8.	renal failure		- ATN*, persistence of hepatorenal syndrome - ***cyclosporin*** nephrotoxicity ± CVVHD
9.	CNS		- IC haemorrhage, hypertension - seizures - ***cyclosporin*** neurotoxicity
10.	graft rejection / liver failure		**~ 5-20%**

- ***Complications***

a. ***pre-operative***
   i. malnutrition
   ii. coagulopathy
   iii. metabolic derangement
   iv. renal failure
   v. acute cerebral oedema & raised ICP
   vi. nosocomial infection / sepsis

b. ***intraoperative***
   i. prolonged procedure ≥ 8 hrs
   ii. massive transfusion ~ 25 units average
   iii. coagulopathy
   iv. electrolyte disorders
   v. VAE
   vi. hypothermia

c. ***postoperative***
   i. fluid requirements
   ii. transfusion - blood, FFP, platelets
   iii. hypothermia
   iv. renal failure - cyclosporin nephrotoxicity
   - ATN*, hepatorenal syndrome
   v. electrolyte changes - hyper-Na^+
   - hyperosmolarity
   - hyperglycaemia / hypoglycaemia
   - hypo-Mg^{++} / Ca^{++} (citrate)
   - hypo-K^+
   - uraemia
   - ***metabolic alkalosis***
   vi. pulmonary - oedema, pneumonia, ARDS
   vii. CNS - seizures
   - IC haemorrhage
   - cyclosporin neurotoxicity
   viii. liver failure

- ***Aetiology of Renal Dysfunction***

a.	pre-existing renal dysfunction	- HRS, pseudo-HRS
b.	hypovolaemia, hypoperfusion	
c.	IVC obstruction	
d.	inefficiency of venovenous bypass	
e.	poor graft	
f.	nephrotoxins	- cyclosporin, aminoglycosides
g.	intra-abdominal hypertension	
h.	septicaemia	

NB: R_X → IV fluids, reduce Cyclosporin dose, ? dopamine

- ***Transplant Rejection***

a.	1° graft rejection	**~ 2%**
	→	- ↑ GGT, fever & tachycardia - later ↑ALP
b.	'preservation injury'	- reversible centrilobular lesion
c.	vascular thrombosis	- ↑ AST & ALT first
d.	intrahepatic cholestasis	- common, spontaneous remission
e.	biliary tract complications	
f.	chronic rejection	

NB:	Acute rejection R_X	- pulse steroids - monoclonal Ig OKT_3
	Maintenance R_X	- azathioprine - cyclosporin A, steroids

HEPATORENAL SYNDROME

Def'n: potentially ***reversible*** renal failure associated with severe liver failure, characterised by,

1. oliguria with - ***low*** urine Na^+
   - high urine osmolality
2. unresponsive to fluids/inotropes
3. may progress to ATN

▪ *Clinical Features*

a. mortality ~ 95%
   * recovery associated with improvement of liver function

b. oliguric renal failure with H_2O/Na^+ retention

c. high urine osmolality with $[Na^+] < 10$ mmol/l

d. low SVR, low cardiac output, hypotension

e. hypervolaemia

f. decreased response to vasopressors

g. high circulating renin, angiotensin II, aldosterone
   - these may ***decrease*** with the onset of HRS

h. increased renal excretion of noradrenaline & TBX_{B2}

i. ***decreased*** renal production / urinary excretion of $\mathbf{PGE_2}$
   - normally ***increased*** in cirrhosis with ascites
   - ie. intrarenal PG's protect GFR against high circulating angiotensin/aldosterone

▪ *Precipitating Factors*

1. paracentesis - probably 2° association
   - ie., the syndrome is associated with ***ascites***
2. diuretics
3. hypovolaemia
4. sepsis
5. NSAID's

Proposed Mechanisms

▪ ***Secondary Tubular Dysfunction***

- completely reversible with return of liver function
- successful transplantation of HRS kidneys
- ***enzymuria*** & b_2***-microglobinuria*** seen in HRS ***not*** seen in ATN or pre-renal failure
- but, absence of histological tubular damage in some studies & able to conserve Na^+
- other studies show ATN-like changes, bile vacuoles in tubular cells and hypertrophied JGA

