FEVER / HYPERTHERMIA

Def'n: ***fever*** is a regulated rise in body core temperature to > 38°C,
due to an increase in the hypothalamic 'set point'

hyperthermia is a sustained rise in body temperature
∝ heat production in excess of the capacity for heat loss

- normal regulation displays ***diurnal variation*** with nadir at 06:00-08:00 and peak at 16:00-20:00
- approximate range of ***survival*** (non-therapeutic) → **26 - 43°C**

Metabolic Changes

1. ↑ VO_2 ~ 7-12% / °C
   - net metabolic effect is ***catabolism***
2. hyperventilation
3. ↑ HR ~ 15 bpm / °C
4. ↑ insensible water & electrolyte losses
5. ↑ levels of
   - fibrinogen
   - haptoglobin, CRP
   - amyloid A, α-macrofetoprotein, caeruloplasmin
6. ↓ availability of
   - iron & zinc
7. ↑ production of humoral mediators of inflammation

Beneficial Effects

1. inhibits replication of some microorganisms
2. ↑ generation of cytotoxic T-cells
3. ↑ B-cell activity & immunoglobulin production
4. ↓ serum iron / ↑ organisms iron requirement for growth

Causes for Apyrexia

1. extremes of age
   - seriously ill newborns & elderly patients
2. uraemia
3. corticosteroids | immunosupression
4. contnuous antipyretic use

- ***Infectious Causes***

i.	common causes	- UTI, urinary catheters - pulmonary - surgical wounds - IV, IA, CVC, PA catheters - ***antibiotic induced*** - bacterial colitis - ischaemic colitis - hepatitis - acalculous cholecystitis - calculous cholecystitis - ascending cholangitis
ii.	uncommon sites	- SBE - subphrenic abscess - cholangitis - sinusitis - decubitus ulcers - prostatitis - endometritis - periodontal abscess - meningo-encephalitis - parasitic, malaria

- ***Non-Infectious***

i.	inflammatory	- AMI - pancreatitis - acute arthritis, gout - familial mediterranean fever - sarcoidosis
ii.	autoimmune	- SLE, RA - polyarteritis, temporal arteritis, other vasculitis - Wegener's granulomatosis - Kawasaki's disease
iii.	blood-borne	- haemolysis, transfusion reaction - DVT, pulmonary embolus - internal haemorrhage (CNS, joints, AAA, retroperitoneal) - cyclic neutropaenia
iv.	allergic	- blood transfusion, blood products - drug induced fever
v.	metabolic	- hypercalcaemia - adrenal insufficiency - delerium tremens, addictive drug withdrawal

vi.	hyperthermic syndromes	- MH, malignant neuroleptic syndrome - heat stroke - hyperthyroidism - central anticholinergic syndrome
vii.	neoplasm	- atrial myxoma - lymphomas, carcinoma (renal, colon) - hepatoma, liver secondaries - carcinoid
viii.	drugs	- sympathomimetics (vasoconstriction & muscle activity) - analeptics - salicylates (↑ BMR) - phenothiazines (CNS regulation) - anticholinergics in O/D - MH & MNS triggers
ix.	others	- Fabry's disease - hyperlipidaemias - granulomatous hepatitis

- ***Drug-Induced Fever***

1. overdose
2. withdrawal
3. allergic reaction
4. interference with temperature regulation
   i. central
   ii. peripheral - sweating, vasoconstriction, etc.
5. alteration of BMR / muscle activity
6. antibiotic induced superinfection
7. MH / NMS triggers

Fever Unknown Aetiology

Def'n: *Petersdorf & Beeson, 1961,* a febrile illness,

1. duration > **3 *weeks***
2. temperature **> 38.3°C**

- ***Causes***

1. infections ~ 30-40%
2. neoplasms ~ 20-30%
3. collagen vascular diseases ~ 15%
4. others ~ 15-20%
   i. drug fever
   ii. multiple PE's
   iii. sarcoid
   iv. inflammatory bowel disease
5. ***undiagnosed*** **~ 10%**

NB: follow-up studies have shown, carefully evaluated but undiagnosed FUO's, generally have a ***good prognosis***

- ***Clinical Approach***

NB: the majority of patients have a ***treatable*** or curable disease, which is presenting in an ***uncommon manner***

1. rule-out common infections & other causes
   i. history & examination
   ii. drug history
   iii. investigations
   - FBE, ESR, CRP
   - LFT's
   - CXR
   - M,C&S - blood cultures, urine culture, stool examination
2. establish true nature of FUO
   - ie. ensure actually present & for > 3 weeks prior to extensive work-up

3. ***FUO workup***
   i. extensive history - geographic origins, travel
      - exposure to TB
      - animal exposure
      - drug use, medical & recreational
      - HIV risk factors
   ii. follow-up ***serial histories*** as required during investigation
   iii. physical examination
      • skin - stigmata of SBE (only present in 20-30%)
        - rash of vasculitis
      • lymph nodes
      • hepatomegaly | splenomegaly
      • other abdominal masses
      • rectal & pelvic examinations
      • cardiac examination
   iv. ***serial physical examination*** is crucial
   v. laboratory investigation
      • viral studies - HBV, HCV, HIV, CMV, EBV
        - respiratory pathogens
      • autoantibodies - RF, ANF, ANCA, ENA, etc.
      • see below

- ***Laboratory Aids in FUO***

1. ***blood cultures***
   i. continuous bacteraemia - eg. endocarditis
      • ***3 sets*** of BC's will recover the organism in ~ 95% of cases
      • prior oral or parenteral AB's will alter this yield
      • some ***fastidious organisms*** may take days/weeks (*Brucella*, *Haemophilus*)
   ii. culture-negative endocarditis
      • accounts for **~ 5-15%** of BE
      • should be considered in all patients with FUO, negative initial BC's and underlying CVS disease
2. ***tissue biopsies***
   i. lymph nodes
   ii. liver - granulomatous hepatitis
   iii. skin nodules & rashes
3. ***skin tests***
   i. intermediate PPD test
      • should be done routinely unless the patient is a known reactor / immunised
   ii. other antigens - *Monilia*, trichophytin, mumps
   iii. fungal skin tests - generally of little value

4. ***serology***
   i. acute phase sample & convalescent titre
   ii. single sample titre **> 1:1024** highly suggestive
   iii. febrile agglutinins - *Salmonella sp.*
   - *Brucella sp.*
   - *Pasturella tularenis*
   - *Proteus*
   - these have shown ***low specificity*** & cross-reactivity
   - poor value as a screening test
   iv. specific disease
   - viral disease - HIV, EBV, HIV
   - toxoplasmosis
   - rikettsial disease
   - Legionaire's disease
   - psittacosis
5. ESR / CRP
6. screening for collagen-vascular diseases
7. XRay contrast studies - IVP, GIT studies
8. radionuclide scans
   i. gallium
   ii. labelled WBC's - ^{111}Indium
   iii. bone scan
   iv. ^{99m}Tecnecium
9. ultrasound
10. CT / MRI
11. exploratory laparotomy

- ***Rare Causes of FUO***

1. juvenile RA
2. familial Mediterranean fever
3. granulomatous hepatitis
4. bacterial hepatitis
5. hyperimmunoglobulinaemia D and periodic fever

SEPSIS

Def'n: ***Infection***: a microbial phenomenon characterised by,

1. an inflammatory response to the presence of microorganisms, or
2. the invasion of normally sterile host tissue by these organisms

Def'n: ***Bacteremia***: the presence of viable bacteria in the blood

Systemic Inflammatory Response Syndrome **:** a characteristic clinical response, manifested by ***two or more*** of the following,

1.	***temperature***	> 38ºC			
		< 36ºC	(rectal)		
2.	***WCC***	> 12,000	/mm^3		
		< 4,000	/mm^3		
		> 10%	immature band forms		
3.	***tachycardia***	**> 90**	adults		
		> 150	children		
		> 160	infants		
4.	***tachypnoea***	**> 20**	adults	or	P_{aCO2} < 32 mmHg
		> 50	children		
		> 60	infants		

Def'n: ***Sepsis*** **:** SIRS secondary to ***infection***

Severe SIRS / Severe Sepsis **:**
SIRS / sepsis with associated organ dysfunction, hypoperfusion, or hypotension

SIRS with Shock / Septic Shock **:**
SIRS / sepsis with associated organ dysfunction or hypoperfusion,
with hypotension ***not responsive*** to fluid resuscitation

Multiple Organ Dysfunction Syndrome **:**
state characterised by physiologic derrangements in which organ function is not capable of maintaining ***homeostasis***

NB: Bone *et al.*, American College of Chest Physicians / Society of Critical Care, 1992

- ***hypoperfusion*** and perfusion abnormalities may include, but are not limited to,
  1. oliguria
  2. an acute alteration in mental status
  3. lactic acidosis

- patients who are on inotropes / vasopressors need not be hypotensive to fulfill criteria
- in paediatrics, hypotension is ***not*** necessary for diagnosis, as it is a late & ominous sign

Def'n: ***paediatric shock*** **:** a clinical state characterised by inadequate delivery of oxygen and substrates to meet the metabolic demands of the tissues

at present there are no graded definitions for paediatric sepsis

- septic shock ***mortality*** ranges from 25% to 75%
- average **~ 40%** and has not altered significantly in last 2 decades
    a. 75% of deaths occur early 2º to ***refractory hypotension***
    b. 25% occur late 2º to ***MODS***

- incidence of sepsis syndrome (US) ~ 176 per 100,000
- this has increased 140% from 1979 to 1987

■ ***Treatment Modalities***

1. antibiotics - bacteriacidal, bacterostatic
2. surgical procedures - debridement, drainage
3. intensive life support
    i. IPPV
    ii. intravascular volume expansion
    iii. inotropic support
    iv. dialysis

■ ***Immunology of Sepsis***

• the hosts inflammatory response contributes substantially to the development of septic shock,

1. plasma factors
   - complement
   - clotting cascade
   - kinins
2. cellular components
   - neutrophils
   - monocytes
   - macrophages
   - endothelial cells

NB: activated cells produce a range of potentially toxic host mediators

i. cytokines
   - TNF
   - IL1, IL6

ii. kinins

iii. eicosanoids

iv. PAF

v. NO

• 1985 Tracey demonstrated passive immunisation against TNF protected mice from endotoxin
• infusion of rTNF mimicked tissue injury & metabolic derrangements of endotoxic shock
• high concentrations of TNF found in patients with severe sepsis/shock
• TNF levels were inversely correlated with survival, however, not present in all patients

• Darville, *et al.*, Infection 1993, four stages of SIRS,

1. induction phase
2. cytokine synthesis & secretion
3. cytokine cascade
4. secondary mediators & end-products resulting in cellular damage

Induction Phase

• SIRS may be initiated by,

1. infection - bacteria, viruses
   - fungi, protozoa
2. trauma
3. ischaemia
4. autoimmune factors
5. other diseases - pancreatitis
   - cirrhosis

• gram negative bacterial sepsis most extensively studied
• the outer membrane of gram negative bacteria possess,

1. O-polysaccharide chain
   - O-side chain
   - highly ***variable*** between bacterial strains
   - ***non-toxic*** on administration to animals
2. core sugar & ***lipid A***
   - embedded deeply in the outer membrane
   - similar structure between bacterial strains
   - ***toxic*** an administration to animals

• administration to animals produces CVS and organ dysfunction similar to septic shock
• however,

1. neither induced tolerance, nor genetic resistance is protective during GN infections
2. increased sensitivity to endotoxin ***does not*** alter the course of GN infections
3. endotoxin & endotoxaemia are not necessary to produce septic shock

• antibodies to the O-side chain produce ***sero-specific***, complement dependent bactericidal activity
• however, serospecificity limits clinical utility
→ core and lipid-A Ab's avoid this problem
• these were believed to mediate anti-endotoxin, or endotoxin clearing effects, however their exact mechanism of action is uncertain

Agent	Possible Effect	Clinical Examples
LPS O-chain Ab	C' dependent bactericidal activity ***Serospecific*** against GN bacteria	Octavalent *P. aeruginosa* vaccine
LPS Core/Lipid A Ab	Enhanced endotoxin clearance in GN septicaemia	HA-1A, E5, J5 immune plasma or serum
Peptides & proteins which bind endotoxin	Neutralisation Enhanced clearance	Cationic peptides • polymixin B, colistin • HDL Bactericidal/permeability increasing protein
Lipid A derivatives	Induce tolerance to endotoxin Direct antagonism of endotoxin	Deacylated endotoxin Lipid X Monophosphorylated lipid A

• core-directed Ab's are the only type to have been subjected to clinical trial
• other agents listed above may reduce the host inflammatory response by,

1. directly neutralising endotoxin
2. increasing endotoxin clearance
3. antagonising endotoxin effects on host cells
4. inducing tolerance

• the first clinical trial using ***J5-antisera*** (Ziegler *et al.* NEJM 1982) showed a reduction in ***sepsis-related*** mortality from 39% → 22%
• in a sub-group requiring inotropes for > 6 hours, the reduction was from 77% to 44%
• however,

1. the effect of J5-antiserum on mortality from all causes was not reported
2. 5 subsequent clinical trials using polyclonal core-reactive antiserum, or Ig have shown ***no survival benefit***

■ ***Monoclonal Ab's***

• were developed in an attempt for more specific antiendotoxin therapy

• **E5** was tested in 2 multicentre, randomised, placebo-controlled trials
• the first showed no overall benefit in survival, however, retrospective analysis inferred benefit to a subgroup ***without*** refractory shock
• the second trial, (Wenzel, Bone *et al.*, 1991, ICAAC), was conducted to confirm this effect, however failed to do so

NB: meta-analysis combining the two studies showed that **E5-Ab** substantially decreased the time to recovery from organ dysfunction and improved survival in a subgroup of patients with GN sepsis and organ dysfunction who were ***not*** in ***refractory shock***

• a third multicentre trial is being conducted to confirm this effect

• **HA-1A** trials also failed to show any increase in survival
• the main study was sponsored by the manufacturers (Centocor) and the study design was changed following production of interim results

1. when analysed using the original design, no improvement of survival ($p = 0.12$)
2. placebo population was not equivalent,
   i. more patients in the placebo arm had inadequate antibiotic therapy
   ii. greater number of risk factors at study entry

• in addition, animal studies showed an increase in ***myocardial dysfunction*** in the HA-1A group
• this may be due to non-specific binding to ***cardiolipin*** (an Ag in myocardium)

NB: a second randomised trial was conducted, however was terminated in Jan'93 after there was a ***higher*** mortality in the HA-1A treated group

- ***Potential Problems***

1. exposure of the innermost core as antigenic determinants on pathogenic smooth gram negative bacteria remains ***purely hypothetical***
2. it has been difficult to demonstrate cross-reactivity of polyclonal antisera to rough mutants, and divergent cross-reactivity results have been seen for monoclonal Ab's (HA-1A)
3. ***has not*** been shown that these Ab's participate in opsonic activity for bacterial or LPS ***clearance***
4. ***neutralisation*** of the effect of endotoxin by anti-core polyclonal or monoclonal Ab's has not been described
5. HA-1A and other monoclonal core Ab's ***do not*** diminish serum TNF or IL-6 levels, cf. Ab's against specific O-side chains

• newer agents which bind to and neutralise endotoxin are being developed, these include,

1. peptides - non-toxic derivates of polymyxin B
   - neutrophil-derived bactericidal / permeability increasing protein
2. lipoproteins - HDL

• Ulevitch *et al.* described a family of proteins with LPS binding sites,

1. ***LPS-binding protein*** - LPB
   - concentration increases ~ 100 fold during acute phase response
   - binds to lipid-A moeity forming a LPS-LPB complex
   - interaction with LPS and its CD-14 receptor on myeloid cells is greatly enhanced
   - LPS-LPB-CD14 results in ***cytokine*** gene encoding
   - depletion of LPB in serum, or blocking of CD14 with Ab's, results in marked reduction of macrophage activation and TNF production
2. ***bactericidal / permeability increasing protein*** - BPI
   - binds to LPS and prevents macrophage activation

Cytokine Synthesis & Secretion

• in general cytokines are not stored preformed, rather their synthesis is initiated by,

1. ***new gene transcription***, or
2. translation from ***preformed RNA***

• transcription activating protein, NF-κB, activated by phosphorylation of cytosolic inhibitor IκB appears a common feature
• post-transcriptional control of biosynthesis is prominent for most cytokines
• levels of TNF-mRNA increase 100 fold in response to LPS-LPB/CD14, cf. *in vitro* increases in gene transcription ~ 3 fold

■ ***Pretranslational Blockers***

• ***pentoxifylline*** and ***amrinone*** → ↑ **cAMP**
• former results in decreased TNF synthesis in murine endotoxic shock model
• amrinone is more potent

NB: concern over *in vitro* experiments which show marked cellular ***hyper-responsiveness*** to LPS following discontinuation of these agents, potentially sensitising the individual to otherwise harmless episodes of endotoxaemia (?? duration not studied)

■ ***Translational Blockade***

• ***corticosteroids*** primarily block translational activation of TNF-mRNA in macrophages
• the steroid effect is entirely ***pre-emptive***, administered post-LPS they are without effect
• the ideal dose is unknown, and there is good animal evidence that increasing the dose beyond an optimal level is associated with increased mortality

NB: Darville *et al.*, "blocking TNF production may be of most benefit where bacteria are rapidly killed by antibiotics, and where the inflammatory response can cause severe sequelae, eg. meningococcaemia or typical childhood meningitis"

The Cytokine Cascade

■ ***Tumor Necrosis Factor***

• ***trimer*** protein hormone
• exerts is biological effects by cross-linking cellular ***TNF receptors***
• TNF-β, ***lymphotoxin***, is produced by TH1 lymphocytes, has 30% amino acid homology and binds to the same receptors as TNF-α
• the temporal rise in cytokines following overwhelming *E.coli* bacteraemia in baboons follows,

1. TNF ~ 90 min
2. IL-1β ~ 3 hrs
3. γ-interferon ~ 6 hrs

• studies of the effects of exogenously administered rTNF show,

1. acute myocardial dysfunction
2. activation of coagulation
3. increased release of neuroendocrine stress hormones
4. significant stimulation of immune function

NB: however, circulating TNF is not consistently detected during conditions of clinical shock, infection, or severe tissue injury

• reasons for failure to detect TNF may be,

1. short biological half-life and sampling at the wrong time
2. local tissue secretion & action → paracrine / autocrine
3. assays affected by circulating ***inhibitors*** of TNF

• organs implicated in significant production of TNF,

1. lung
2. spleen
3. kidney
4. pancreas
5. heart
6. uterus

• morbidity & mortality following TNF administration is synergistically ***enhanced*** by even low concentrations of IL-1 & γ-IFN

■ ***Interleukin-1***

• exists as two distinct molecules, **IL-1α** and **IL-1β**
• these are structurally related ***polypeptides*** with ~ 25% AA homology
• most IL-1α remains in the cytosol in its precursor form, or is associated with the cell membrane
• **IL-1β** is cleaved by IL-1β ***converting enzyme*** within the cell and subsequently secreted
• clinical effects include,

1. fever
2. anorexia
3. sleep
4. increased
   - concentrations of colony stimulating factors
   - IL-6
   - hepatic acute phase reactants
   - collagenase synthesis
5. bone and cartilage resorption
6. inhibition of lipoprotein lipase
7. induction of PGE_2
8. capillary leak
9. hypotension

NB: however, IL-1 ***has never*** been shown to be directly lethal in animals, cf. TNF

thus, the TNF component is necessary for servere sepsis/SIRS & MODS

■ ***Interleukin 6***

• has also been known as,

a. B-cell stimulating factor

b. hybridoma / plasmacytoma growth factor

c. hepatocyte stimulating factor

d. cytotoxic T-cell differentiation factor

• temporal relationship in sepsis models strongly suggests ***antecedent*** **TNF** & **IL-1** stimulation
• if TNF or IL-1 are inhibited then IL-6 levels are markedly reduced
• clinical effects include,

a. endogenous pyrogen, cf. IL-1

b. induction of hepatic acute phase reactants

c. ***does not*** result in haemodynamic decompensation, regardless of dose

d. suppresses,

i. LPS-induced TNF production

ii. LPS and TNF induced IL-1 production

e. production of numerous anti-inflammatory proteases

NB: the general evidence is that IL-6 is ***anti-inflammatory*** in nature, however, it may play an adverse role in endotoxaemia

■ ***TNF Antagonism***

1. no adequate clinical trials of ***anti-TNF Ab's*** in human sepsis have yet been published
   • Ab therapies in humans have limitations, therefore,
2. most attention has focused on ***soluble TNF receptors***
   • naturally occurring proteins represent the extracellular domains of the two TNF receptors
   • thought to act as naturally ocurring ***TNF antagonists***
   • have prevented *E.coli* induced sepsis in baboons & death in mice
3. ***TNF-receptor-Fc chimeric proteins***
   • artificial soluble TNF receptor linked covalently to the Fc portion of IgG
   • specific inhibitor of TNF with the affinity of a natural receptor, but the half-life of naturally occurring Ab
   • single dose significantly reduces haemodynamic instability in animal models

- ***IL-1 Antagonism***

1. ***any*** attempt to treat sepsis by modulating TNF will have to occur soon after onset, cf. IL-1, where a window of several hours theoretically exists
2. ***IL-1 receptor antagonist*** is a naturally occurring competitive antagonist to IL-1
3. has to be administered in large quantities to block IL-1 activity *in vivo*
4. recently conducted multicentre phase III trial showed ***no decrease*** in mortality

Secondary Mediators & Toxic Byproducts

• the ***endothelium*** plays an important role both as,

1. a target for cytokines, and
2. as a source of additional mediators

• cytokines increase expression of ***adhesion molecules*** on both endothelial cells and PMNs
• activated neutrophils and endothelial cells produce,

1. arachidonic acid metabolites
2. free oxygen radicals
3. nitric oxide ← ↑ iNOS

NB: these appear to be the direct mediators of the physiological derangements of SIRS;
platelet activating factor interacts with the cytokines and may either,

i. ***enhance***, or
ii. ***down-regulate*** mediator release

- ***Arachidonic Acid Metabolites***

• LPS, TNF and IL-1 → ↑ ***prostaglandins*** from endothelial cells
• elevated levels of PGI_2 have been found to correlate with the severity of septic shock in humans
• indomethacin given 1 hr prior to TNF blocks the metabolic acidosis, shock & death in rats
• animal studies have employed combination therapy with cyclo-oxygenase inhibitors and

1. leukotriene receptor antagonists
2. lipoxygenase inhibitors

NB: clinical trials of efficacy are lacking,
potential problems of ***renal failure*** & ***bronchospasm***

Oxygen Derived Free Radicals

• generated upon reperfusion or re-oxygenation
• anions which are generated activate a ***superoxide-dependent chemoattractant***
• this produces an influx of neutrophils, with further production of superoxide
• Bernard, AJM 1991, a preliminary report of a randomised trial with N-acetylcysteine in patients with established sepsis-induced ARDS shows some promise (subsequent NFG)

Nitric Oxide

• synthesized by ***constitutive NO synthase*** and activates soluble ***guanylate cyclase***
• resultant increase in cGMP produces,

i. vasodilatation
ii. inhibition of platelet aggregation
iii. modulation of leukocyte adhesion
iv. modulation of spinal neurohumoral transmission

• endotoxin & cytokines → ↑ ***inducible NO synthase*** which is expressed in various cells,

i. endothelium
ii. vascular smooth muscle
iii. macrophages
iv. neutrophils

• effects of NO can be reversed *in vitro & in vivo* by N_G-monomethyl-L-arginine (NMLA)
• there have been some early reports of NMLA in sepsis, however main concern is reduction in ***tissue perfusion***
• some animal studies have reported damage to organ structure with NO-synthase inhibition in the setting of sepsis
• another concern is enhanced platelet activation with subsequent ***microvascular thrombosis***

Platelet Activating Factor

• LPS produces PAF from,

i. neutrophils
ii. macrophages
iii. platelets
iv. endothelial cells

• a potent phospholipid inflammatory mediator which increases cell adhesion and activates endothelial cells, either by a direct effect or via formation of toxic O_2 species or arachidonic acid metabolites
• evidence for haematologic growth factors & cytokines interacting with PAF amplifying mediator release in septic shock
• PAF mediates many of the toxic effects of TNF & IL-1
• phase III trials of ***PAF antagonists*** in septic shock are currently underway

Clinical Use of Immunotherapy in Sepsis

• major problem is which therapy, or combination of therapies will provide the best outcome for a given patient with SIRS, depending on the time course of the illness
• anti-LPS Ab's have been shown to be ineffective,

a. they target only a subset of patients - ie. gram negative septicaemia

b. once the patient is clinically septic, the cytokine cascade is already activated

• now believed that anti-TNF and anti-IL-1 have more promise on theoretical grounds
• however, neither is consistently demonstrable in all patients with sepsis/SIRS
• the possible existence of recurring, or ongoing tissue cytokine production, and the required duration of therapy has not been addressed

NB: very few studies have assessed the effectiveness of these agents administered ***after*** the onset of shock

• also, there is evidence that a total lack of cytokine activity is detrimental
• it is possible that anti-cytokine therapies would only be beneficial if used at a particular dose and during a certain window period
• there is considerable evidence that TNF serves an essential role in immune ***ontogeny*** & regulation during development
• disruption of TNF activity in the newborn may have irreversible consequences

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NB: *"there must be some concern using agents which act against an endogenously produced substance which has been **teleologically conserved**"*

Multiple Organ Dysfunction Syndrome MODS

Def'n: presence of altered organ function in an acutely ill patient, such that ***homeostasis*** cannot be maintained without intervention

specifically the term ***dysfunction*** infers a continuum of serverity and dysfunction, cf. the previous dichotomy of ***organ failure***, definitions for which varied between institutions and researchers

- onset usually 7-10 days after precipitating event,
  a. septic shock
  b. severe trauma
  c. burns
  d. pancreatitis
  e. intra-abdominal sepsis, etc.

- high ***mortality*** ~ 25-40% overall
  ~ 50% of these die from ***nosocomial pneumonia***

a.	1 organ system	~ 24%	~ 45% (elderly)
b.	2 organ systems	~ 53%	~ 70% (elderly)
c.	3 organ systems	~ 93-100%	

- syndrome is usually maintained by ***ongoing sepsis*** ± (+)'ve blood cultures
- high risk factors include,
  a. initial disease severity - APACHE II score
  b. systemic sepsis
  c. respiratory infection
  d. elderly

NB: following are ***organ failure definitions***, which are no longer applicable to MODS these give an indication of organ system involvement & dysfunction in SIRS

- ***Organ Failure Definitions***

a. ***liver failure***
- sine qua non ~ ***intrahepatic cholestasis***
- hyperbilirubinaemia ≥ 100 µmol/l *disproportionate to enzyme levels
- mild ALP elevation ≡[t] "obstructive jaundice" pattern
- severe hypoalbuminaemia
- INR ≥ 1.4
- reduced protein synthesis, AA clearance, low redox potential

b. ***respiratory failure*** ~ ARDS & ventilator dependency
- tachypnoea, RR < 5 or > 49
- diffuse lung infiltrates
- reduced lung compliance ≤ 50 ml/cmH_2O
- hypoxia, increased $\delta P_{A\text{-}aO2}$ ≥ 350 mmHg
- hypercarbia, P_{aCO2} ≥ 50 mmHg

c. ***cardiovascular failure***
- bradycardia ≤ 55 bpm
- tachyarrhythmias * VF or VT
- hypotension, MAP < 50 mmHg
- high CO, low SVR, high VO_2
- lactic acidosis, pH < 7.25
- arrhythmias, bacterial endocarditis, ischaemia LV ± RV
- receptor down-regulation, reduced response to catecholamines
- reduced catecholamine stores
- minimal requirements for survival - ***Schumaker***

CI	≥ 4.5 l/min/m^2	~ 8 l/min CO	
DO_2	> 600 ml/min/m^2	~ 1000 ml/min, or	15 ml/kg/min
VO_2	> 170 ml/min/m^2	~ 280 ml/min, or	4 ml/kg/min

d. ***renal failure*** ~ ATN
- oliguria < 500 ml/day or < 20 ml/hr for 8 hrs
- high urea > 36 µmol/l
- high creatinine > 0.3 mmol/l

oliguric renal failure, ATN ± hepatorenal syndrome

e. ***haematological failure***
- WCC ≤ 1000/µl
- thrombocytopaenia ≤ 20,000/µl ± thrombocytopathy
- anaemia, Hct. ≤ 20%
- ± DIC, fibrinolysis, thromboembolism

f. ***neurological failure***
- GCS < 7 *in absence of sedation at any point of the day
- if intubated, use clinical judgement for ***verbal responses*** as follows,

i. patient unresponsive 1
ii. patient's ability to converse in question 3
iii. patient appears able to converse 5

- septic encephalopathy
- critically ill polyneuropathy
- cerebral oedema
- central pontine myelinolysis / osmotic demyelination syndrome

■ ***Associated Organ System Failure***

a. ***gastrointestinal***
- stress ulceration & haemorrhage
- ileus, pseudo-obstruction
- acute acalculous cholecystitis
- acute ischaemic pancreatitis
- culture negative diarrhoea, gram (-)'ve colonisation
- bacterial & endotoxin mucosal translocation, enterocolitis

b. ***immune suppression***
- lymphocytopaenia < 1000/µl
- severe anergy, reduced T_4/T_8 ratios
- reduced fibronectin
- infections with resistant/unusual pathogens (fungal, protozoal, bacterial)

c. ***hypermetabolic state***
- fever
- high VO_2 > 150 ml/min (paralysed, ventilated)
- high energy requirement > 30 kcal/kg/day
- high urea & CO_2 production
- persistent hyperglycaemia, lipolysis, protein catabolism, malnutrition
- acute vitamin deficiencies - folate, thiamine
- electrolyte disorders

■ ***Treatment Principles***

1. source control
2. microcirculatory control
3. maintain oxygenation
4. metabolic support
5. prevention of complications

■ ***French ICU Group for Severe Sepsis JAMA 1995***

• inception cohort study, 2 month prospective survey of 11,828 admissions to 170 adult ICUs
• patients meeting clinical criteria for ***severe sepsis*** were included and classified as,

a. documented severe sepsis n = 742
b. culture-negative severe sepsis n = 310

• measures of hospital and 28-day mortality

a. suspected sepsis ~ 9.0/100 admissions
   • 28d mortality ~ 60%
b. confirmed severe sepsis ~ 6.3/100 admissions
   • 28d mortality ~ **56%**

• risk factors for,

1. ***both*** early (<3 days) and 28d deaths were,
   i. SAPS II
   ii. number of acute organ system failures
2. ***early*** deaths,
   i. pH < 7.33
   ii. shock
   iii. ***bacteremia*** in patients with documented sepsis
3. ***late*** deaths,
   i. admission category
   ii. rapidly, or ultimately fatal underlying disease *McCabe & Jackson, 1 or 2
   iii. pre-existing liver or cardiovascular insufficiency
   iv. hypothermia
   v. thrombocytopenia
   vi. multiple sources of infection

• conclusions,

1. ~ 75% patients with clinically ***suspected*** severe sepsis have documented infection
2. patients with culture negative and proven severe sepsis share ***common risk factors*** and have a similarly high risk of death
3. in addition to the severity of illness score, ***acute organ failures*** and the characteristics of ***underlying diseases*** should be accounted for in stratification of patients and outcome analyses

ANTIBIOTICS

Antibiotic Guidelines - Septicaemia		
Source	Organisms	Antibiotic
Urinary tract • community • nosocomial	*E.coli* Enterobacteriaceae[1] *Strep. faecalis* *Pseudomonas* spp. Staphlococci, Candida	Amoxicillin 1g q6h Amoxicillin 1g q6h Gentamicin 1.5 mg/kg q8h
Bowel	Enterobacteriaceae *Strep. faecalis* anaerobic cocci *Bacteroides faecalis*	Amoxicillin 1g q6h Gentamicin 1.5 mg/kg q8h Metronidazole 500 mg q8h
Female genitalia	anaerobes Enterobacteriaceae Strep., (Staph.)	Amoxicillin 1g q6h Gentamicin 1.5 mg/kg q8h Metronidazole 500 mg q8h
LRTI • community	*Strep. pneumoniae*	Penicillin 2MU q4h
LRTI • hospital	Enterobacteriaceae Strep., Staph. oral anaerobes	Cefotaxime 2g q8h or Penicillin 2MU q4h Gentamicin 1.5 mg/kg q8h
LRTI • aspiration		Amoxicillin 1g q6h Gentamicin 1.5 mg/kg q8h Metronidazole 500 mg q8h
LRTI • either	Pseudomonas	Tobramycin 1.5 mg/kg q8h Timentin 3.1 g q4h
IV catheter or skin	Staph., gram (-)'ve	Flucloxacillin 2g q4h + Gentamicin 1.5 mg/kg q8h
Neutropaenic patient		Flucloxacillin 2g q4h + Gentamicin 1.5 mg/kg q8h + Timentin 3.1g q4h
Meningitis	Streptococci, Meningococci Haemophilus	Cefotaxime 2g q6h
Cerebral abscess	Staph., anaerobes	Penicillin 2MU q4h + Metronidazole 500mg q8h

[1] Enterobacteriaceae: E.coli, Klebsiella, Enterobacter, Proteus Sp., Serratia

Penicillin G

• penicillin is a generic term for a broard spectrum of agents, including penicillin G
• the precise mechanism of action is ***unclear*** → ***bactericidal***
• provides good levels in,

a. serum
b. urine
c. synovial fluid
d. pleural fluid
e. pericardial fluid

NB: ***does not*** penetrate significantly into the ***cerebrospinal fluid***

• excretion primarily by ***tubular secretion*** and ***GFR***, thus require dose adjustment in renal failure
• the penicillinase resistant agents are an exception to this, see later

• ***penicillinase*** is a beta-lactamase enzyme which cleaves the β-lactam ring, with the resultant ***penicillinoic acid*** inactive against bacteria
• this is the principal mechanism of resistance for,

a. resistant, coagulase-positive *S.aureus*
b. *E.coli*
c. *Proteus* spp.
d. *Pseudomonas* spp.
e. *Bacteroides fragilis*

■ ***Activity Spectrum***

a. gram positive aerobic cocci
   • very effective against *S. pneumoniae, S. pyogenes* (gp A), *S. viridans, S.bovis,* and penicillin-sensitive *S. aureus*
   • ***not*** effective for ***enterococcal*** infections
b. gram-negaive aerobes
   • minimal spectrum of activity
   • agent of choice for - *N. meningitidis, Pasteurella multocida*
c. anaerobes
   • very effective against anaerobic cocci, *Clostridium* spp., *Fusobacterium* spp.
   • effective against most *Bacteroides* spp. (esp. oral)
   • ***not*** effective against *B. fragilis* from bowel
   • agent of choice for *A. israelii*
d. *T. pallidum* - agent of choice

- ***Dosage***

1. high-dose therapy ~ 3-4 MU q4h
   - indicated for severe infections - meningitis
     - endocarditis
     - clostridial infections
   - requires reduction in renal failure
   - no indication for doses > 30 MU/day - ↑ neurotoxicity
     - alternative agents available
2. intemediate doses ~ 8-12 MU / day
   - often used to achieve synergistic effect with aminoglycosides
   - used in aspiration pneumonias, lung abscess, moderate to severe soft tissue infections
3. lower doses ~ 2.4 MU / day
   - used in pneumococcal pneumonia
   - higher doses are not required and promote superinfection

- ***Adverse Effects***

1. allergy and hypersensitivity reactions
2. drug fever
3. ***eosinophilia***
   - therapy should be ceased if level > 15% of peripheral WCC
4. interstitial nephritis
5. CNS toxicity - GABA antagonist

- ***Dose Modification***

a. renal failure

b. dialysis - removed, but amount uncertain

c. probenicid use

Penicillinase-Resistant Penicillins

- synthetic agents produced by modification of the common penicillin side-chain
- bactericidal agents produced principally to treat *S. aureus*

Activity Spectrum

a. gram positive aerobic cocci
   i. *S. aureus*
      - preferred as first line agents in suspected infection
      - majority of community & hospital acquired *S. aureus* penicillin resistant
      - penicillin G is the preferred agent if susceptible due to lower cost, better *in vitro* activity
   ii. other gram positives
      - effective against *S. pneumoniae, S. pyogenes* (gp A) and viridans streptococci but the MIC's are higher than for penicillin G, ∴ this is the preferred agent
      - in mixed infections with resistant *S. aureus* and *S. pyogenes* these agents can be used as sole therapy
      - ***not*** effective for ***enterococcal*** infections

b. gram-negative aerobes
   - not effective against the Enterobacteriaceae or *Pseudomonas* spp.
   - not recommended for the R_X of gonorrhoea

c. anaerobes
   - cf. penicillin, they have ***less activity*** against sensitive anaerobes
   - not effective against *B. fragilis* from bowel

Agents

1. flucloxacillin
   - ***hepatitis*** with prolonged administration has been described
2. oxacillin
3. nafcillin
4. methicillin
   - avoid in adults due to high risk of ***interstitial nephritis***

■ ***Interstitial Nephritis***

• may occur with any penicillin derivative, but is more common with ***methicillin***
• does not appear dose-related → probably a ***hypersensitivity reaction***
• signs & symptoms usually appear several days following the start of therapy,

a. fever
b. eosinophilia
c. morbilliform rash
d. haematuria, proteinuria
e. renal failure ~ 50%

• urinary sediment shows eosinophils and renal biopsy shows interstitial nephritis with eosinophillic aggregations
• cross-sensitization with the ***cephalosporins*** has been documented & renal failure may be aggravated
• agent of choice is therefore ***vancomycin***

Broad-Spectrum Penicillins

• these possess variable activity against ***gram negative*** organisms
• often subdivided into,

1. second generation - ampicillin, amoxicillin
2. third generation - carbenicillin, ticarcillin
3. fourth generation - piperacillin, azlocillin, mezlocillin

■ ***Ampicillin & Amoxicillin***

• active against all of those agents listed for ***penicillin G***
• when an organisn is susceptible, the narrower spectrum agent is preferrable
• the expanded spectrum for these penicillins includes,

1. ***Enterococcus***
2. *Haemophilus influenzae* *10-25% of strains resistant, ∴ use cephalosporin
3. *Listeria monocytogenes*
4. many, but not all strains of
   i. *E.coli*
   ii. *Proteus mirabilis*
   iii. *Salmonella* spp. - amoxicillin is better
   iv. *Shigella* spp. - amoxicillin is ***ineffective***

NB: oral bioavailability of amoxicillin ~ 2x that of ampicillin

• ***not active*** against,

1. penicillinase producing staphylococci
2. *Pseudomonas* spp.
3. many Enterobacteriaceae - especially hospital acquired
4. Shigellosis - amoxicillin only

■ ***Augmentin***

• combination of amoxicillin & ***clavulanic acid***
• later has ring structure similar to β-lactams and acts as a ***suicide inhibitor***
• inhibits the β-lactamases of,

1. *S. aureus* → ~ 80% resitance of these organisms
2. *H. influenzae, H. ducreyi*
3. *N. gonorrhoea*
4. *Branhamella catarrhalis*
5. many of the gram-negative bacilli - *E. coli, Kelbsiella, Proteus*

• ***not active*** against,

1. *Enterobacter*
2. *Pseudomonas* spp.
3. *Serratia* spp.