▪ ***Mediator Imbalance***

- xenon studies show maldistribution of RBF

a. ↓ ***renin-angiotensin*** activity
   - ↓ renin substrate in HRS
   - improved filtration with FFP or AII infusion

b. ↓ "***glomerulopressin***"
   - hormone , MW ~ 500, synthesized in the liver
   - increased by AA infusion & glucagon
   - reduces afferent aa. tone and increases GFR
   - synthesis blocked by NSAID's

c. ↓ PGE_2 / PGI_2
   - ↓ substrate & enzyme activity
   * normal in ATN

d. ↑ TBX_{A2}
   ? 1° or 2° to hypovolaemia & high circulating catecholamines
   * little evidence to support this (Maxwell & Kleeman)

▪ ***Other Factors***

1. intra-abdominal hypertension
   - increased renal vein pressure
   - improved filtration with paracentesis and colloid infusion, or peritovenous shunt
2. high SNS tone → reversible ***cortical ischaemia***

- factors probably ***not involved***,

a. fall in ANF
   - levels are only marginally reduced
   - infusion ***does not*** improve filtration

b. high renin-angiotensin II ?

c. aldosterone
   - levels correlate ***poorly*** with the degree of Na^+ retention

NB: however, ***plasma renin activity*** correlates with ***survival*** in cirrhosis, those with, (Maxwell & Kleeman)

i. high PRA → ~ 6 months mean survival

ii. normal PRA → ~ 28 months

Treatment

a. prevention
b. optimise volume status
c. paracentesis + FFP, HSA-20%
d. ?? LeVeen shunt
   - ↑ preload & cardiac output
   - ↑ RBF & GFR
   - high operative mortality → ***no*** improved survival
   - problems with ***thrombocytopaenia***
e. liver transplantation

- other modalities tried with little or ***no success***,

a. vasodilators - dopamine
b. lumbar sympathectomy
c. vasopressors - transient improvement
d. A-II inhibitors - marked hypotension
   - no increase in GFR
e. Ca^{++} entry blockers - transient effect
f. PGE_2 infusion
g. selective TBX_{B2} inhibitors
h. water immersion - increases venous pressure
i. dialysis
j. plasma exchange

Pseudo-Hepatorenal Syndrome

- occurs where primary disease process involving the liver also affects the kidneys,

1. autoimmune - SLE, PAN, systemic sclerosis
2. drugs
3. toxins - CCl_4, amanita poisoning
4. severe sepsis
5. cardiogenic shock

Intra-Abdominal Pressure / Hypertension

- ***Aetiology***

  a. haemorrhage - intra-abdominal / retro-peritoneal
  b. ascites
  c. severe pancreatitis
  d. bowel obstruction
  e. gas insufflation - laparoscopy
  f. external pressure - eg. abdominal binder

- ***Methods of IAP Measurement***

  a. intra-vesical pressure
  b. intra-gastric pressure
  c. direct intra-peritoneal pressure
  d. rectal or vaginal pressure

- ***Complications of Raised IAP***

  a. CVS - ↓ venous return & cardiac output
     - ↑ SVR
  b. renal - ↓ RBF/GFR resulting in oliguria
  c. respiratory - ↓ FRC, respiratory impairment, high P_{IP}
     - ↑ V/Q mismatch, hypoxia
  d. GIT - ↑ intra-gastric pressure
     - regurgitation and aspiration
  e. opening of congenital pleuroperitoneal connection

- ***Clinical Effects***

a. normal IAP ~ 0-5 mmHg

b. post-operatively levels ≤ 12 cmH_2O (9 mmHg) occur without renal impairment

c. as IAP is raised ³ **25 cmH_2O** (20 mmHg) there is,

i. ↑ venous return and cardiac output, but
- later followed by ↓ VR

ii. ↑ SVR ~ 30%

iii. ↑ ***renal-VR*** ≤ 500% → 25% ↓ RBF/GFR

NB: the dramatic rise in renal vascular resistance and oliguria lead to ***anuria*** at IAP ≥ ***30 mmHg***