■ ***Ticarcillin (Carbenicillin)***

• ***carboxypenicillins*** → ↑ activity against ***gram negative*** bacteria
• not acid resistant, therefore IV only
• effective against,

1. most strains of *P. aeruginosa* - especially combined with an aminoglycoside
2. indole-positive *Proteus* spp.
3. other gram-negatives resistant to amoxicillin
4. penicillin sensitive anaerobes * including majority of *B. fragilis*

• ***not active*** against,

1. *Klebsiella*
2. *Serratia* spp.
3. penicillinase producing staphylococci

NB: carboxypenicillins have a global effect on ***platelet membrane receptors***,
↑ SBT appears dose & time - dependent, probably worse with carboxypenicillin

• problems with ***carbenicillin***,

a. high sodium load
b. platelet dysfunction
c. hypokalaemia

NB: therefore, replaced by ***ticarcillin*** in most institutions

• seldom used as a single agent, due to high risk of ***resistance*** emerging
• major indication is in combination with an ***aminoglycoside*** for severe gram-negative infections, especially,

1. pseudomonad infections
2. febrile leukopaenic patients
3. second line agent for *B. fragilis*
   - 75-85% are susceptible, but risk of resistance developing (β-lactamase)

■ ***Timentin Ticarcillin / Clavulanate***

• active against the β-lactamases of organisms listed for Augmentin
• very active against ***anaerobes***, including *B. fragilis*
• class 1 Richmond-Sykes β-lactamases (cephalosporinase) are ***not inhibited*** by clavulanate
• organisms ***not susceptible*** to this combination include strains of,

1. *Enterobacter*
2. *Citrobacter*
3. *Pseudomonas* spp.
4. *Serratia* spp.
5. MRSA

NB: ***enterococci*** are moderately resistant

• side-effects,

1. hypersensitivity reactions
2. eosinophilia
3. mild LFT abnormalities
4. hypernatraemia | hypokalaemia
5. oral candidiasis
6. diarrhoea

Piperacillin

- 4th generation, broad spectrum, ***ureidopenicillin***
- derived from amoxicillin, as are all members of this class
- cf. the 3rd generation agents, they possess greater *in vitro* activity against,

1. *Klebsiella* spp.
2. *Serratia marcescens*
3. *P. aeruginosa*

NB: however, this is ***not clinically significant*** as prospective comparative studies show no clear advantage cf. 3rd generation agents

Summary

1. 4th generation agents show ***no*** clear clinical advantage
   - possibly less ***bleeding tendency***, ie. platelet dysfunction
   - lower ***sodium load***, if this is deemed critical
2. ***monotherapy*** in severe infections is ***not advised***
   - not bactericidal, except at high concentrations
3. no agent shows clear advantage * piperacillin | azlocillin | mezlocillin

Beta-Lactams

- ***Side Effects***

1. ***hypersensitivity***
   i. rash
   ii. fever
   iii. eosinophilia
   iv. anaphylaxis
2. ***haematological***
   i. haemolytic anaemia - Coomb's positive
   ii. platelet dysfunction / thrombocytopaenia
   iii. neutropaenia
3. ***renal***
   i. interstitial nephritis
4. other
   i. seizures
   ii. diarrhoea
   iii. pseudomembranous colitis
   iv. elevated LFT's - rarely hepatitis
   - more common with flucloxacillin
   v. hypokalaemia - antipseudomonal agents
   - carbenicillin, ticarcillin, piperacillin, azlocillin

Cepaholsporins

- ***Advantages***

a. bactericidal - cf. the penicillins

b. effective against penicillinase producing *S. aureus*
   - especially 1st generation agents, ie. Cephalothin

c. broad spectrum of activity - gram positive & gram negative organisms

d. wide therapeutic index - therapeutic:toxicity ratio
   - lower frequency of allergic reactions

- ***Disadvantages***

a. poor CSF penetration of older agents
   i. especially 1st & 2nd generation → ***not recommended***, even if susceptible
   ii. 3rd generation agents → agents of choice
      - extremely active against routine organisms causing meningitis
      - provide good bactericidal concentrations

b. limited activity against ***enterococci*** & ***pseudomonads***
   - 3rd generation maybe effective, but ***not recommended*** as sole agent

c. enhanced nephrotoxicity when combined with aminoglycosides
   - probably ***not correct***, but most reports implicated cephalothin

- ***Clinical Uses***

1. surgical prophylaxis
   i. 1st generation - mainstay, especially where *S. aureus* is possible
   ii. 2nd generation - cefoxitin, cefotetan suitable for GIT procedures
   iii. 3rd generation * ***not indicated***

2. bacteraemia / septicaemia
   i. unclear aetiology - 1st generation & aminoglycoside
      - 3rd generation as sole agent
   ii. post-splenectomy / aetiology unclear
      - need to cover, *S. pneumoniae, H. influenzae, N. meningitidis*
      - cefuroxime (2nd) or 3rd generation agent suitable
   iii. susceptible infections - ***non-neutropaenic*** patient
      - emergence of resistance is ***not*** a concern
      - desirable to ***avoid*** an aminoglycoside
   iv. ***not indicated*** as sole therapy for,
      - *P. aeruginosa*, except for sensitive meningitis
      - enterococcal infections

3. skin & soft tissue - 1st generation agents preferrable

4. dental / oral infections
   - penicillin remains the drug of choice
   - in allergic patients, or those not responding, ***clindamycin*** is second choice
   - ***cefoxitin*** (2^{nd}) is an alternative as it has reasonable anaerobic cover
5. CNS infections
   i. 1^{st} / 2^{nd} generation * ***not indicated***
   ii. 3^{rd} generation
      - currently the ***drug of choice*** for enteric gram negative meningitis
      - this is uncommon, except in neonates & following neurosurgical procedures
   iii. meningitis in children
      - neonates → cefotaxime ***and*** amoxicillin
      - children > 3 months → cefotaxime, or ceftriaxone
   iv. brain abscess
      - useful agents, but combination therapy preferred
6. respiratory infections
   i. *S. aureus* or *S. pneumoniae* in a penicillin allergic patient may be treated with a 1^{st} generation agent
   ii. severe community acquired pneumonia - 3^{rd} generation
      - *Enterobacter* spp. and other nosocomial GN organisms risk development of resistance, ∴not effective as sole agent
      - if atypical pathogens are likely, then ***erythromycin*** should be added
   iii. *Pseudomonas* infections should not be treated using a sole agent
7. cardiac infections
   i. gram positive organisms → 1^{st} generation agent
      - ***no cephalosporin*** currently available is active against ***enterococci***
   ii. GNB endocarditis → 3^{rd} generation agent may be useful
   iii. MRSA
      - even if sensitive *in vitro*, cephalosporins are of no use *in vivo*
8. intra-abdominal sepsis
   - mild / moderate community acquired infections
   - cefoxitin, or other 2^{nd} generation agent may be useful
   - moxalactam is no longer used due to ***bleeding problems***
   - 3^{rd} generation agents have ***less*** anaerobic cover,
     ∴have little to offer unless enhanced GN cover is desirable
9. urinary tract infections
   i. community acquired pyelonephritis - 1^{st} generation agent
   ii. complicated recurrent UTI's - 2^{nd} / 3^{rd} generation agent
   iii. non-bacteraemic *P. aeruginosa* - 3^{rd} generation agent

- ***Spectrum of Activity***

1. ***first generation*** *cephalothin
   i. gram positive organisms
      - penicillin susceptible & resistant *S. aureus, S. pneumoniae, S. pyogenes* and other aerobic streptococci
      - ***not active against enterococci***
   ii. gram negative organisms
      - some Enterobacteriaceae are susceptible
      - only modest activity against *H. influenzae*
      - many *Serratia, Enterobacter* and *Proteus* are resistant
      - *Pseudomonas* spp. are resistant
   iii. anaerobes
      - active against penicillin sensitive anaerobes
      - not effective against *B. fragilis*
2. ***second generation*** *cefoxitin
   i. gram positive organisms
      - same spectrum, but slightly less active than 1st generation
      - ***not active against enterococci***
   ii. gram negative organisms
      - extended activity but separate ***sensitivity testing*** must be performed
      - active against *N. gonorrhoea*
      - *Enterobacter cloacae* and *Pseudomonas* spp. are resistant
      - bacterial resistance frequently develops
   iii. anaerobes
      - active against penicillin sensitive anaerobes
      - effective against 80-95% of strains of *B. fragilis*
      - more effective than newer 3rd generation agents

3. ***third generation***
   i. gram positive organisms
      - 1st / 2nd generation agents are 2-4x as active against *S. aureus*
      - mixed infections, there is ***no need*** to add separate anti-staphylococcal cover
      - streptococci, groups A, B, C, G, viridans and bovis are susceptible
      - *S. pneumoniae* are highly susceptible
      - ***no cephalosporin*** is active against - ***coagulase negative staphylococci***
        - ***enterococci***
      - ***not active*** against ***L. monocytogenes***

   ii. gram negative organisms
      - *H. influenzae* and other *Haemophilus* spp.
      - active against *N. gonorrhoea* and other *N*. spp.
      - enhanced activity against the ***Enterobacteriaceae***, being their major advantage over the earlier agents
      - *Enterobacter* spp., especially *E. cloacae* ~ 10-30% resistant
      - only ***ceftazidime*** is active against *P. aeruginosa* (± *P. cepacia*)

   iii. anaerobes
      - activity is suitable for respiratory (oral) anaerobes only
      - none of these agents is truely stable to *B. fragilis* β-lactamase
      - less effective than the 2nd generation agents

- ***Indications 3rd Generation***

1. enteric GNB meningitis → agents of choice
2. empiric therapy for meningitis in children
   - neonates - cefotaxime preferred as doesn't displace bilirubin
     - plus ***amoxicillin*** to cover *Listeria monocytogenes*
3. GN infections resistant to older agents
4. susceptible multiresistant organisms (aminoglycoside resistant)
5. severe bacteraemias & infections where enhanced bactericidal activity is desirable
6. with an aminoglycoside for *P. aeruginosa* in penicillin allergic patients
7. severe *H. influenzae* infection pending sensitivities
8. mixed infections where use of a 3rd generation agent allows monotherapy
9. severe community acquired infections - eg. pneumonia
   - ie. where *P. aeruginosa* is ***not*** a concern

- ***Side Effects Cephalosporins***

1. phlebitis
2. primary ***allergic reactions*** **~ 5%**
   i. urticarial and morbilliform rashes
   ii. fever
   iii. eosinophilia
   iv. serum sickness
   v. anaphylaxis
   - in ***penicillin allergic*** patients reported cross-reaction rates ~ 5-15%
   - however, more recent reports are much lower → ~ **1%**
   - with a history of ***immediate generalised reaction*** to penicillin, the cephalosporins should be avoided, unless careful skin testing is performed
   - in patients with delayed mild reactions, cephalosporins may be used
3. ***nephrotoxicity***
   - used as sole agents, they are infrequently associated with toxicity

   i. cephaloridine is no longer available due to toxicity
   ii. conflicting data regarding ***cephalothin*** and aminoglycosides
4. ***haematological***
   i. positive Coomb's reaction * haemolytic anaemia is rare
   ii. granulocytopaenia / thrombocytopaenia are rare
   iii. ***hypoprothrombinaemia*** and bleeding diathesis
      - described with ***moxalactam***, cefamandole, cefotetan, cefoperazone
      - moxalactam has also been associated with platelet dysfunction
      - cefamandole → hypoprothrombinaemia ~ 10%
        bleeding much less
      - mechanisms - destruction of ***menaquinone*** producing gut flora
        - ***N-methylthiotetrazole*** inhibition of synthesis
      - later effect limited to agents with the NMTT side chain
5. ethanol intolerance * disulfiram-like reactions
6. antibiotic related ***diarrhoea***
7. ***resistance*** | superinfection
   - development of resistance highest with the ***second generation*** agents
   - ***cefoxitin*** actually used to induce/study resistance by some laboratories

Carbepenems Imipenem / Cilastatin

- first agent of this class, released early 1987
- widest spectrum of the **β-*lactam*** agents,

1. ***imipenem***
   - parent compound is ***thienamycin***, which is unstable chemically
   - ∴use the crystalline amidine derivative, *N-formimidoyl thienamycin* (imipenem)
2. ***cilastatin***
   - this is not an antibiotic, nor a β-lactamase inhibitor
   - acts as a selective enzyme inhibitor, with 2 actions,

   i. inhibits ***dehydropeptidase-I*** on the brush border of the nephron
      - given in a 1:1 ratio, prevents degradation in the tubule
        → enhancing urinary concentrations

   ii. "nephroprotective effect"
      - high dose imipenem given over months to animals produces ***nephrotoxicity***
      - coadministration of cilastatin prevents tubular accumulation of antibiotic and subsequent toxicity

■ ***Activity Spectrum***

- inhibits > 90% of all clinically significant infective organisms worldwide
- this is currently being reduced, especially in Europe, where resistance is increasing
- this spectrum of activity is due to 3 factors,

1. no ***permeability barrier*** to gram negative bacteria
2. stability against attack from β-lactamases
3. ***high affinity*** for penicillin-binding proteins

NB: imipenem is a potent ***inducer*** of β-lactamases which can cleave other β-lactam agents, and has shown antagonism when given concomitantly, eg *P. aeruginosa*

imipenem ***does not*** penetrate into mammalian cells, therefore is unsuitable for ***intracellular pathogens***

- specific organisms,

a. ***gram positive aerobes***
   - similar efficacy to the penicillins and first generation cephalosporins
   - majority of Staph's and Strep's, including penicillin-resistant *S. pneumoniae*
   - ***Enterococci*** are usually susceptible, however some ***S. fecium*** strains are resistant
   - MRSA and coagulase-negative staphylococci are routinely ***resistant***
   - some strains of *L. monocytogenes* are susceptible, but readily develop tolerance

b. ***gram negative aerobes***

i. nonenteric pathogens
- MIC's for β-lactamase positive and β-lactamase negative *H. influenzae* and *N. meningitidis* are identical
- other *N.* spp. and *H.* spp. are also ***highly susceptible***

ii. Enterobacteriaceae *three levels of sensitivity
- *Proteus* spp. being less sensitive ~ 2-4 µg/ml
- *Serratia, Enterobacter* & *Citrobacter* spp. ~ 1-2 µg/ml
- all other organisms highly susceptible < 1.0 µg/ml

iii. *Pseudomonas*
- *P. aeruginosa* are moderately susceptible ~ 5.0 µg/ml
- imipenem shows synergism with ***aminoglycosides***
  → now routinely recommended for *P. aeruginosa*
- *P. maltophilia* and *P. cepacia* are routinely ***resistant***

iv. *Acinetobacter*
- usually very susceptible

c. ***anaerobes***
- based on *in vitro* testing, imipenem is the most active β-lactam agent, being comparable in efficacy to clindamycin, chloramphenicol and metronidazole
- MIC for *C. perfringens* is slightly higher at 4.0 µg/ml and some *C. difficille* are relatively resistant at ~ 10 µg/ml

• other ***resistant organisms*** include,

a. *Flavobacterium* spp.

b. *Corynebacterium* spp.

c. *Mycobacterium fortuitum*

d. *C. trachomatis*

e. ***mycoplasma***

- ***Adverse Effects***

1. phlebitis ≤ 5%
2. GIT symptoms ~ 5%
   - with high dose therapy ~ 20%
3. allergic reactions
   - drug fever, rash, pruritis < 3%
   - patients showing an immediate generalised response to penicillin should be considered imipenem allergic
4. ***seizures***
   - unclear aetiology ~ **1.5%**
   - increased frequency with,
   i. prior history of seizure disorder
   ii. CNS lesion
   iii. renal failure
   iv. higher doses
5. haematological effects
   i. eosinophilia ~ 4%
   ii. positive direct Coomb's test ~ 2%
      - usually ***without*** haemolysis
   iii. neutropaenia / thrombocytopaenia rarely
      - largest report actually → platelets ***increased***
      - others have shown decrease in collagen-induced platelet aggregation
   iv. increased prothrombin time has been reported
6. ***nephrotoxicity*** has rarely been described
7. ***colonisation*** / superinfection
   - superinfection appears to be less problematic, but colonisation is common,
   i. resistant *P. aeruginosa* *usually aminoglycoside sensitive
   ii. fungi

- ***Contraindications***

1. not as sole therapy for severe infections with,
   i. ***P. aeruginosa***
   ii. ***enterococci***
2. other ***Pseudomonas*** infections
3. the majority of community acquired infections
4. surgical prophylaxis
5. MRSA

Aztreonam

• this is another new (1987) β-***lactam*** antibiotic, first of the ***monobactam*** class
• general niche is as a safer agent for the treatment of ***gram negative*** infections

1. interfers with bacterial cell wall synthesis
2. bactericidal concentrations ~ inhibitory concentrations, ∴tolerance is ***unusual***
3. highly resistant to β-lactamases produced by GN bacteria
4. poor inducer of chromosomal β-lactamase production
5. virtually ***no nephrotoxicity***

■ ***Activity Spectrum***

a. gram positive aerobes * little or ***no activity***
b. anaerobes * little or ***no activity***
c. ***gram negative aerobes***
   - highly active against Enterobacteriaceae
   - activity is comparable to the aminoglycosides and 3rd generation cephalosporins
   - against *P. aeruginosa*, required concentrations are ~ 2x those of ceftazidime and it is less active than imipenem
   - organisms generally ***resistant*** include,

   i. *Citrobacter freundii*
   ii. *Enterobacter aerogenes* and *E. cloacae*
   iii. *Legionella pneumophilia*
   iv. the majority of strains of *Acinetobacter* sp.
   v. many strains of *Pseudomonas* spp. (*maltophilia, cepacia*)

■ ***Clinical Uses***

• penetrates most body fluids well, except the ***meninges***, ∴a 3rd generation cephalosporin is preferrable in this setting
• may be useful for oral prophylaxis in immunocompromised patients, effectively selectively decontaminating the GIT without significantly altering the anaerobic flora

• compared with the aminoglycosides, aztreonam

1. has an almost ***identical*** spectrum of activity
2. is effective in anaerobic conditions, acid pH, and abscesses
3. lacks nephrotoxicity
4. is considerably more ***expensive***

NB: ∴may be cost effective if requirement for routine ***drug levels*** is included

Aminoglycosides

a. "micin" - gentamicin, netilmicin, produced from *Micromonospora*

b. "mycin" - tobramycin, derived from a *Streptomyces* species

c. ***amikacin*** - semi-synthetic, derived from kanamycin-A

• penetrate the cell wall & membrane & bind to 30S bacterial ***ribosomes***, resulting in misreading of messenger RNA → nonfunctional proteins & cell death, ***bactericidal***
• factors supporting the recent change to ***once daily dosage***, (4.0-5.0 mg/kg/day)

1. bacterial killing is ***concentration dependent***
   - high peak levels are more effective and less toxic than intermittent low doses
   - studies show a clear positive relationship between the ratio of ***peak*** plasma levels, bacterial MIC, and clinical outcome
   - therapeutic levels require a ***peak* > 6 mg/l**, with no advantage > 10 mg/l
2. with respect to GNB, the is a prolonged ***post-antibiotic effect***
   - persistent suppression of bacterial growth following exposure to antibiotic
   - both concentration and time dependent
   - there may not be a requirement to administer AB immediately calculated drug levels fall below bacterial MIC
3. both *in vitro* and *in vivo* evidence that administration of subsequent aminoglycoside, while there is still trace aminoglycoside levels, may reduce or abolish the bacteriacidal effect → ***"adaptive resistance after first exposure"***
   - this is due to down-regulation of bacterial aminoglycoside uptake
   - models with *P. aeruginosa* show most bactericidal activity has not returned < 24 hours after the first exposure
4. ***renal cortical uptake*** and concentration is greater with infusions or multiple dose regimens, cf. single daily dosage of equal amount
   - renal toxicity relates directly to renal cortical aminoglycoside concentration

NB: 28 published trials comparing single daily with multiple dose regimens

→ ***efficacy*** 27 showed no statistical difference, 1 increased
nephrotoxicity lessened or delayed in 5, no different in remainder
ototoxicity 2 showed decrease, remainder no difference

no study has shown an advantage for conventional multiple dose regimens

• studies in ***neutropaenic*** patients support once daily dosing in this group
• while there has been no increase in toxicity, there is concern regarding the use of the same ***trough level*** for single daily dosage

1. trough of 1.5-2.0 µg/ml at 24 hours representing significant accumulation
   → AUC ~ **2.5** times that for the same trough and 8 hourly interval
2. patients with normal renal clearance have ***an undetectable trough level at 24 hours***
   → ∴ may be more appropriate to aim for same AUC, or trough < **0.8**

- ***Activity Spectrum***

a. gram positive aerobes
   - not recommended as sole agents
   - some activity, primarily against Staphylococci
   - ***synergistic*** with penicillins against,

   i. enterococci
   ii. viridans and other streptococci
   iii. MRSA & coagulase negative staphylococci (+ vancomycin)
   iv. *L. monocytogenes*

   - not active/synergistic against pneumococci

b. gram negative aerobes
   - particularly active against the Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* sp., *Providencia* sp.
   - ∴very useful in initial therapy of ***nosocomial infections***, usually in combination with a cephalosporin or extended spectrum penicillin
   - minimally active against *Neiserria* and *Haemophilus* sp.

c. anaerobes * ***no significant*** activity

NB: against susceptible pathogens, these agents have been shown to be equally effective;

tobramycin may be slightly more effective against *Pseudomonas aeruginosa*
gentamicin is slightly more effective against the *Enterobacteriaceae*

- poor oral absorption, ∴IV only, except if trying to minmise enteric bacterial load
- limited CSF penetration & narrow margin of safety preclude use in CNS infections
- if absolutely required, then give intraventricuarly (gentamicin ~ 4-8 mg, ***no formalin***)

- ***Side Effects***

1. ***nephrotoxicity*** * usually ***reversible***
   - overall incidence **~ 5-15%**
   - tobramycin may be slightly less nephrotoxic, but studies variable & small numbers

   i. high ***trough levels***
   ii. prolonged therapy
   iii. previous aminoglycoside therapy < 1 year
   iv. female gender
   v. dehydration, shock
   vi. bacteraemia / septicaemia
   vii. liver disease
   viii. other nephrotoxic drugs
      - loop diuretics
      - vancomycin
      - cephalosporins * follow-up multivariate study → ***no difference***

2. ***ototoxicity*** * usually ***irreversible***
   - clinically detectable hearing loss < 0.5%
   - audiometric deterioration **~ 2-12%**
   - selective destruction of the outer hair cells of the ***organ or Corti***
   - also ***vestibular*** dysfunction - nausea, vomiting, vertigo, nystagmus
   - increased with increasing duration of therapy
3. prolonged neuromuscular blockade
4. fever & rash

- ***Prevention of Nephrotoxicity***

1. correction of hypotension, hypovolaemia
2. use single daily (or longer) dosing, individualised to the patient & serum levels
3. use the shortest appropriate course
4. consider alternative agents for susceptible organisms
5. avoid the indiscriminate use of concomitant nephrotoxic agents

- ***Barza et al. BMJ 1996***

• metanalysis to assess relative efficacy and toxicity of aminoglycosides given by single daily dose compared with multiple daily doses
• 21 randomised trials overviewed with fixed effects and random effects models and with meta-regression analysis
• 3,091 patients with bacterial infection, most ***without*** pre-existing renal disease
• randomised to once daily or multiple dose regimens with similar total dose
• outcome measures for ***single daily dose*** against traditional regimen,

1. clinical failure of treatment
   - a non-significant decrease in risk of antibiotic failures
     (risk ratio 0.83 (95% CI 0.57 to 1.21))
   - benefit was greater when ***pseudomonas*** isolates in a trial were higher
2. nephrotoxicity, ototoxicity
   - reduced risk of nephrotoxicity (fixed effects risk ratio 0.74 (0.54 to 1.00))
   - similar trends in ***children*** & patients with ***febrile neutropenia***
   - no significant difference in ototoxicity, but the pooled power was low
3. mortality
   - there was no significant difference in mortality

NB: ∴ once daily administration in patients ***without*** pre-existing renal impairment is as effective as multiple daily dosing, has a lower risk of nephrotoxicity, and no greater risk of ototoxicity; thus, should be the preferred mode of administration

Erythromycin

- is a ***macrolide*** with a different chemical structure from the β-lactams
- inhibits protein synthesis at a ***ribosomal*** level & is usually ***bacteriostatic***
- believed one of the safest antibiotics in clinical use

Activity Spectrum

1. ***bacterial pathogens***
   - i. gram positive organisms
     - streptococci groups A, B, C, G, and *S. pneumoniae*
     - *S. aureus* is usually susceptible, but other agents are preferred
     - drug of choice for *C. diphtheriae*, and active against other *Corynebacterium*
   - ii. gram negative organisms
     - agent of first choice for - *L. pneumophilia, Legionella* spp.
       - *Bordetella pertussis*
       - *H. ducreyi*
       - *Campylobacter jejuni*
     - alternative for *Branhamella catarrhalis*, active against *N. gonorrhoea*
     - resistant organisms - Enterobacteriaceae
       ~ 40% of *H. influenzae*
   - iii. anaerobes * no clinically significant activity
2. ***nonbacterial pathogens***
   - i. mycoplasms - *M. pneumoniae* and *Ureaplasma urealyticum*
   - ii. clamydiae - *C. trachomatis, C. pneumoniae* (TWAR strain)
   - iii. spirochetes - *T. pallidum*, *Borrelia burgdorferi* (Lyme disease)

Drug of Choice

1. *M. pneumoniae* - may use tetracycline
   - erythromycin ~ 50x more potent
2. *L. pneumophilia, Legionella* sp. pneumonias
3. *C. trachomatis* pneumonia
4. *Bordetella pertussis* - whooping cough
5. *Campylobacter jejuni*
6. *Corynebacterium haemolyticum* - nonstreptococcal pharyngitis
7. *Corynebacterium diphtheriae*
8. *H. ducreyi* - chanchroid genital lesions

- ***Alternative in Penicillin Allergic Patient***

1. group A streptococcal URTI
2. *S. pneumoniae* pneumonia
3. dental prophylaxis for bacterial endocarditis
4. superficial staphylococcal infections *resistance may emerge during therapy
5. rheumatic fever prophylaxis
6. *T. pallidum* infections

- ***Drug Interactions***

1. theophylline → ↑ levels with erythromycin use
2. warfarin → ↑ hypoprothrombinaemic effect
3. carbamazepine → ↓ hepatic metabolism with erythromycin use
4. digoxin → ↑ GIT absorption with erythromycin use

- ***Adverse Effects***

1. GIT upset
2. cholestatic jaundice - rare, but only with the ***estolate*** (oral) preparation
3. transient deafness - reported rarely with high dose therapy
4. *C. difficile* diarrhoea
5. hypersensitivity reactions
   - fever, rash and eosinophilia are relatively ***uncommon***

Vancomycin

• early preparations contained substantial fermentation broth impurities with associated toxicity
• increased use in the 1980's due to,

1. infections with MRSA and coagulase negative staphylococci
2. resistant gram positive organisms
3. *C. difficile* diarrhoea complicating broad spectrum agents

• structurally ***unrelated*** to the β-lactams, ∴ useful in penicillin allergic patients
• ***bactericidal*** by inhibition of bacterial cell wall synthesis

NB: however, there is ***no*** competition for ***penicillin-binding proteins***
→ cross-resistance does not occur

■ ***Activity Spectrum***

1. gram positive organisms
   • active against virtually ***all*** GP organisms, including,
   i. enterococci - may only be bacteriostatic against some strains
      - occasional *E. fecium, E. faecalis* resistant
      * usually combined with ***aminoglycoside***
   ii. penicillin-resistant *S. aureus* and MRSA
   iii. MRSE - occasional isolates may be resistant, *S. haemolyticus*
2. gram negative organisms * ***no*** clinically useful activity
3. anaerobes * ***no*** clinically useful activity
   • does cover *Clostridium* spp., but clinically unimportant

• penetrates inflammed meninges, but treatment failures have occurred
• excreted primarily by the ***kidneys*** and requires dose adjustment with renal insufficiency,

a. peak levels ~ 30-40 µg/ml
b. trough ~ 5-10 µg/ml

■ ***Adverse Effects***

1. ototoxicity - generally only with levels > 80 µg/ml
2. nephrotoxicity - now believed to be ***uncommon***
3. red man syndrome * non-IgE mediated ***histamine*** release ∝ administration rate
4. skin rashes ~ 5%
5. phlebitis
6. ***neutropaenia*** - rarely with prolonged use

NB: ototoxicity & nephrotoxicity may be additive with aminoglycosides

Teicoplanin

- chemically similar, but with significant structural differences to vancomycin
- spectrum of activity virtually mirrors that of ***vancomycin***
- significant features,

1. long half-life allows ***once-daily*** administration
2. excellent gram positive ***bacteriacidal*** activity
3. useful for patients with allergic or neutropaenic responses to vancomycin
4. potentially ***less toxic*** than vancomycin
5. lesser requirement for dose adjustment in ***renal insufficiency***

Cloramphenicol

- ***Activity Spectrum***

a. gram positive aerobes
   - majority of GPC are susceptible, though the MIC's are moderately high
   - not considered a drug of choice against staphylococci or enterococci

b. gram negative aerobes
   - virtually all strains of *Haemophilus* and *Neisseria*
   - Enterobacteriaceae are susceptible, require sensitivity testing
   - *Pseudomonas* sp. are generally ***resistant***

c. anaerobes * ***virtually all***

d. Rickettsiae * most

- ***Adverse Effects***

1. bone marrow suppression
   i. dose related bone marrow suppression
   ii. rare $\rightarrow$ ***irreversible fatal aplastic anaemia***
2. grey baby syndrome
3. haemolysis with G6PD deficiency
4. ?? childhood leukaemia

Clindamycin

- lincomycin isolated in 1962, side-chain modified to produce clindamycin which is more active
- can be ***bactericidal*** or ***bacteristatic*** depending upon the concentration
- inhibits protein synthesis at the ***ribosomal*** level

Activity Spectrum

a. gram positive aerobes
   - active against group A *streptococci* and most strains of *S. aureus* (80-95%)
   - may be used as an alternative in penicillin/cephalosporin allergic patients
   - active *in vitro* against pneumococci
   - not active against ***enterococci***

b. gram negative aerobes * ***no significant*** activity

c. ***anaerobes***
   - active against both GP & GN anaerobes, including *B. fragilis* and *C. perfringens*
   - ***resistant*** ~ 20% of other *Clostridium* sp.
     ~ 10% of *Peptostreptococci*
     ≤ 5% of *B. fragilis*[§]

NB: severe infections, ***metronidazole*** is preferred due to small frequency of resistance[§]

Dosage

a. oral - 75 & 150 mg tablets
   ~ 300 - 450 mg q6h

b. IV ~ 600 mg q6-8h

Side Effects

1. hypersensitivity reactions ≤ 10%
2. higher frequency of *C. difficile* diarrhoea cf. metronidazole
3. minor elevation of LFT's is common
   - overt hepatitis is rare
4. bone marrow suppression has been reported, but rare
5. metallic taste when given IV

NB: nephrotoxicity does ***not*** appear to occur

Metronidazole

- ***Activity Spectrum***

  a. gram positive aerobes * ***no significant*** activity

  b. gram negative aerobes
     - some minor activity, but none clinically useful
     - *Gardnerella (H.) vaginalis* is susceptible

  c. ***anaerobes***
     - very active & ***bactericidal*** against both GP & GN anaerobes
     - including *B. fragilis* and other *Bacteroides* spp., *Clostridiidium* sp., *Fusobacterium* sp., *Peptococcus* and *Peptostreptococcus* sp.
     - *Proprionibacterium acnes* is highly ***resistant***

  d. ***parasites***
     - very active against *Entamoeba histolitica*, *Giardia lamblia* and *T. vaginalis*

- ***Limitations***

  a. pregnancy - reports of carcinogenesis in mice & rats

  b. lactating women

  c. pulmonary anaerobic infections
     - relative resistance of ***microaerophilic streptococci***

- ***Adverse Effects***

  a. carcinogenic potential
     - metronidazole ***has not*** been shown to be teratogenic in humans

  b. alcohol intolerance

  c. peripheral ***neuropathies*** - seizures have rarely been reported

  d. potentiation of warfarin

  e. minor GIT symptoms

Trimethaprim / Sulphamethoxazole

• both agents inhibit ***folate synthesis*** but at sequential steps, therefore combination,

1. produces ***synergistic*** activity
2. reduces development of ***resistance***

• optimal plasma ratio TMP:SMZ ~ 1:20
• penetrates the CNS well, with CSF levels ~ 40% of plasma

Activity Spectrum

a. gram positive aerobes
   - virtually all GP cocci, including many MRSA, *L. monocytogenes*
   - ***not*** active against enterococci

b. gram negative aerobes
   - ***most Enterobacteriaceae***, *Salmonella & Shigella* spp.
   - *H. influenzae* (amoxicillin sensitive/resistant), *Branhamella catarrhalis*
   - *P. cepacia & P. maltophilia (Xanthomonas)* usually susceptible
   - ***not*** active against *P. aeruginosa*
   - other organisms usually susceptible,

   i. *L. pneumoniae, L. micdadei*

   ii. *Yersinia enterocolitica, H. dulcreyi*

c. anaerobes * ***no significant*** activity

d. others - *P. carinii*
- *Nocardia* spp.