- mechanisms of ***renal failure*** with intra-abdominal hypertension,

a. ↓ venous return + ↑ afterload → ↓ cardiac output

b. ↑ RVR + ↓ cardiac output → ↓ RBF

c. renal vein compression

d. redistribution of RBF, cortical → medullary

- ***Cullen CCM 1989***

- syndrome of massively increased IAP ~ 30-80 cmH_2O
- all patients had,

a. hypovolaemia but high filling pressures

b. good EF ~ 55% but low stroke volume & cardiac output

c. oliguria ≤ 10 ml/hr

d. hypoxia - all patients required IPPV

e. small improvement with volume challenge (10ml/kg)

f. considerable improvement in cardiac, renal and respiratory function with decompression

NB: similar picture to ***cardiac tamponade***

- ***Jacques AIC 1988***

- case report of traumatic retroperitoneal haematoma causing oliguria and high IAP ~ 32 cmH_2O
- no response to volume, mannitol, or dopamine

PANCREATITIS

- ***Aetiology***

a.	ethanol*	
b.	gallstones*	* (a + b) account for **~ 85%**
c.	idiopathic	~ 7%
d.	traumatic	
e.	post-ERCP	
f.	familial / hereditary	
g.	cystic fibrosis	
h.	SIRS, ARDS, MODS	? ischaemic pancreatitis
i.	metabolic	- hyperlipidaemia - hyperparathyroidism, hypercalcaemia - renal failure - acute fatty liver of pregnancy - haemochromatosis
j.	infections	- viral hepatitis, mumps - Coxsackie, Echovirus and other viruses - Mycoplasma, Ascariasis
k.	autoimmune diseases	→ "pancreatic vasculitis" - SLE, TTP, necrotising vasculitis
l.	drugs	- thiazides, frusemide, valproate - vit D, oestrogens - sulphonamides, tetracyclines, azathioprine
	possible associations	- steroids, methyl dopa, procainamide, chlorthalidone, ethacrynic acid, β-blockers, cimetidine, clonidine, rifampicin, phenformin, paracetamol
m.	toxins	- methanol - scorpion envenomation - organophosphate poisoning
n.	renal transplant	- surgery - hypercalcaemia - steroids (?), diuretics - viral infections, immunosuppressives
o.	GIT disease	- duodenal ulcer, penetration / perforation - Crohn's disease - obstruction of the Ampulla of Vater - pancreas divisum

■ ***Pathophysiology***

- ***exocrine*** gland secretes ~ 1500-2000 ml fluid/d
  ~ 150-200 mmol HCO_3^-/d ∝ ***secretin***
- also secretes lipolytic & proteolytic enzymes ∝ ***cholecystokinin***
  muscarinic ACh stimulation
- proenzymes: ***trypsinogen*** → trypsin
  + other enzymes → kallikrein, elastase, phospholipase
  under the influence of ***enterokinase*** secreted by the duodenal mucosa
- bile contents, especially ***lipase*** → more specific for pancreas cf. amylase
- kinins → proteolysis
- activation of these enzymes results in,

  a. connective tissue & fat necrosis

  b. pancreatic destruction

  c. vasodilatation

  d. shock, haemorrhage

  e. trypsin → ***complement activation***, C_3 & C_4
  activation of coagulation, kinin system & fibrinolytic cascades

- mechanisms for activation,

  1. duodenopancreatic reflux
     - allows duodenal ***enterokinase*** to activate trypsinogen, which in turn activates phospholipase A_2 → lysolethecin which causes duct damage
  2. hypersecretion
     - rare cause → scorpion envenomation, organophosphate poisoning
  3. pancreatic duct 'hypertension'
     - not supported by animal studies of obstruction → ***atrophy***
     - pancreatic obstruction by a gallstone is rare in pancreatitis (4% of 2653 pts)