Drug of Choice

1. *Shigella* spp.
2. *Yersinia enterocolitica*
3. *Aeromonas* spp.
4. *P. cepacia & P. maltophilia (Xanthomonas)*
5. *P. carinii*

- ***Adverse Effects***

1. mild GIT sympotoms
2. ***skin rashes*** **~ 3.5%**
   - exfoliative dermatitis, Stevens-Johnson syndrome occur rarely
3. bone ***marrow suppression***
   - megaloblastic marrow changes are rare, except in patients with pre-existing folate store depletion (alcoholics, elderly, pregnancy, malnourished, phenytoin)
   - concomitant administration of ***folinic acid*** will reverse the antifolate effects
   - main problem group appears to be paediatric, non-AIDS patients ??
4. potential teratogenesis
5. potential kernicterus

Tetracyclines

• ***bacteriostatic*** agents, acting by interference with protein synthesis at the ***ribosomal*** level
• there are ***no important*** clinical differences in terms of activity

- ***Activity Spectrum***

a. gram positive aerobes
   - many strains of streptococci, staphylococci, and even pneumococci are ***resistant***
   - ∴ ***not*** recommended for GP infections

b. gram negative aerobes
   - most *Enterobacteriaceae & Pseudomonas* spp. are ***resistant***
   - uncomplicated *E. coli* infections are susceptible to urinary concentrations
   - effective against *Brucella* sp., *Calymmatobacterium granulomatis, Vibrio* spp., *Clamydia trachomatis*

c. anaerobes * ***no significant*** activity

d. ***other organisms***

i.	spirochetes	- *B. burgdorferi, B. recurrentis* - *T. pallidum, Leptospira* spp.
ii.	rickettsiae	- Q fever, typhus, etc
iii.	mycoplasms	- *M. pneumoniae, Ureaplasma urealiticum*
iv.	Clamydiae	- *C. psittaci, C. trachomatis, C. pneumoniae*
v.	mycobacterium	- *M. marinum, M. fortuitum*
vi.	*Nocardia* spp.	
vii.	short term prophylaxis for chloroquine-resistant *P. falciparum* malaria	

- ***Adverse Effects***

1. teeth & bone - depression of growth, discolouration
2. hypersensitivity - uncommon
3. GIT effects - frequent following oral administration
4. exacerbation of prerenal azotaemia
5. benign intracranial hypertension
6. oesophageal ulcerations
7. thrombophlebitis

Quinolones

• original prototype of this class was ***nalidixic acid***
• newer synthetic agents have modified the 2-member ring → 7-piperazine / 6-fluorine
• ciprofloxacin & norfloxacin were released in 1987
• action by interferring with DNA synthesis, inhibiting ***bacterial DNA gyrase***

■ ***Activity Spectrum Ciprofloxacin***

a. gram positive aerobes
   • *S. aureus* are moderately susceptible → MIC ~ 0.5-1.0 µg/ml
   • *S. epidermidis* is slightly more susceptible → MIC ~ 0.12-0.5 µg/ml
   • *S. pyogenes* & enterococci are moderately susceptible
   • other streptococci (pneumococcus, viridans, GBS) are relatively ***resistant***

b. gram negative aerobes *susceptibility ***break-point* < 1.0 µg/ml**
   i. highly susceptible
      • *N. gonorrhoea, N. meningitidis & H. influenzae* (± β-lactamase)
      • *Enterobacteriaceae* : *E. coli, Klebsiella, Enterobacter, Serratia, Salmonella, Shigella*
      • *L. pneumophilia, Acinetobacter, Campylobacter, Aeromonas, Yersinia, Pasturella, Branhamella*
   ii. intermediate sensitivity
      • *P. aeruginosa* → MIC ~ 0.5 µg/ml
   iii. ***resistant***
      • *P. cepacia, P. maltophilia*

c. anaerobes * ***no significant*** activity

d. others
   • *Mycoplasma pneumoniae, Bordetella pertussis*

• appear to penetrate the CSF adequately
• emergence of ***resistance*** is relatively ***uncommon***, with the exception of *S. aureus, P. aeruginosa*
• synergistic combinations vary, eg ciprofloxacin plus,

a. anti-pseudomonal penicillin ~ 20-50% of *P. aeruginosa* isolates
b. aminoglycoside ~ ***no synergy*** for *P. aeruginosa*

- ***Adverse Effects***

1. N,V & D ~ 5%
2. mild CNS problems ~ 1-4%
   - ***seizures*** have been reported but very rare
   - avoid with history of seizure disorder & avoid use with NSAIDs
3. skin reactions ~ 1-2%
4. cartilage erosions
   - not recommended for children or pregnant women
   - various studies now showing efficacy in children, without adverse effects
   - ∴ use on an as indicated basis
5. may increase plasma theophylline levels

Antibiotic Dosage

NB: adjustment in severe ***liver disease***

1. chloramphenicol
2. clindamycin
3. erythromycin
4. flucloxacillin
5. isoniazid
6. metronidazole
7. nafcillin
8. rifampicin
9. vancomycin

Antibiotic	Sensitive	Resistant
Cephalothin 1° Cefazolin	gram (+)'ves gram (-)'ves + *H. influenzae*	Enterococci, MRSA, *Pseudomonas*, *Acinetobacter*, *Proteus*, *Enterobacter*, *Serratia*, *B. fragilis*
Cefoxitin 2° Cephamandole	gram (+)'ves gram (-)'ves + *H. influenzae* anaerobes ± *B. fragilis*	Enterococci, MRSA, *Pseudomonas*, *Enterobacter*, *Listeria* *B. fragilis* if mixed infection
Cefotaxime 3°	gram (+)'ves gram (-)'ves + *H. influenzae* anaerobes ± *B. fragilis*	Enterococci (*S. faecalis*), MRSA, *Listeria*, *Pseudomonas*, *Acinetobacter* C. *difficile* ± *B. fragilis*
Ceftriaxone 3°	gram (+)'ves gram (-)'ves + *H. influenzae* ± *Pseudomonas* anaerobes ± *B. fragilis*	Enterococci, MRSA, *Acinetobacter*, *Listeria* C. *difficile*
Ceftazidime 3°	gram (+)'ves (weak) gram (-)'ves + *H. influenzae* + *Pseudomonas* anaerobes	Enterococci, MRSA, *Campylobacter*, *Listeria* *C. difficile*, *B. fragilis*

Antibiotic	Sensitive	Resistant
Imipenem	gram (+)'ves + *Strep. faecalis* gram (-)'ves anaerobes + *Bacteroides*	*S. epidermidis*, MRSA, *S. fecium*, Corynebacterium, *P. maltophilia*, *P. cepacia*, Flavobacterium C. *difficile*
Timentin	gram (+)'ves gram (-)'ves anaerobes	MRSA, ± Pseudomonas, Enterobacter (some species)
Gentamicin	Staph. (most) ± Strep. *faecalis* gram (-)'ves	*S. pneumoniae*, most *S. faecalis*, MRSA, Neisseria, Acinetobacter, Providentia & resistant Pseudomonas, ***all*** anaerobes
Tobramycin	Staph. (most) ± Strep. *faecalis* gram (-)'ves + Pseudomonas + Acinetobacter	Strep. *pneumoniae*, some Strep. *faecalis*, MRSA, Neisseria Providentia & resistant Pseudomonas ***all*** anaerobes

Amphotericin

- still the most effective agent for the majority of fungal infecions
- binds to ***ergosterol***, the main component of susceptible fungal cell membranes
  → increasing ***permeability*** resulting in cell death
- ***outcome*** does not appear to be related to plasma levels
- poorly absorbed from the GIT
- poor penetration into,
  a. spinal fluid
  b. aqueous humour
  c. urine & dialysis fluid

- elimination occurs slowly via the ***biliary tract***
- no uniform agreement on the optimal mode of administration
- we use,

1.	test dose	~ 1-5 mg + hydrocortosone 100 mg IV	
2.	incremental doses	~ 5-10 mg/day	
3.	maximal doses	~ 50 mg/day	(some use 0.7-1.0 mg/kg)

- standard infusion rate is 4-6 hours
- some believe the incidence of adverse reactions may be ***reduced*** by ***faster*** infusion
- however, results in release of ***potassium*** from mammalian cells
- therefore may produce hyperkalaemia & infusion should be over ≥ 1 hr
- most agree that if Cr > 200-300 µmol/l then should either,
  1. decrease dose
  2. use alternate day regimen
  3. hold therapy until renal function improves

- ***Combination Therapy***

  1. ***flucytosine***
     - synergistic with, especially for cryptococcal infections in non-AIDS patients
  2. rifampicin
     - preliminary studies suggest may also be synergistic

- ***Toxicity***

1. fever & rigors
2. anorexia, N&V
3. ***nephrotoxicity***
   - early toxicity → dose related
   - late toxicity → proportional to ***cumulative dose***
   - usually reversible early, later may become dialysis dependent
   - frequency may be reduced by ***saline loading***
4. ***anaemia***
   - direct bone marrow depression occurs in ~ 75%
   - usually mild, leukopaenia & thrombocytopaenia are rare
5. ***hypokalaemia***
   - secondary to renal tubular dysfunction ~ 25%
6. phlebitis

Flucytosine 5FC

- converted to ***5-fluorouracil*** within sensitive fungal cells, then interfers with protein synthesis
- widely distributed to all body fluids, especially CSF
- > 90% eliminated unchanged in the urine
- dose,

1. normal renal function ~ 12.5-37.5 mg/kg po q6h
2. renal dysfunction
   - according to plasma levels ~ 50-100 µg/ml

- rapid emergence of ***drug resistance*** precludes use as a single agent
- often combined with Amphotericin B in non-AIDS patients

- ***Toxicity***

1. hepatic dysfunction ~ 5%
2. leukopaenia / thrombocytopaenia
   - potentially lethal & more common in conjunction with Amphotericin B
3. GIT intolerance
4. teratogenic effects
5. severe ***marrow depression*** in AIDS patients with Amphotericin

Fluconazole

• ***bis-triazole*** antifungal agent, released early 1990
• mechanism similar to ketoconazole, inhibition of ***sterol-14-α-demethylase***, with subsequent membrane enzyme dysfunction & growth inhibition

NB: depletes ***ergosterol***, to which amphotericin binds,
∴ co-administration theoretically ***contraindicated***

• reliable GIT absorption > 90%
• renal excretion ~ 80%
• plasma elimination $t_{½\beta}$ ~ 25 hrs
• good penetration into,

a. CSF - levels ~ 60-80% of plasma
*cf. amphotericin & ketoconazole
b. urine - effective in urinary tract candidiasis
c. sputum, saliva and skin

■ ***Dosage***

a. oropharyngeal candidiasis - 200 mg first day, then 100 mg daily
oesophageal candidiasis
b. cryptococcal meningitis
i. suppression - 200 mg daily
ii. therapy - 400 mg first day, then 200 mg daily
c. Rex study ~ 400 mg/day

■ ***Side Effects***

a. rash ~ 4-5%
b. nausea & vomiting ~ 8-10%
c. Stevens-Johnson syndrome
d. thrombocytopaenia
e. ***hepatotoxicity***
• transient ↑ LFTs common, especially in AIDS patients
f. adrenal suppression virtually ***absent***, cf. ketoconazole

■ ***Metabolism of Imidazoles***

• imidazole antifungal agents include ketoconazole, fluconazole, and itraconazole
• they work by inhibiting a P_{450} enzyme in fungi, ***lanosterol 14-demethylase***
• they are potent human P_{450} inhibitors
→ ***ketoconazole*** is often used in hepatocyte cultures to inhibit ***3A***
• both ketoconazole and itraconazole have been shown in human volunteers to increase midazolam peak concentration 3-4 fold, presumedly through 3A inhibition
• although *in vitro* the relative potencies are debated, for cyclosporin metabolism the order is,

a. ketoconazole > itraconazole > fluconazole
b. with ketoconazole 500 times more inhibitory than fluconazole

NB: ∴ ***fluconazole*** is likely to be clinically interaction-free for 3A drugs

• however, some impairment of phenytoin clearance has been demonstrated
• they have also been shown to have an ***immunosuppressive*** effect, strongly diminishing CD_3-induced human ***T cell proliferation***, due to a marked inhibition of IL-2 synthesis
• this may explain the report of decreased ARDS mortality with ketoconazole therapy

■ ***Savino et al. J-Trauma 1994***

• a PRCT to determine if ***prophylactic*** antifungal agents prevented ***yeast colonization*** (YC) or ***yeast sepsis*** (YS), or if they diminish ***mortality***
• 292 adult (nontransplant / nonburned) surgical and trauma patients, SICU > 48 hours
• randomized to receive,

1. group I - no therapy
2. group II - clotrimazole 10 mg tds
3. group III - ketoconazole 200 mg per day, or
4. group IV - nystatin 2 MU qid

• patients were stratified by the criteria of Slotman and Burchard (14 risk factors) into,

1. high risk ≥ 3 risk factors
2. low risk < 3 risk factors

NB: ***no significant*** difference between the four groups with regard to YC (23%, 18%, 12%, and 15%, respectively), YS (3%, 1%, 2%, and 7%, respectively), or mortality (15%, 14%, 6%, and 20%, respectively)

• 50 patients (17%) had yeast colonization, nine (3.1%) had yeast sepsis, and 41 (14%) died
• stepwise LR analysis for significant predictors of yeast colonization and sepsis →

1. treatment with three or more antibiotics
2. APACHE II > 10
3. ventilatory support > 48 hours

■ ***Winston et al. Ann-Intern-Med. 1993***

• PRCT (multicenter) of 257 adults undergoing chemotherapy for acute leukemia to evaluate the efficacy and safety of ***fluconazole*** for prevention of fungal infections
• patients assigned to receive either,

1. fluconazole - 400 mg orally once daily, or
   fluconazole - 200 mg IV bd
2. placebo

• the study drug was started at initiation of chemotherapy and continued until recovery of neutrophil count, development of proven or suspected invasive fungal infection, or the occurrence of a drug-related toxicity
• fluconazole decreased,

1. fungal colonization p < 0.001
   i. placebo patients - 83 of 122 68%
   ii. fluconazole patients - 34 of 119 29%
2. proven fungal infections p = 0.02
   i. placebo patients - 27 of 132 21%
   ii. fluconazole patients - 11 of 123 9%
3. superficial fungal infections p = 0.01
   i. placebo patients - 20 of 132 15%
   ii. fluconazole patients - 7 of 123 6%
4. invasive fungal infections p = 0.3
   i. placebo patients - 10 of 132 8%
   ii. fluconazole patients - 5 of 123 4%

• fluconazole was especially effective in eliminating colonization and infection by Candida species other than *Candida krusei*
• Aspergillus infections were infrequent in both fluconazole (3 cases) and placebo groups (3 cases)
• the use of amphotericin B, the incidence of drug-related side effects, and overall mortality were similar in both study groups

NB: prophylactic fluconazole prevents ***colonization*** and ***superficial infections*** by Candida species other than *Candida krusei* in patients undergoing chemotherapy for acute leukemia

fluconazole ***could not*** be clearly shown to be effective for preventing ***invasive*** fungal infections, reducing the use of amphotericin B, or decreasing ***mortality***

■ ***Rex, et al.*** ***The Candidaemia Study Group*** ***NEJM 1994***

• multicentre, randomized trial of amphotericin ~ 0.5 mg/kg/day
versus fluconazole ~ 400 mg/day,

a. 206 ***non-neutropaenic*** patients

b. mean APACHEII ~ 16 - not different between groups

c. mostly renal failure, non-haematological cancer & GIT disease

d. predominant species was *Candida albicans* ~ 60% of isolates

i. peripheral venipuncture ~ 64%

ii. CVC sample ~ 16%

e. ***vascular catheters*** were the most likely source ~ 72% of cases

• results,

1. no statistically significant difference in ***outcome*** by primary analysis
   - except for secondary analysis of patients treated for at least 5 days
   - successful outcome for amphotericin (86%) vs fluconazole (75%) [p = 0.05]
2. ↑ Cr/BUN
   - amphotericin ~ 37%
   - fluconazole ~ 2% [p < 0.001]
3. hypokalaemia
   - amphotericin ~ 10%
   - fluconazole ~ 2% [p = 0.006]
4. ↑ LFTs
   - amphotericin ~ 10%
   - fluconazole ~ 14% [p = 0.43]

NB: renal dysfunction resulted in cessation of amphotericin in 3 patients,
liver dysfunction resulted in cessation of fluconazole in 2 patients

• the most frequent site of ***secondary spread*** was the eye, with retinal lesions in 29/206 patients
• problems,

a. patient group only included ~ 10 patients with deep/intra-abdominal infection
   - ie. how applicable is this data to deep seated infection in ICU ?

b. 62 patients in each group underwent complete catheter exchange on day one
   - in 10 of the amphotericin group and 7 for fluconazole this was ***over wire***

Antibiotic Resistance

• first resistance reported in 1940 by Abraham & Chain

→ *E.coli* (*B. coli*) producing ***penicillinase***

• 1944 Kirby reported similar resistance in *S. aureus*
• multiple other isolated of *in vitro* resistance ***prior to*** the widespread use of antimicrobial agents

NB: ∴ resistance is not simply a consequence of antibiotic use,
but is integral to the bacteriums natural defence mechanisms

• early 60's & 70's recognition of strains of *H. influenzae* and *N. gonorrhoeae* which had acquired genetic information for production of β-lactamase

■ ***Factors Producing Resistance***

1. ***common gene mutation***
   - best example is current emergence of ***extended spectrum β-lactamases***
   - ESBL's first reported in 1982 in *E. coli*
   - that ESBL was only 3 AA different from the 'wild-type' β-lactamase of ampicillin resistant *E. coli* strains
   - ESBL's now number **> *30 types***
   - other mutations may affect resistance,

   i. genes coding for ***membrane permeability***

   ii. genes coding for target ***protein synthesis***

2. ***genetic exchange***
   - mechanisms of exchange include,

   i. ***transformation*** - uptake of naked DNA

   ii. ***transduction*** - transfer of DNA by bacteriophage

   iii. ***conjugation*** - cell to cell transfer, ie. ***plasmids***
   - process may extend to include highly ***unrelated*** groups of organsisms,
     eg. *Campylobacter coli* & *enterococci*
   - however, differences in genetic control mechanisms between species may limit ***expression*** & functionality of acquired DNA
   - though, clinically relevant examples exist, eg. *enterococcal* genes coding for gentamicin resistance and β-lactamase were acquired from *staphylococci*
   - USA nosocomial *enterococci* isolates resistant to vancomycin, VRE
     → 0.4% in 1989 → ↑ **13.6%** in 1993

3. ***selective pressures*** *institution & community
   - hypothesised mutant cells would not survive if not for selection
   - Atlanta, USA, **25%** of *pneumococcus* penicillin resistant, 9% to cephalosporins
   - among 3 children with 3rd generation resistant pneumococcal meningitis, ***all*** had received prior therapy with cephalosporins for otitis media

Resistance Testing

• vancomycin resistance in *enterococci* is difficult to detect by automated methods
• major problem with cephalosporin resistance in GNB's, especially that mediated by ESBL's

1. MIC ***breakpoints*** for "susceptibility" were set prior to the existence of these enzymes
   - based on bacterial population susceptibilities
   - now effectively 3 populations, not 2
2. MIC's for ESBL containing bacteria may vary from 4 µg/ml to 256 µg/ml
   → ie. from "susceptible" to highly resistant
3. usual MIC of *Klebsiella pneumoniae* to ceftazidime ~ 0.06 µg/ml,
   ∴ may have ***50-fold*** decrease in sensitivity & still be reported as "susceptible"

Optimising Hospital Antibiotic Use JAMA 1995

1. optimise choice and duration for ***surgical prophylaxis***
2. optimise choice and duration of ***empiric therapy***
3. achieve 1&2 by educational & administrative means
4. establish system to monitor & feedback on occurrence of ***resistance***
5. develop institutional guidelines for use of "important" types of antimicrobials

Minimising Organism Resistance

1. system to monitor, recognise, and rapidly report changes in ***resistance patterns***,
   i. at an institutional level
   ii. at a patient-caregiver level
2. increased adherence to standard ***infection control*** measures
3. develop a plan for identifying, transferring, discharging & readmitting patients colonised with ***specific antimicrobial-resistant pathogens***

ANAEROBIC INFECTIONS

Def'n: ***anaerobic bacteria*** require a reduced O_2 tension for growth, failing to grow on solid media in 10% CO_2 in air

microaerophilic bacteria require oxygen for growth, can grow in 10% CO_2 in air, or in aerobic conditions

facultative bacteria can grow in the presence or absence of air

NB: organisms causing human infections are usually ***aerotolerant***, ***mixed*** infections with anaerobic, facultative, and aerobic species

- most important anaerobes,
  a. *Bacteroides* *out of proportion to gut content
  b. *Fusobacterium*
  c. anaerobic Streptococci - *Peptostreptococci*, microaerophilic strep.
  d. Clostridia

- anaerobic ***virulence*** features,
  a. adherence factors
  b. low immunogenicity of capsule
  c. enzyme production - protease
     - superoxide dismutase
  d. produce antibacterials - β-lactamase
  e. lipopolysaccharides which reduce effectiveness of phagocytosis