■ ***Presentation***

a. severe central abdominal ***pain***, nausea and vomiting

b. paralytic ***ileus***

c. jaundice

d. systemic inflammatory response syndrome, coagulopathy

e. hypovolaemic ***shock***

f. respiratory failure - pain, pleural effusion
- ARDS

g. tetany from hypocalcaemia and hypomagnesaemia

- ***Clinical Signs***

a. Cullen's sign — - blue discoloration of the periumbilical area
- haemoperitoneum

b. Gray-Turners sign — - blue discoloration of the flanks
- retroperitoneal haematoma, usually > 48 hrs

c. petechiae ± purpura

d. thrombophlebitis

e. warm, dry erythema of SIRS

f. jaundice

g. Peach's retinopathy — - retinal artery fat emboli

- ***Investigations / Diagnosis***

a. clinical — * high suspicion in critically-ill

b. serum ***amylase*** — ≥ 3x rise (> 600 IU/l), usually > 3 hrs, **P-type** cf. S-type
- peaks at 12-24 hrs and returns to normal by 3-5 days, cleared by GFR
- ***poor*** correlation with disease severity & outcome
- if elevated > 5 days then → ***pseudocyst***
- also found in the liver, lung, prostate, fallopian tubes, and ovaries
  → different amylase (S-type), cleared by non-renal mechanisms

i. false negative — - early mild, or severe necrotising pancreatitis

ii. false positive — ~ 300-600 IU/l
- perforated or ischaemic bowel, salivary disease or biliary colic
- tumours of lung, ovary, or pancreas
- pregnancy, acidaemia, DKA, ARF

c. urinary amylase — > 750 IU/l (N: 10-300)
peritoneal amylase — * grossly elevated, may be > 50,000 IU/l

d. amylase:creatinine ratio = $\frac{[Cr]_P}{[Cr]_U} \times \frac{[Ams]_U}{[Ams]_P}$

< 5 → non-pancreatic amylase
~ **5-10** → pancreatitis

- invalid in the presence of renal failure

e. serum ***lipase*** — - more specific for pancreas, elevated in ~ 75%
- remains elevated for 10-14 days

f. FBE / blood film

i. leukocytosis — ~ 15-20,000/µl

ii. haemolysis — - free Hb, ↓ haptoglobin, ↑ methaemalbumin

iii. thrombocytopaenia — - ? DIC

iv. methaemalbuminaemia

g.	biochemistry		- ↑ AG metabolic acidosis - hypocalcaemia, hypomagnesaemia, hypokalaemia - hyperglycaemia - hypertriglyceridaemia (~ 15%, may normalise amylase) ± rising creatinine/urea
h.	LFT's		- high bilirubin / low albumin ± alcoholic hepatitis | obstructive jaundice
i.	AGA's		~ 25% will be hypoxaemic
j.	ECG		- non-specific ST/T wave changes, tachycardia
k.	AXR	~ 50%	- regional ileus → "sentinal loop" ± gallstones | pancreatic calcification | ascites
l.	CXR	~ 40%	- basal atelectasis, pleural effusions - raised left hemidiaphragm ± cardiac failure | ARDS
m.	U/Sound	< 60%	- often fails to visualise pancreas - assessment of biliary tracts / gallbladder
n.	CT Scan		- good sensitivity for oedematous pancreatitis - identification of late complications * grading of severity
o.	diagnostic laparotomy		

- ***Electrolyte Disorders***

a. hypocalcaemia
b. hypomagnesaemia
c. hypo/hyper-K^+
d. hyperglycaemia
e. hyperlipidaemia
f. high anion gap metabolic acidosis
g. elevated urea and creatinine

- ***Acidosis in Pancreatitis***

a.	lactic acidosis	- types I & II
b.	diabetic ketoacidosis	
c.	alcoholic ketoacidosis	
d.	renal failure	
e.	respiratory failure	
f.	rarely 2° to ingested toxin	

- ***Respiratory Dysfunction / Failure***

a. mechanical - pain, sputum retention
- pleural effusion, increased IAP
- often pre-existing lung disease

b. V/Q mismatch - kinin, C' activation

c. central depression- analgesics, sedatives, treatment of DT's

d. acute lung injury / ARDS

e. infection - nosocomial pneumonia, aspiration

- ***Investigation of Cause***

a. history - alcohol, gallstones, drugs

b. examination

c. baseline investigations
   i. FBE
   ii. U,C&E's, Ca^{++}, Mg^{++}, glucose
   iii. amylase, LFT's
   iv. CXR, AXR
   v. CT scan

d. other investigations
   - serum lipids
   - hepatitis and other viral serology
   - ANF, ANA
   - cholecystogram

CT Grading of Pancreatitis		
Grade A	• normal	• normal
Grade B	• focal or diffuse pancreatic oedema	• focal
Grade C	• extension of inflammation to peripancreatic fat	• extension
Grade D	• phlegmon, or • single ill-defined pancreatic fluid collection	• 1 collection
Grade E	• 2 or more fluid collections, or • the presence of pancreatic gas	• >1 collections

- ***Treatment Principles***

a. rest the pancreas/gut

i. nil orally - on recovery, low fat, low protein diet

ii. NG tube and suction - only if severe, otherwise just ***nil orally***

- no therapeutic value in controlled studies of mild disease

iii. analgesia - parenteral narcotics
- epidural analgesia (exclude coagulopathy)

iv. aprotinin - inhibitor of proteolytic enzymes
* ***no*** proven benefit

b. prevent / treat complications

i. IV fluids - large deficit may be present
- crystalloids / colloids

ii. O_2 therapy - all but mild cases
- ABG's if clinical respiratory failure

iii. monitor vital signs - fluid balance, urine output, CVP
- PA catheter PRN

iv. maintain urine output ≥ 0.5 ml/kg/hr
- fluids / inotropes (?? mannitol, dopamine)

v. electrolyte shifts - give K^+, Ca^{++}, Mg^{++} if low

- ***calcium*** replacement is rarely if ever required and may exacerbate disease

vi. TPN - with additional ***insulin***

vii. antibiotics - ***not*** for uncomplicated cases
- suspected ***cholangitis*** or septicaemia
- pancreatic abscess

viii. ***peritoneal lavage***

- tried in severe cases - 2l isotonic dialysate + Heparin 1000^U
  + Amoxycillin 250 g
  - drain every hour & continue 24-48 hrs
- stabilises haemodynamics & reduces early mortality
- however, ***no*** decrease in overall mortality

ix. CT guided drainage - pseudocyst, ***not*** abscess

x. ***surgery*** - indicated in ~ 15%, if

- diagnosis uncertain
- pancreatic abscess - persistent high WCC, (+)'ve cultures
  - fever and pain > 1-3 weeks, CT scan
- pancreatic pseudocyst ~ 10%
- biliary tract disease
- ? peritoneal debridement to prevent progressive deterioration

c. prevent relapse

i. avoid precipitating factors

ii. drain pseudocyst

■ ***Peritoneal Lavage***

• proposed advantages,

a. decreased sepsis & sepsis-related mortality

b. decreased overall mortality

c. improved early haemodynamic stability

d. decreased severity

• technique,

a. 2000 ml isotonic dialysate + Heparin 1000^{U}
+ Amoxicillin 250 mg

b. drain every hour

c. continue 2-7 days

• variables,

a. volume

b. frequency

c. additives (antibiotics, antiproteases)

d. duration

NB: reduces ***early mortality*** and stabilises haemodynamics
however, no long-term decrease mortality

• SGO, 1980 ***controlled*** multi-centre British trial showed,

a. ***no*** improvement in outcome

b. increased protein loss

c. higher incidence ***bacterial peritonitis***

• SGO, 1990 Perderzoli, ***uncontrolled***, unblinded study of 191 pts all given peritoneal, or retroperitoneal lavage
• method = 1000 ml 4-6 hrly, hypertonic solution + aprotinin
• three groups, commenced on day ≤ 2, 2-4 days, or > 4 days
• decreased mortality with early lavage, and (-)'ve blood cultures

• SGO, 1990 Ranson, ***uncontrolled*** study with 2 days vs 7 days lavage,

a. decreased overall mortality 43% vs 27%

b. decreased incidence of sepsis 83% vs 33%

c. decreased mortality associated with sepsis 20% vs 0%

Prognosis

- overall ***mortality* ~ 20%**
- poor prognostic factors defined by ***Ranson*** 1976
- predictive criteria for ***severe pancreatitis*** ³ **3** of the following,