- ***Antibiotics Effective Against Anaerobes***

a. good against ***all*** anaerobes
- Imipenem
- Timentin
- Chloramphenicol
- Clindamycin / Lincomycin

b. Penicillin G
- highly effective against anaerobic cocci
- active against many *Bacteroides* species, especially oral
- ***not effective*** for *B. fragilis* from bowel sources, 2° β-lactamases

c. Cephalosporins
- cefotaxime, ceftriaxone suitable for respiratory pathogens (oral anaerobes)
- the 2nd generation agents are more active than 3rd generation agents
  → effective against 80-95% of strains of *B. fragilis*
- none of the 3rd generation agents suitable for colonic anaerobes
- less Clostridial cover

d. Metronidazole
- drug of first choice for enteric anaerobes
- not effective against Actinomyces, *Proprionibacterium acnes* is highly resistannt

- ***Manifestations***

a. Oral
- dental abscesses
- Ludwig's angina
- necrotizing gingivitis

b. Cerebral
- subdural/intracerebral abscess
- chronic otitis media or sinusitis
- otogenic meningitis

c. Skin
- necrotizing cellulitis, fasciitis
- wound abscess
- gangrene
- human bite infections

d. Lung
- aspiration pneumonia
- lung abscess, empyema

e. GIT
- hepatic abscess, peritoneal abscess
- pelvic abscess, pelvic cellulitis

f. GUT
- pyelophlebitis
- tubo-ovarian abscess
- endometritis
- pyometra

- ***Clinical Features***

  a. foul odour

  b. abscess, necrotic tissue, gangrene

  c. crepitus from gas production

  d. septic thrombophlebitis

  e. sites as above

  f. spread through tissue planes - subcutaneous
  - fascia, muscle

- ***Bacteroides Sp.***

  - brain abscesses ~ 50%
  - post-op. wound infections ~ 50% (emergency or elective bowel surgery)
  - aspiration pneumonitis ~ 30-40%
  - hepatic/pelvic abscesses ~ 20-45%

Specific Cases

- ***Bacterial Synergistic Gangrene***
  - mixed-anaerobic infection
    i. anaerobic and microaerophilic Strep.
    ii. gram (-)'ve bacilli
    iii. ± *Staph aureus*
  - occurring also at surgical wound but causing spreading necrotic infection with little systemic effect
  - R_X: gentamicin/tobramicin 1.5 mg/kg/q8h + clindamycin 600 mg/q6h
    ± penicillin for ↑ clostridial cover
    early surgical review
  - requirement for cover for *B. fragilis* is determined by the likelihood of penetration of an abdominal viscera
  - if no penetration, then penicillin & an aminoglycoside will suffice

- ***Fournier's Gangrene***
  - mixed anaerobic cellulitis of scrotum, perineum, anterior abdominal wall
  - rapidly spreading along deep fascial plains
  - best considered a form of bacterial synergistic gangrene

- ***Meleney's Ulcer***
  - anaerobic and microaerophilic Streptococcal infection of surgical wound producing undermined ulcer and systemic toxicity

- ***Meleney's Cellulitis***
  - synergistic infection with Staph. and anaerobic Strep.
  - best considered a form of bacterial synergistic gangrene

- ***Necrotizing Fasciitis***
  - acute streptococcal (***not anaerobic***) widespread fascial necrosis
  - see over

Necrotizing Fasciitis

Def'n: ***aerobic***, usually gram (+)'ve spreading superficial infection of skin and subcutaneous tissues, resulting in skin necrosis

- ***Clinical Features***

a. superficial widespread fascial necrosis
b. blue/brown skin discolouration due to ***ecchymoses***
c. cutaneous gangrene, oedema, tenderness
d. frequently lower limbs, following minor trauma or infection
e. subcutaneous emphysema is ***rare***
f. vesicles occasionally form
g. systemic features
   - jaundice
   - septic shock
   - acute lung injury
h. wide range of ages

- ***Causative Organisms***

a.	Streptococci	~ 45%	- haemolytic, ? pyogenes
b.	Staphlococci	~ 45%	- haemolytic
c.	gram negatives	~ 10%	- *Pseudomonas, E. coli*

- ***Preceding Event***

a.	minor trauma	~ 80%
b.	postoperative	~ 10%
c.	diabetes	~ 5%

Synergistic Necrotizing "Cellulitis"

Def'n: mixed aerobic/anaerobic, (usually gram (+)'ve & anaerobic Strep.), causing widespread infection of ***deep fascial layers*** and muscle (similar to gas gangrene), with little superficial involvement
→ ie. this is a ***misnomer***

- ***Clinical Features***

a.	discharging ulcer with foul-smelling "dish-water" pus	
b.	subcutaneous ***emphysema***	~ 25%
c.	severe ***tenderness*** without obvious superficial infection	
d.	skin changes uncommon	
e.	systemic toxicity common	~ 65%
f.	site of infection	~ 50% perineum ~ 25% thigh ~ 13% leg - feet, arms, neck
g.	associations	~ 75% diabetes ~ 70% obesity ~ 33% CVS + renal disease - cachexia
h.	systemic features	- fever, anaemia - diabetic ketoacidosis
i.	high ***mortality***	~ 70%

- ***Causative Organisms***

a.	aerobes	~ 40% Klebsiella ~ 30% E. coli ~ 40% Proteus - Pseudomonas
b.	anaerobes	~ 50% Streptococci ~ 25% Bacteroides

NB: ***Meleny's synergistic cellulitis*** is a similar mixed infection, but involves *Staph. aureus* and anaerobic Strep.

Botulinism

NB: rare neuromuscular disorder resulting from ***bacterial neurotoxin***

a. neurotoxin from *Clostridium botulinum*
   - anaerobic, spore forming, gram-positive rod

b. 8 serotypes:
   i. **type A** ~ 58%
   ii. type B ~ 25%
   iii. type E ~ 17%
   iv. C_1, C_2, D, F, & G

c. bilateral ***descending*** weakness - starting with cranial nn.

d. risk of toxin ingestion (food borne) or GIT colonization

e. ***absence*** of - sensory deficit
   - fever
   - altered mental status

f. heat labile ~ 80°C for 15 minutes

g. spores are heat stable & germinate if - pH < 4
   - presence of H_2O
   - T > 4°C

h. ***prejunctional***, non-competitive blockade → ↓ ACh release
   - binds ***irreversibly*** to motor nerve terminals, ∴ require ***new synthesis***
   - anti-toxin is of ***no value*** once clinical signs evident

- ***Clinical Features***

a. incubation period ~ 6 hrs - 8 days
   ~ 24 hrs average

b. mortality ~ 15%

c. presentation types,
   i. infantile
   ii. adult intestinal infection
   iii. food borne
   iv. wound infection
   v. source unknown

d.	***CNS symptoms***	- dysphagia	~ 96%
		- dry mouth	~ 93%
		- diplopia	~ 91%
		- dysarthria	~ 84%
		- UL weakness	~ 73%
		- LL weakness	~ 69%
		- blurred vision	~ 65%
		- dyspnoea	~ 60%
		- paraesthesiae	
e.	***CNS signs***	- UL weakness	~ 75%
		- ptosis	~ 73%
		- LL weakness	~ 69%
		- loss of gag reflex	~ 65%
		- ophthalmoplegia	~ 65%
		- facial weakness	~ 63%
		- tongue	~ 58%
		- dilated pupils	~ 44%
		- nystagmus	~ 22%
		- ataxia	~ 17%
f.	GIT signs	- constipation	~ 73%
		- nausea	~ 64%
		- vomiting	~ 59%
		- cramps	~ 42%
		- diarrhoea	~ 20%

■ ***Diagnosis***

• clinical features as above, plus

1. positive ***toxin assay*** * blood or faeces
   - < 24 hours after onset
   - toxin may be detected for 7-30 days following exposure
2. ± stool culture for *Cl. botulinum*
3. CSF protein levels are normal
4. ± peripheral nerve stimulator → ***tetanic recruitment***
   no fade

NB: the ***tensilon test*** may be falsely positive

Differential Diagnosis

• of bulbar and pseudobulbar palsy,

1. myasthenic crisis
2. atypical GBS
3. early tetanus
4. multiple sclerosis - acute exacerbation
5. motor neurone disease
6. poisoning - organophosphates, shellfish, tick paralysis
7. drugs - nitrofurantoin, perhexiline, dapsone
8. acute intermittent porphyria
9. pontine disease - infarction, central pontine myelinolysis
10. polyarteritis nodosa - mononeuritis multiplex
11. infections - poliomyelitis, diphtheria, infectious hepatitis
12. malignancy - Eaton-Lambert syndrome (mainly limb girdle)

• risk factors for intestinal colonisation,

a. infants ~ 2-6 months
b. broad spectrum antibiotics
c. achlorhydria*
d. post-gastrectomy* *loss of gastric acidity

Treatment

a. ABC support ± ETT & mechanical ventilation
   - respiratory muscle weakness may last for up to ***3 months***

b. ***antitoxin*** - two doses 4 hrs apart
   - however, 20% get an ***adverse reaction***
   - probably of no use once symptoms occur
   - no evidence that mortality is reduced

c. high dose ***penicillin***
   i. wound infection
   ii. GIT colonisation
   iii. unknown origin
   iv. ? Vancomycin

d. gastric lavage & enemas

Tetanus

Def'n: a ***toxi-infection*** which occurs when *Clostridium tetani* invades a host and produces the neurotoxin ***tetanospasmin***, which enters the nervous system resulting in,

1. disordered neurotransmission both centrally and peripherally
2. widespread CNS ***hyperexcitation***

■ ***Aetiology***

• *Clostridium tetani* is a ***gram positive obligate anaerobe***
• spors are ubiquitous in soil and feces
• following access to devitalised tissue, spors proliferate in the vegetative state producing,

1. ***tetanospasmin*** TT - the principal neurotoxin
2. tetanolysin - clinically less significant

■ ***Pathogenesis***

• TT is distributed widely via the bloodstream
• taken-up exclusively by the NMJ of motor neurones & is transported proximally to the CNS
• TT is concentrated in cell bodies, from which it diffuses & gains access to the ***presynaptic*** terminals of adjacent neurones, preferentially ***inhibitory interneurones*** (glycine/GABA-ergic)
• prevents neurotransmitter release $\propto$ calcium influx in all affected neurones
• there is a resultant ***disinhibition*** both from higher centres and locally within the spinal cord
• this affects both agonist and antagonist ***motor*** units simultaneously, and in severe cases also affects the ***autonomic*** nervous system

■ ***Immunisation***

• natural immunity ***does not*** occur
• the lethal dose of TT is well below the dose required to invoke humoral immunity
• all patients should be actively immunised following control of infection
• mothers of affected neonates should also be immunised

■ ***Outcome***

• theoretically recovery should be complete
• followup studies have shown subtle CNS and muscular abnormalities in long-term survivors
• in ***non-neonates***, mortality relates directly to,

1. the ***age*** of the patient
2. the inverse of the ***incubation period***

NB: average mortality (USA) ~ **10%**

■ ***Clinical Features***

• the ***incubation period*** is related directly to the time required for TT production, uptake and distribution within the CNS
• this may vary from 1 day to several months, with an average time of 3 days to 3 weeks
• periods ***less than 24 hours*** are associated with significantly higher ***mortality***
• 75% of non-neonatal cases present with ***trismus*** and the disease usually progresses in a ***descending*** fashion,

1. trismus
2. dysphagia
3. risus sardonicus
4. muscle spasms
   i. spine - neck stiffness, opisthotonus
   ii. limbs - flexion and abduction of the arms, with extension of the legs
   iii. larynx & diaphragm - respiratory arrest
   - these are frequently very ***painful*** due to discordinate activity
   - may be associated with tendon separation or bony damage
5. ***autonomic dysfunction***
   - occurs in severe cases
   - onset is usually several days ***after*** the onset of spasms
   - increased basal sympathetic tone, with episodic marked ***sympathetic overactivity***
   - raised plasma noradrenaline levels, plus adrenaline from ***adrenal disinhibition***
   - may also manifest periods of sympathetic failure, with bradycardia, hypotension and occasionally cardiac arrest (especially IV drug abusers)
6. ***neonatal tetanus***
   - presents most commonly about day 7 with a short history of failure to feed
   - the typical spasms are present however may be mistaken for convulsions
   - vomiting due to raised intra-abdominal pressure may be prominent

■ ***Differential Diagnosis***

1. strychnine poisoning - receptor blockade on ***post-synaptic*** inhibitory neurones
   - clinically may appear very similar
2. dystonic reaction - tricyclics, phenothiazines, propofol
3. temporomandibular disease
4. local oral disease
5. convulsions
6. muscular tetany
7. CNS infections or haemorrhage
8. psychiatric disorders

- ***Complications***

1. hypoxaemia
2. those 2° to mechanical ventilation
3. those 2° autonomic instability
4. myoglobinuria ± renal impairment
5. septic complications - especially nosocomial pneumonia
6. those of prolonged bed rest
   i. pressure sores
   ii. deep venous thrombosis ± embolic phenomena
   iii. prolonged ileus
   iv. muscle wasting & osteoporosis
7. SIADH
8. psychiatric

- ***Treatment***

• the objectives of management are,

1. to neutralise ***circulating neurotoxin***
2. to eradicate the ***source*** of the toxin
3. to minimise the effects of already ***bound toxin***
   i. muscle spasms
   ii. autonomic dysfunction
4. provision of general ***supportive care***

• ***tetanus immune globulin*** 500^{U} IM is as effective as higher doses & should be given immediately
• TIG ***cannot*** penetrate nerve fibres or the blood brain barrier, and is ineffective intrathecally

• the infected site should be located & aggressively debrided surgically
  → however, in ~ 20% no infective site can be found
• ***metronidazole*** is the drug of choice, being more effective than penicillin
• it has a narrow spectrum against anaerobes & penetrates devitalised tissue well
• ***penicillin*** is a GABA antagonist in the CNS and may aggravate spasms
• randomised trial in Lancet (?BMJ) showing lower mortality in metronidazole group

• the presence of ***muscle spasms*** mandates early securing of the ***airway***
• much of the increase in muscle tone may be managed with ***heavy sedation***
• this will also allay much of the autonomic dysfunction
• where the respiratory muscles are involved ***paralysis*** is required
• vecuronium has the least cardiac side-effects, pancuronium having the propensity to exacerbate tachycardia & hypertension

• traditionally a combination of **α/β-*blockade*** has been used
• α-blockade should be instituted first, as the use of unopposed β-blockade may increase TPR and result in CCF and and arrest
• ***chlorpromazine*** is a useful agent, as it also has CNS sedative effects
• ***esmolol*** allows titration of the level of β-blockade but is excessively expensive
• SNS blockade, if not readily reversible, has the potential to worsen periods of bradycardia and hypotension

• a more logical approach is to decrease CNS outflow
• as stated above ***heavy sedation*** will reduce SOA
• both morphine and benzodiazepines act centrally to minimise the effects of TT
• ***clonidine*** has been used successfully to reduce CNS outflow & avoids the problems of receptor downregulation
• ***magnesium*** may be useful as an additional agent, between 2.5-4 mmol/l

a. producing a significant drop in SVR with a small fall in CO
b. inhibiting the release of,
    i. adrenaline from the adrenal medulla
    ii. noradrenaline from peripheral nerve terminals
c. reducing the sensitivity of α/β receptors
d. neuromuscular blockade

• however, Mg^{++} cannot be used without sedation, and supplemental Ca^{++} may be required
• intrathecal ***baclofen*** has been used in refractory cases, however may result in respiratory depression

■ ***Supportive Therapy***

a. fluid & electrolyte balance
b. pulmonary care - ***early tracheostomy***
    - regular toilet & secretion clearance
c. nutrition - ***enteral*** preferrably if ileus is not profound
d. bowel care - avoidance of constipation
e. DVT prophylaxis
f. physiotherapy - muscle contractures
    - respiratory function
g. posture & pressure sores
h. psychotherapy if required
i. ***active immunisation*** - patient
    - plus mother if a neonate

Other Clostridial Infections

Species	Clinical Syndrome
Cl. tetani	• tetanus
Cl. botulinum	• botulinism
Cl. perfringens *Cl. septicum* *Cl. bifermentans* *Cl. novyi*	• gas gangrene → clostridial ***myonecrosis***
Cl. perfringens (type A)	• food poisoning • puerperal sepsis • massive intravascular haemolysis • cellulitis (with gas formation) • gaseous cholecystitis
Cl. difficile	• pseudomembranous colitis

- ***Rare Presentations***

a. surgical wound infection
b. cystitis & pneumaturia
c. osteomyelitis
d. arthritis, bursitis
e. endocarditis

DISSEMINATED TUBERCULOSIS

- incidence is increasing, especially among adults
- presentation of fatal TB,
    a. ARDS
    b. pneumothorax
    c. meningitis
    d. hepatic failure
    e. adrenal failure
    f. acute pericarditis
    g. TB aneurysm

- aetiological agent ***Mycobacterium tuberculosis*** (var. hominis)
- culture positive in 6-8 weeks
- ***acid fast bacillus*** →
    a. stain with Zeihl-Neelsen process
    b. ***fluorescent stains*** ~ 3x more sensitive

    NB: diagnostic criteria → microscopy ≥ 10^5 organisms/ml

- histologically forms ***granulomata***, with
    a. central Langerhan's giant cells
    b. mid-zone of "epithelial" cells
    c. peripheral zone of lymphocytes
    d. progression to central ***caseation*** and destruction of surrounding tissue

- pathogenesis of ***dissemination*** is haematogenous spread of multiple bacterial emboli,
    a. spread from 1° infection ~ 5%
    b. decreased host defence mechanisms
    c. erosion of granulomata into vessel with "reactivation"

- organ involvement,
    a. lungs ~ 20%
    b. lymph nodes ~ 14%
    c. multiple sites ~ 39%
    d. multiple organ involvement without granuloma formation *terminal event

    NB: → kidneys, adrenals, CNS, liver, pleura, pericardium, GIT, eyes, joints

- ***Predisposing Factors***

NB: ***all*** probably act by impeding ***CMI***

a. higher incidence in Negroid races[§] [§]***genetic*** factors
b. B_{W15} antigen[§]
c. alcoholism
d. malnutrition
e. pregnancy
f. uraemia
g. leukaemia → ***acquired*** factors
h. steroid therapy
i. cytotoxic chemotherapy
j. immunosuppression
k. AIDS

- ***Diagnosis***

a. ***symptoms***
- usually non-specific and insidious
- mean interval from onset to seeking medical attention ~ 16 weeks
- prior exposure is known in only ~ 61%
- anorexia, weight-loss, fatigue
- fever → low-grade or high spiking
  night sweats ~ 60%
- cough, pleuritic pain, haemoptysis is rare
- meningeal symptoms

b. ***signs***

• fever	~ 80%	
• weight loss	~ 70%	
• respiratory signs	~ 60%	(most common organ)
• hepatomegaly	~ 30%	
• splenomegaly	~ 10%	
• lymphadenopathy	~ 30%	
• fundi/choroidal tubercules	?	
• erythema nodosum, lupus pernio		

c. ***lab tests***

i. FBE
- normochromic, normocytic anaemia ~ 60%
- WCC is usually normal ± neutrophilia, monocytosis ± lymphopaenia, pancytopaenia ± leukaemoid reaction
- ↑ ESR ~ 90% *with 30% > 100mm

ii. Coags - DIC rare

iii. U&E's ± hyponatraemia (? SIADH)

iv. LFT's ~ 80% raised ALP
~ 50% raised GGT

d. ***CXR*** - primary focus
- Ghon complex
- hilar adenopathy
- apical fibrosis
- diffuse infiltrates
- miliary TB
- "ARDS"

e. ***mantoux***
- 5 IU s/c of tuberculin purified protein → **≥ 10 mm** induration after 48 hrs
- (+)'ve → previous exposure
  no information re current active infection
- (-)'ve → no previous exposure, or ***anergy***

■ ***Causes of Anergy***

1. disseminated TB
2. some elderly patients
3. renal failure
4. metastatic carcinoma
5. steroids / immunosuppresives / cytotoxics
6. AIDS
7. severe viral infections
8. sarcoidosis
9. syhpilis

- ***Microscopy Results***

a. sputum ~ 40% Zeihl-Neelsen stain (+)'ve
~ 70% culture (+)'ve

b. gastric asp. ~ 40% culture (+)'ve

c. CSF
pleural fluid ~ 50% culture (+)'ve
ascitic fluid

d. CSF
i. decreased glucose
ii. increased protein ~ 30% (+)'ve
iii. AFB by Zeihl-Neelsen

e. urine - "sterile pyuria" common
- microscopy often negative
* culture often (+)'ve, despite absence of urinary symptoms & (-)'ve sputum culture

f. liver B_X ~ 90% have ***granulomas***, 30% with caseation

g. bone marrow < 90% granulomas on B_X
> 50% with aspirate

h. node B_X - useful if clinically involved

- ***Life-Threatening Complications***

a. meningitis ~ 40% of disseminated TB
~ 65% mortality

b. "ARDS" * sputum often (-)'ve
- CXR atypical for TB
- D_X by open/transbronchial ***lung*** $\mathbf{B_X}$
- DIC often associated

c. pneumothorax

d. adrenal failure ~ 12%

e. acute fibrinous pericarditis - Z-N stains (-)'ve
- cultures ~ 40% (+)'ve
- D_X by culture/micro of pericardial B_X

f. thoracic/abdominal aortic aneurysm

g. acute liver failure with encephalopathy

- ***Treatment***

1. ***isoniazid***
   - single oral dose ~ 300 mg/day
   - toxicity - liver, kidney, epilepsy
2. ***rifampicin***
   - single oral dose ~ 600 mg/day
   - toxicity - liver, bone marrow
3. ***pyrazinamide***
   - dose q8h ~ 8 mg/kg/day
   - toxicity - liver, hyperuricaemia
4. ethambutol
   - single oral dose ~ 20 mg/kg
   - toxicity - kidney, liver
     - ***eye***
     - marrow

Enterococcal - Group D Streptococcal - Infections

1. Enterococcal Gp.D Strep. - *Strep. faecalis*
   - *Strep. faecium*
   - *Strep. durans*
2. Non-enterococcal Gp.D Strep. - *Strep. bovis*
   - *Strep. equinis*

NB: facultative anaerobes

- ***Infections***

a. GIT origin septicaemia
b. cholecystitis, cholangitis
c. abscesses - intra-abdominal, pelvic
d. UTI
e. endocarditis
f. synergistic infections - bacterial synergistic gangrene

- ***Antibiotic Resistance***

a. penicillins - oral penicillins, methicillin, flucloxacillin
b. cephalosporins * ***all***
c. lincomycin
d. imipenem * *Strep. faecium*
e. cotrimoxazole & "sulpha's"

- ***Antibiotic Sensitivity***

a. penicillins - high dose ***amoxicillin***
   - benzylpenicillin
   - ticarcillin, piperacillin, azlocillin
b. aminoglycosides - gentamicin, tobramycin
   * ***synergistic*** with penicillins
c. vancomycin
d. teicoplanin
e. ciprofloxacin
f. imipenem * *Strep. faecalis*
g. chloramphenacol

COMMUNITY ACQUIRED PNEUMONIA

• ***sensitivity*** of various diagnostic tests,

a.	sputum gram stain	~ 69%	
b.	sputum culture	~ 60%	
c.	blood culture	~ 16%	
d.	serology	~ 84%	
e.	pneumococcal antigen	~ 68% ~ 62%	sputum serum
f.	mycoplasmal antigen	~ 63%	
g.	viral culture	~ 22%	
h.	nasopharyngeal washing	~ 15%*	
i.	sputum immunofluorescence	~ 15%*	

NB: * useful for Legionella, influenza, parainfluenza, RSV, adenovirus

Incidence of Pathogens

	MJA, Adelaide 1989	Lancet, UK 1987	Chest[1], France 1994
No. of patients	106	236	132
Pathogen identified	**77%**	55%	**72%**
S. pneumoniae	**42%**	**35%**	**33%**
H. influenzae	9%	10%	10%
GN bacilli	8%		11%
M. pneumoniae	8%	3%	0.7%
Cl. psitticae	5%		0.7%
S. aureus	3%		4%
Legionella	3%	3%	3%
TB	3%		
Viruses	**18%**	**13%**	5%
(influenza)	?	(8%)	

[1] Moine *et al.*, Chest 1994, 15 French centres, "Severe community acquired pneumonia"

■ ***Moine et al. Chest 1994***

• 132 patients with ***severe community acquired pneumonia*** (SAPS ≥ 8, R_X in ICU)

a. frequent underlying conditions
   i. CAL ~ 39%
   ii. chronic alcoholism ~ 35%
   iii. diabetes ~ 10%

b. 27% were in ***septic shock***

c. 61% required mechanical ventilation

d. aetiological diagnosis ~ 72%

e. most common pathogens
   - Streptococcus
   - Haemophilus
   - GNB's

f. ***mortality*** **~ 24%**

g. factors significantly associated with increased mortality
   i. aetiology → *Strep pneumoniae, Enterobacteriaceae*
   ii. age > 60 years
   iii. SAPS > 13 (*TQEH median SAPS ~ 15)
   iv. septic shock at presentation
   v. altered mentation
   vi. requirement for mechanical ventilation
   vii. bacteraemia - ie. positive blood cultures

h. recommended initial therapy
   i. high dose ***amoxicillin*** plus a ***macrolide***, or
   ii. fluorinated quinolones, or
   iii. 3rd generation cephalosporin & macrolide *QEH protocol

• CAP currently 5th most common cause of death in USA
• of those admitted to hospital ~ 18-36% require admission to ICU → ***mortality*** **~ 47-76%**
• gastrointestinal symptoms were infrequent in entire cohort, and absent from the 4 cases with *Legionella pneumophilia*
• deterioration of conscious state ***was not*** related to the level of hypoxaemia on admission

NB: after comparing all clinical, laboratory and radiographic data, few differences were found between the different aetiologies

• the strongest associations were those for ***pneomococcal pneumonia***,

1. chest pain
2. fever > 39°C
3. WBC's > 5% immature neutrophils
4. alveolar consolidation in a ***lobar*** distribution

Diagnostic Yield (Severe CAP - 132 Patients)			
Test		Number	% Yield
Blood Cultures	BC	127	27%
Expectorated Sputum	ES	38	45%
Transtracheal Aspiration	TTA	22	**59%**
Distal Protected Aspiration	DPA	67	**61%**
Protected Telescoping Catheter	PTC	50	33%

• prior therapy with ***antibiotics***, especially active against pneumococci, significantly reduced the rate of aetiological diagnosis
• only 7% of patients were found to have proven mixed infection

• DPA and PTC should give greater diagnostic yield, but results relatively poor cf. those obtained in ***nosocomial pneumonia***
• postulated reasons for this lack of sensitivity,

1. high percentage of antibiotics prior to investigation ~ 35%
2. that the innocculum is lower in CAP than in nosocomial infection
   → the ***quantitative threshold*** of **10^3 CFU** may be inappropriate for CAP

• technique of Matthew (DPA), passing a catheter through an ETT and blindly wedging it in a distal bronchus had equal sensitivity to PTC, therefore may be useful in diagnosis of CAP

• ***unable*** to show correlation of mortality with factors previously shown by others,

1. underlying clinical condition *McCabe & Jackson
2. radiographic evidence of spread
3. WCC

Causes of Infective Pneumonias

a. ***viruses***
- influenza A & B, parainfluenza
- CMV, RSV, rhinoviruses, adenoviruses
- enteroviruses, varicella

b. ***bacteria***

i. gram (+)'ve cocci
- aerobic — Staphlococci, Streptococci
- anaerobic — Micrococci

ii. gram (-)'ve cocci — Branhamella, Acinetobacter

iii. gram (+)'ve rods
- Bacillus, Clostridia
- Lactobacillus, Nocardia

iv. gram (-)'ve rods
- aerobes
  - Haemophilus, E. coli, Klebsiella
  - Enterobacter, Proteus, Serratia
  - Pasteurella, Yersinia, Citrobacter
  - Salmonella, Shigella
- anaerobes — Bacteroides, Pseudomonas, Fusobacterium
- obligate aerobes — Legionella, Bordetella, Brucella

v. acid fast bacilli — Mycobacterium tuberculosis, M. kansii

c. ***cell wall deficient bacteria*** * obligate intracellular parasites
- Mycoplasma pneumoniae
- Coxiella burnetti, Chlamydia psittaci

d. ***fungi*** — Aspergillus niger, A. fumigatus

e. ***yeasts*** — Candida albicans, Cryptococcus

f. ***dimorphic***
- Histoplasma, Coccidioides
- Sporotrichium, Blastomyces

g. ***protozoa***
- Pneumocystis (?)
- Toxoplasma
- Entamoeba, Strongyloides, Ascaris lumbricoides
- Toxocara carnis (visceral larva migrans)
- Echinococcus (hydatid disease)
- Schistosomiasis (blood fluke)
- Paragonomiasis (lung fluke)

Environmental Factors

a. ***minerals***
- silicon, asbestos
- coal, bauxite, beryllium, diatomaceous earth, talc
- iron, barium, silver, tin, manganese, vanadium

b. ***fumes***
- nitrogen monoxide
- chlorine, bromine, ammonia
- phosgene, sulphur dioxide
- acetylene, kerosene, carbon tetrachloride, hydrogen fluoride
- hydrochloric, nitric, picric acids

c. ***antigens***
- Farmer's lung
- pigeon fanciers lung
- humidifiers, air-conditioners
- maple bark, wood pulp, oak
- mushroom, malt, sugar cane
- furrier's
- detergents, vineyard sprayers
- fish, cheese, wheat weevil

d. ***drugs***
- hydrallazine
- busulphan, bleomycin, methotrexate
- nitrofurantoin, sulphas
- methysergide
- **amiodarone**

- ***Investigation Stage 1***

a. ***history***
- age, family history, smoking
- occupation, pets/animals, environment
- personal contacts, friends/relatives
- overseas travel
- nature, severity & time course of symptoms
- exacerbating / relieving factors
- past medical history - especially drugs
  - CVS

b. ***examination***

i. general
- vital signs
- nutrition, wasting
- liver / spleen size, lymph nodes
- fundi
- skin manifestations (purpura, erythema, nodules)

ii. respiratory
- upper & lower respiratory tracts
- hands / nails / clubbing / HPOA
- amount & type of sputum
- presence / severity of respiratory failure

iii. cardiac
- cardiac bruits | failure
- loud | split S_2, RV heave, pulmonary SEM
- cor pulmonale, RV failure

- ***Investigation Stage 2***

a. FBE & ESR + blood film
- RBC's - anaemia, haemolysis
- WBC's - left shift, eosinophilia, blasts

b. CXR

c. sputum
- M,C&S, immunofluorescence
- cytology
- AFB micro and culture

d. blood cultures

e. urine - M,C&S

f. U&E's

g. liver function tests

h. ECG

- ***Investigation Specialized***

1. ***blood***
   - i. paired serology for
     - viruses
     - Legionella, Q fever, Chlamydia
     - Mycoplasma
     - fungi/parasites
   - ii. cold agglutinins
   - iii. HIV Ab titre
   - iv. autoantibodies - RF, ANA, ENA, Anti-Bm, cANCA
   - v. coagulation profile - INR, APTT, FDP's, fibrinogen
   - vi. protein electrophoresis
     - immune complexes, myeloma
     - α_1-antitrypsin
2. ***sputum***
   - i. Ziehl-Neilson stain & culture for AFB's
   - ii. wet preparation
     - parasites (ova, cysts, larvae)
     - yeasts (hyphae)
   - iii. immunoflorescence microscopy
     - Legionella
     - Influenza
   - iv. silver stain
     - Pneumocystis
     - * 3% saline induced sputum
3. ***nasopharyngeal washings*** - viruses
4. ***mantoux skin test***
5. ***viral cultures***
   - throat swabs
   - faecal and sputum samples
6. ***faecal specimens*** (x3-6)
   - micro (protozoan cysts, ova)
   - culture (bacterial, viral)
7. ***PA catheter*** - exclude/confirm LVF
8. ***echocardiogram***
   - SBE (low sensitivity)
   - atrial myxoma
   - LV function, valvular lesions
9. ***ultrasound***
   - liver / spleen / kidneys
   - fluid collections, abscesses
   - tumours
10. ***CT chest & abdomen***
    - abscess, tumour
    - lymphadenopathy
    - CT directed biopsy

    + ***fine cut***
    - interstitial lung diseases
    - alveolar proteinosis

11. ***bronchoscopy***

i.	brushings	- M,C&S - cytology, immunofluorescence - differential WCC
ii.	washings	- as above
iii.	bronchioalveolar lavage	- M,C&S - effector cell type & count - lipid / haemosiderin laden macrophages
iv.	biopsy	- tumours - asthma - transbronchial lung biopsy

- recent review suggests increased yield without increased risks in neutropaenic/immunocompromised pneumonia patients

12. ***open lung biopsy***, if

i. diagnosis remains unclear after the above

ii. the condition deteriorates despite empirical treatment

iii. prior to a trial of immunosuppressives or steroids

iv. no other (more accessible) organ is involved in the disease

→
- M,C&S
- M&C for AFB's
- histopathology & frozen section
- silver stain for Pneumocystis
- immunoflorescence for Legionella

13. ***pleural fluid***
- M,C&S
- cells, pH, LDH, protein

14. ***renal biopsy***
- autoimmune diseases
- Goodpasture's

15. ***bone marrow biopsy***
- metastatic carcinoma
- myeloma leukaemia, lymphoma
- TB culture

Pneumococcal Infections

a.	pulmonary	- lobar pneumonia, pleural effusion ~ 1% empyema - lung abscess - epiglottitis, adult or children - often have chest pain, pleurisy
b.	neurological	- meningitis ± cranial nerve palsy (VIII)
c.	cardiovascular	- pericarditis, endocarditis
d.	systemic	- septicaemia, septic shock - ***purpura fulminans***
e.	GIT	- spontaneous peritonitis - hepatic impairment - intestinal pseudo-obstruction
f.	skin	- herpes labialis

• ***high mortality*** **~ 10-18%**, poor prognostic signs being,

a.	patient factors	- age < 1 yr, or > 55 yrs - previous splenectomy - pre-existing severe illness (not in French study)
b.	pathogen factor	- pneumococcus ***type 3***
c.	disease factors	- multilobar involvement - extrapulmonary infective focus - bacteraemia / septicaemia - leukopaenia

• indications for ***pneumococcal vaccine***,

1.	post-splenectomy	- anatomical or functional
2.	epidemic contacts	≥ 55 yrs old - chronic systemic illness
3.	sickle cell anaemia	≥ 2 yrs old * effective ~ 80-90% for age ≥ 3 yrs

Haemophilus Infections

a. facultative, aerobic, ***gram negative bacillus***

b. difficult to culture

c. ***pleomorphic***, variable shape & colour on gram stain, easily missed

d. important pathogenic subtypes,

i.	*influenzae*	
ii.	*parainfluenzae*	- otitis, chronic sinusitis - pneumonia - cerebral abscess
iii.	*pertussis*	- synon. *Bordetella pertussis* - whooping cough - acute bronchitis
iv.	*aegypticus*	- conjunctivitis
v.	*aphrophilus*	- sinusitis, abscesses - pneumonia
vi.	*vaginalis*	- septic abortion, vaginitis - puerperal fever
vii.	*parapertussis*, *ducreyi*	- chancroid

e. liposaccharhide capsule - 6 antigens, "a" - "f"

f. variable degree of capsulation - affects pathogenicity
- ***encapsulated, type "b"*** most common (~ 90%)

g. ~ 80% carriage rate in humans - no other source

- ***Clinical Presentation***

a.	upper respiratory tract	- otitis media - sinusitis - ***epiglottitis*** (1-5 yrs, adult)
b.	lower respiratory tract	~ 10% of community acquired ***pneumonia***
	• lobar pneumonia	± ***empyema*** in ~ 50%
	• bronchopneumonia	- CAL, elderly, smokers, ETOH, etc.
c.	neurological	- ***meningitis***, 1-4 yrs
d.	CVS	- pericarditis, 2° pneumonia
e.	***septicaemia***, 1° unknown	- children - immunocompromised, chemotherapy - post-splenectomy - hypogammaglobulinaemia
f.	pyogenic arthritis	
g.	facial cellulitis	- 6-24 months - usually 1 cheek, red/blue ± meningeal spread/septicaemia
h.	***purpura fulminans***	- *H. haemolyticum*

- ***Treatment***

a.	Cefotaxime	~ 200 mg/kg/day q6h ≤ 1g q6h, or
b.	Ceftriaxone	~ 100 mg/kg/day q12h ≤ 1g q12h, or
c.	Chloramphenacol	~ 100 mg/kg/day q6h ≤ 750 mg q6h, or
NB:	R_X contacts	- Rifampicin 600 mg bd 4 days

Pneumocystis carinii Pneumonia

- ***History***

a.	1909	- first described by Chagas in the lungs of guinea pigs
b.	1912	- recognised as separate organism
c.	1952	- recognised as cause of interstitial plasma cell pneumonia - predominantly malnourished & premature infants
d.	1967	- the first outbreak in malnourished children in Hungary
e.	1976	- routine prophylaxis introduced
f.	1980's	- adjuvant corticosteroids used

• definitive ***taxonomy*** remains uncertain → ? ***protozoan***, 1-2 µm diameter

1. antibiotic susceptibility
2. ultrastructure

NB: ***but***, recent rRNA studies link it to ***fungal phylogeny***,
& more success using fungal culture mediums