Multiple Prognostic Scales					
Ranson - 1976			**Imrie - 1978**		
On Admission					
• age	> 55	yrs			
• glucose	> 11	mmol/l			
• WBC	> 16,000				
• AST	> 120	U/l[1]			
• LDH	> 350	U/l			
During the First 48 hrs[2]					
• IVT	> 6000	ml	• WBC	> 15,000	
• ↓ Hct	> 10%		• glucose	> 10	mmol/l
• ↑ urea	> 10	mmol/l	• P_{aO2}	< 60	mmHg
• HCO_3^-	< 20	mmol/l	• BUN	> 16	mmol/l
• ↓ P_{aO2} (air)	< 60	mmHg	• AST	> 200	U/l
• ↓ calcium	< 2.0	mmol/l[3]	• LDH	> 600	U/l
			• Alb	< 32	g/l
			• Ca^{++}	< 2.0	mmol/l[3]

NB: ***amylase*** level ***not*** useful as a predictor of severity

[1] Ranson's original criteria was SGOT (AST) > 250 Frankel Units

[2] Severe Acute Pancreatitis if **> 2 criteria** met in first 48 hours

[3] uncorrected plasma calcium

Surg Gynaecol Obstet, 1990	
"Ranson" score	Mortality
0 - 2	~ 8%
3 - 5	~ 25%
³ **6**	**~ 65%**

- another factor associated with high mortality is (+)'ve ***blood cultures*** (2x)
- more recent studies assessing validity of ***APACHE II*** scores showed 77% predictive value
- if re-evaluated for first 48 hours, then,

a. APACHE II prediction **~ 88%** ? Tan *et al.*

b. Ranson score ~ 69%
Imrie score ~ 84%

NB: ***severe acute pancreatitis*** → admission **APACHE II > 9**

▪ ***Complications***

1. ***local***
   - i. pancreatic
     - phlegmon
     - pseudocyst ~ 4% of patients
       ~ 30% develop complications
     - abscess ~ 100% mortality without surgery
     - haemorrhage
     - necrosis
   - ii. ascites
     - may respond to somatostatin / octreotide
   - iii. retroperitoneal - abscess
     - haemorrhage
   - iv. venous thrombosis - splenic, renal, or portal vv.
2. ***systemic***
   - i. pulmonary - effusion, atelectasis
     - ARDS
     - chylothorax
     - mediastinal abscess
   - ii. cardiovascular - hypotension | shock
     - tachycardia
     - pericardial effusion
     - ST/T changes $\equiv^{T}$ AMI
   - iii. DIC
   - iv. gastrointestinal - acute stress ulceration / peptic ulceration
     - oesophageal variceal haemorrhage
     - ileus
   - v. renal - ARF
   - vi. CNS - encephalopathy
     - seizures
     - psychosis
     - sudden blindness (Purtscher's retinopathy)

PSEUDOMEMBRANOUS COLITIS

Def'n: infective colitis due to *Clostridium difficile* cytopathogenic toxin

- uncommon but reversible cause of infective diarrhoea
- causative agents,

a.	cephalosporins	→ most common case
b.	Clindamycin	~ 2-10%
c.	Lincomycin	
d.	Amoxicillin	
e.	Chloramphenicol*	
f.	tetracyclines*	
g.	Cotrimoxazole*	*rarely

▪ ***Clinical Features***

- onset within 2-25 days of antibiotic use,

a.	profuse watery diarrhoea, bleeding uncommon	
b.	cramping abdominal pain	
c.	dehydration, hypoalbuminaemia	
d.	dilated bowel, toxic megacolon	
e.	sigmoidoscopy	- oedematous friable mucosa - white-yellow raised plaques (fibrin, cells, polymorphs, mucus) ± ulceration or sloughing
f.	Barium study	- dilated bowel - distortion of haustra - ulcers - thumb-printing - cobblestone appearance

▪ ***Treatment***

a.	removal of causative antibiotic	
b.	correction of fluid and electrolyte deficiencies	
c.	Vancomycin or Metronidazole orally	
d.	? cholestyramine	- binds toxin

NB: steroids no use
recovery usual within 3 weeks