- ***Transmission***

a.	***reactivation***	~ 85% seroprevalence - subclinical cases
b.	*de novo*	- outbreaks - animal studies - low autopsy yield (PCR)
c.	? vertical	

- ***Susceptibility***

a.	infants	
b.	malnutrition	
c.	severe anaemias	
d.	renal failure	
e.	steroids, immunosuppressives	
f.	autoimmune diseases	
g.	malignant reticular disorders	- ALL, CML, NHL
h.	cyclic neutropaenia	

NB: defective ***T-cell immune function*** → congenital | acquired | iatrogenic

• most common opportunistic infection in AIDS patients,

a. 60% of first infective presentations

b. 80% of all AIDS patients will develop PCP during their disease course

c. 25% of all AIDS ***deaths***

NB: in AIDS patients the ***onset*** is insidious and prolonged
→ ~ ***1-2 months*** incubation period

- ***Clinical Features***

a. ***fever*** is common

b. some may complain of only fever, weight-loss and malaise

c. dyspnoea, tachypnoea, cyanosis, hypoxia, dry cough

d. CXR features
- usually ***severe***
- widespread alveolar opacities
- perihilar or peripheral nodular opacities

e. $\delta P_{A\text{-}aO2}$ & CXR much ***worse*** than clinical examination

f. high LDH

g. complications
   i. respiratory failure
   ii. pneumothorax - emphysematous bleb

h. ***CEA*** may be used as a disease marker

NB: ***non-HIV*** associated disease onset over ~ 5 days → ***fulminant***, and associated with a ***worse prognosis***

Hospital Mortality Rates

	Total	ARF	Ventilated
Non-AIDS	50%		
AIDS	10-15%	20-40%[1]	80-90%

[1] survivors of AIDS + ARF + PCP **~ 15%** at 4 years

■ ***Diagnosis***

• PCP can only be diagnosed by demonstrating ***pneumocysts*** in sputum, BAL fluid, or lung biopsy specimen
• *P. carinii* ***cannot*** be cultured and there are ***no*** reliable serological tests (? new PCR)

1. induced sputum sample ~ 60-70% positive
   - 3% saline aerosol & fractionate sample
2. brochoalveolar lavage ~ 85-90% positive
3. transbronchial biopsy ~ 85%
   • combined with BAL ~ 97%
4. open lung biopsy * effectively last resort and should not be required

NB: 1 & 2 → reduced ***sensitivity*** with aerosolised pentamidine prophylaxis & AZT

• because PCP in AIDS tends to be recurrent, and many patients do not tolerate bronchoscopy well, indirect methods ***suggestive of PCP*** include,

1. CXR - diffuse reticulo-nodular pattern
   • however, may show cysts, cavitation, pleural effusion, pneumothorax, or may be entirely normal
2. gallium scanning ~ 100% sensitive, ***but*** specificity ~ 40%
   • may show uptake for months after acute infection
3. ABG's - high A-aDO_2
4. single breath diffusion capacity

■ ***Treatment***

a. ***Bactrim*** ~ 19% mortality
   ~ 30% toxicity (folate)
   ~ 36% relapse
   • 2 weeks in non-AIDS, 3 weeks in AIDS patients
b. Pentamidine - IV, aerosol
c. ***adjuvant corticosteroids***
   • reduced mortality in AIDS patients
d. Dapsone
e. Pyrimethamine
f. ***prophylaxis***
   • any patient with a history of PCP, or a CD4 count < 200 / mm^3
   i. Pentamidine aerosol - 60-150 mg biweekly
   ii. Bactrim - 1 DS tablet 5/7 days/week
   iii. Dapsone

NOSOCOMIAL INFECTION

• J-L Vincent, *et al.* EPIC International Advisory Committee JAMA 1995
• 1 day point-prevalence study to determine,

1. the ***prevalence*** of ICU acquired infections
2. the ***risk factors*** for these infections
3. the predominant infecting ***organisms***
4. the relationship between ICU-acquired infection and ***mortality***

• 1,417 ICUs in Western Europe, excluding CCUs, pediatric and special care infant units
• 10,038 patients (age > 10 yrs) occupying an ICU bed over a 24-hour period
• outcome measures,

1. rates of ICU-acquired infection
   - 4501 patients were infected ~ 44.8% "½ → infected"
   - 2064 had ***ICU-acquired*** infection **~ 20.6%** "½ → ICU acquired"
2. prescription of antimicrobials
3. resistance patterns of microbiological isolates
4. potential risk factors for ICU-acquired infection and death

• most frequent types of ICU infection,

a. ***pneumonia*** ~ 46.9% "½ → pneumonia"
b. lower respiratory tract infection ~ 17.8%
c. urinary tract infection ~ 17.6%
d. bloodstream infection ~ 12%

• most frequently reported micro-organisms were,

a. ***Enterobacteriaceae*** ~ **34.4%**
b. ***Staphylococcus aureus*** ~ **30.1%** (*60% MRSA)
c. Pseudomonas aeruginosa ~ 28.7%
d. coagulase-negative staphylococci ~ 19.1%
e. fungi ~ 17.1%

• risk factors for ICU-acquired infection were,

1. increasing length of ICU stay > 48 hrs
2. mechanical ventilation
3. diagnosis of trauma
4. central venous, pulmonary artery, and urinary catheterization
5. stress ulcer prophylaxis

• increased the risk of ICU death,

1. clinical sepsis - odds ratio ~ 3.50
2. ICU-acquired pneumonia - odds ratio ~ 1.91
3. bloodstream infection - odds ratio ~ 1.73

- ***Conclusions***

1. ICU-acquired infection is common and often associated with microbiological isolates of resistant organisms
2. the potential effects on outcome emphasise the importance of specific measures for infection control in critically ill patients

• not clear from study how they discriminated between ***colonisation*** and ***infection***
• eg. the 30% incidence of *Pseudomonas sp.* may represent many cases of colonisation

Nosocomial Pneumonia

NB: USA, CDC Definitions....

- ***Nosocomial***

1. no evidence that infection was present, or incubating at the time of hospital admission
2. special exceptions
   i. infection acquired in hospital and becoming evident post-discharge
   ii. newborn infection that results from passage through the birth canal
3. no specific ***time-frame*** is set for during admission or after discharge
   - ie. each infection must be assessed on individual merits
   - LIGW states > 48-72 hrs is a general rule if the incubation period is unknown

- ***Pneumonia***

NB: must meet ***one of*** the following 4 criteria:

1. rales or dullness to percussion on ***physical examination***,
   plus ***any*** of the following
   i. new onset of purulent sputum, or change in character of sputum
   ii. organism isolated from - blood culture
   - tracheal aspirate, bronchial brushing, or biopsy
2. examination shows new or progressive ***CXR infiltrate***, consolidation, cavitation, or pleural effusion, plus ***any*** of the following
   i. new onset of purulent sputum, or change in character of sputum
   ii. organism isolated from - blood culture
   - tracheal aspirate, bronchial brushing, or biopsy
   iii. isolation of virus, or detection of viral antigen in respiratory secretions
   iv. diagnostic single Ab (IgM) titre, or
   4-fold increase in paired samples (IgG) for pathogen
   v. histopathological evidence of pneumonia
3. patient **≤ 12 months** has ***two of*** - apnoea, tachypnoea, bradycardia
   - wheezing, ronchi, cough

   plus ***any*** of the following
   i. increased production of resiratory secretions
   ii. any factor in (2) above
4. patient **≤ 12 months** with CXR examination shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion, plus ***any*** of the following
   i. increased production of resiratory secretions
   ii. any factor in (2) above

- ***Risk Factors for Gram Negative Colonisation***

a. ***patient*** factors
   i. elderly
   ii. past history of chronic disease
      - respiratory - chronic bronchitis, emphysema, smoking
        - bronchiectasis, cystic fibrosis
      - other - diabetes, CRF/uraemia, Cushing's
        - autoimmune diseases

b. ***disease*** factors
   i. altered reflexes - ETT, tracheostomy
      - coma, CNS depressants
   ii. treatment - antibiotic therapy
      - steroids / immunosuppressants
      - surgery
      - NG tube
      - gastric acid neutralisation
      ? blood transfusion
   iii. other - hypotension, shock
      - acute lung injury

c. ***institution*** factors
   i. admission to ICU
   ii. local infection control practices
   iii. local antimicrobial prevalence / distribution

- from McLaws, MJA 1988, looking at ***general*** hospital populations
  a. nosocomial infections occur in ~ 6-7% of patients
  b. 15-35% of these are ***pneumonia*** with a mortality rate of 50-70% (Chastre)
  c. most are endogenous ***gram negative*** bacteria, many are polymicrobial
  d. a higher proportion occur in ICU patients

- from Daschner, ICM 1982, ***ICU patients***
- the overall ***incidence*** of nosocomial infections in ICU patients **~ 12-20%**
  a. UTI ~ 40%
  b. septicaemia ~ 20%
  c. pneumonia ~ 16%

NB: patients with ARDS → incidence ~ 70%

this spectrum differs from European point prevalence survey, but these are infections acquired post-hospital admission, not total infection numbers

ICU Pneumonias

Def'n: "For practical purposes, an infection is commonly defined as nosocomial when diagnosed 48-72 hrs following admission. However, infections not immediately apparent at the time of admission, but incubating at that time, are not included in a more precise definition, and should not be mixed with ICU pneumonias occurring later." *Brun-Buisson*, Current Opinion, 1995

1. early onset, EOP ≤ 4 days
2. ***nosocomial***, late onset, or VAP

- the ***incidence*** of ICU acquired pneumonia ~ 21% (published range 9-70%)
- and ~ 54% of these occur within the first 4 days
- ***risk factors*** include,

1. duration in ICU ~ 1% / day (Fagon *et al.*)
2. shock on admission
3. surgical ICU admission
4. steroid or chemotherapy
5. serum creatinine > 130 µmol/l
6. impaired airway reflexes
7. severity of underlying pathology

- ***Early Onset Pneumonia***

1. occurs within 4 days
2. very common
3. unrelated to
   - age
   - type of illness
   - immune suppression
4. frequently oropharyngeal pathogens, "community-acquired sensitivities"
5. mainly in intubated patients, more common following trauma
6. little affected by antibiotic prophylaxis

- ***Late Onset Pneumonia***

1. usually gram (-)'ve pathogen
2. frequently impaired airway reflexes
3. should (?) be influenced by antibiotic prophylaxis

- ***Aetiology***

a.	gram negative bacilli	**~ 70%** - E. coli, Pseudomonas, Enterobacter, Klebsiella
b.	gram positive cocci	**~ 15-25%** - Staphlococci - Enterococci
c.	fungal	~ 5% - Candida

- ***Mortality***

a.	*Pseudomonas*	~ 70%
b.	*Klebsiella* *Serratia* *Enterobacter*	~ 40%
c.	*E. coli*	~ 30%
d.	gram positives	~ 5-25%
e.	viruses	~ 7%

NB: overall mortality **~ 50-56%**

mortality appears proportional to severity of ***underlying disease***, ie. organisms with highest mortality require greater immunosuppression & susceptibility

Risk Factors	
Host Factors	Therapeutic Factors
• newborn	• ICU or SCN
• elderly > 60	• systemic antibiotics
• multiple trauma	• invasive catheters
• severe 1° disease	• large transfusion
• granulocytopaenia	• need for haemodialysis
• immunosuppression	• corticosteroids

- ***Meduri Chest 1990***

1. diagnosis of nosocomial pneumonia in an intubated patient is difficult
2. ***tracheal aspirate*** in ventilated patients is often ***inaccurate*** & misleading
3. ***colonisation*** rate **> 60%**
4. risk factors for colonisation and infection are similar
5. other conditions can simulate pneumonia and may go untreated
6. recognition of a ***specific pathogen*** is important for effective treatment
7. a large number of patients ***do not*** have pneumonia
8. inappropriate antibiotics - ↑ colonisation risk, superinfection
   - side effects
9. many diagnostic techniques * histology + culture = "gold standard"

Technique	Sensitivity	Specificity
Clinical	**64%**	80%
Tracheal Aspirate	80-95%	40-60%
LRS	100%	40%
Bronchio-Alveolar Lavage	75-100%	30-75%
Protected Sputum Brushings	40-100%	40-100%

* these figures are from different studies, animal and patient, with different diagnostic criteria for pneumonia

- ***Andrews Chest 1981***

• histology at PM versus ***clinical diagnosis*** in 24 patients,

1. ***fever***
2. ***leukocytosis*** *sensitivity ~ 64%
3. purulent ***tracheal aspirate*** *specificity ~ 80%
4. ***pulmonary infiltrate*** on CXR

• of 24 patients, 14 were diagnosed with pneumonia, 10 with DAD
• overall 29% of cases were misdiagnosed,

a. 36% in the pneumonia group
b. 20% with DAD

• pathogenic bacteria were isolated in TA of 86% in pneumonia group & 70% in DAD

NB: ARDS patients with a new infiltrate frequently do have pneumonia;
non-ARDS patients with a new infiltrate frequently ***do not*** have pneumonia

- ***Definition for Diagnosis Andrews***

1. fever > 38.3°C
2. WCC > 10 x 10^9 / l
   < 5 x 10^9 / l ? > 10% band forms
3. pathogenic bacteria in pulmonary secretions / pulmonary wedge specimens
4. new and persistent radiographic abnormality
5. ***response to therapy*** with antibiotics

- ***Fagon, Chastre ARRD 1989***

• nosocomial pneumonia in 567 ICU patients ventilated > 3 days
• diagnosed with PSB with ***semiquantitative culture*** → sequential incidence,

a. day 10 6.5%
b. day 20 19%
c. day 30 28% → overall incidence ~ 9%

NB: ie. approximate incidence **~ 1% / day**

i. 40% of these were ***polymicrobial***
ii. mortality was 70% cf. 29% in the non-pneumonia group
iii. use of ***prophylactic antibiotics*** selects out resistant Pseudomonas, Acinetobacter and MRSA

- ***Salata ARRD 1987***

• 51 intubated ICU patients, looking at the effectiveness of ***tracheal aspirate*** to distinguish colonisation from infective pneumonia

	Nosocomial pneumonia	Colonisation
PMN's	> 1+ > 10/hpf > 30,000/µl	< 2+
Bacteria	> 1+ > 1-10/oil field	< 2+
CFU	> 100,000 **10^5**	< 100,000 **10^5**
Elastin Fibres	+'ve 52% gram(-)	+'ve 9%
IC organisms	> 1-5% of PMNs	< 1%
Squamous cells	< 10/hpf	< 10/hpf

- ***Johanson ARRD 1982***

• ventilated animal study of diagnostic tools

Investigation	Sensitivity	Specificity
TA	80%	60%
BAL	74%	?30%
PSB	40%	?60%
needle Bx	50%	?50%

- ***Multiple Studies***

Investigation	Sensitivity	Specificity
LRS[1]	~ 100%	40%
PSB[1]	80%	~ 100%
PSB[2]	70%	~ 100%
PSB[3]	~ 100%	60%
BAL[4]	~ 100%	75%
BAL[5]	86%	

[1] Richard, ICM 1988, comparison of bronchoscopic samples suction samples (LRS) versus PSB

[2] Higuchi, ARRD 1982, primate model of acute lung injury ± pneumonia

[3] Chastre, ARRD 1984, PSB versus immediate post-mortem histology

[4] Gassorgues, ICM 1989, BAL vs PM in 13 intubated patients

[5] Mann, Chest 1987, BAL in 18 HIV pneumonia patients

- ***Kirkpatrick ARRD 1988***

• 8 "normal" subjects studied with BAL & PSB looking at the sterility of the samples, ie. contamination of the specimen

1. PSB = 7/8 but < 10^4 CFU
2. BAL = 1/8

■ ***Chastre AJM 1988***

• BAL vs. PSB in 21 intubated ICU patients,

1. WCC and semi-quantitative cultures less useful
2. BAL → (+)'ve gram stain with ***intracellular bacteria*** rapid and useful
3. PSB → > 10^3 CFU useful in diagnosis but results delayed 48 hrs
4. PSB gives some ***false negatives***

NB: "both useful and complimentary" in diagnosis

■ ***Papazian AJRCCM 1995***

• prospective post-mortem study of diagnostic tool efficacy in diagnosis of VAP
• histology & culture performed within 30 min of death in 38 patients ventilated > 72 hrs

a. histology (+) - 18/38 patients ~ 47%
b. culture (+) - 12/18 patients **~ 32%** ***definite VAP***

	Threshold[1]	Sensitivity %	Specificity %
CPIS	> 6	72	85
mini-BAL	> 10^3 cfu/ml	67	80
BAL	> 10^4 cfu/ml	58	95
PSB	> 10^3 cfu/ml	**42**	95
BBS	> 10^4 cfu/ml	83	80

[1] Figures for ***definite VAP***, ie histology & culture positive

• conclusions,

1. as BBS is more sensitive & non-invasive, ∴ preferrable to PSB
   • lower specificity, but this is probably more acceptable
2. due to ***low sensitivity***, results of a negative PSB should be viewed with caution
3. overall diagnostic ***accuracy*** was greatest for BBS/BAL at 81%

• CPIS, Pugin *et al.*, ARRD 1991 (Clinical Pulmonary Infection Score)

1. clinical - temp., quantity & character of tracheal asp.
2. biological - WCC, P_{aO2}/F_IO_2 ratio
3. radiographic - CXR
4. microbiological

■ ***Bonten et al. AJRCCM 1995***

• evidence for a causal relationship between ***gastric colonization*** and VAP based on studies relating colonization to species causing pneumonia Torres *et al.*, ARRD 1993

1. VAP diagnosed by ***clinical criteria*** *poor sensitivity/specificity
2. no chronological relationship established
3. gastric pH values determined only once daily by indicator slide test
4. no studies used double-blind PRCT study

• PRCT of 141 patients, of whom **112** had continuous gastric pH monitoring

a. group 1 58 - antacids, (Al/Mg-OH), 30 ml q4h
b. group 2 54 - sucralfate 1g q4h

NB: no significant differences in ***median pH values***

• stratifying patients by ***colonization***,

a. median pH values were higher in patients with gastric bacterial colonization
b. ***no difference*** seen for oropharyngeal or tracheal colonization

• ***ventilator associated pneumonia***,

a. diagnosed by BAL (> 10^4 CFU) / PSB (> 10^3 CFU)
b. occurred in ~ **22%** → same in both groups
c. polymicrobial in 19/31 episodes → 51 isolates
   i. prior tracheal isolation ~ 96%
   ii. prior oropharyngeal isolation ~ 75%
   iii. prior gastric isolation ~ 31%

NB: in ***one case*** the organism resulting in VAP initially colonized the stomach, in five cases, colonization occurred ***simultaneously***

• this is supported by Inglis *et al.*, Lancet 1993, who showed ***chronological*** colonization from stomach to trachea in only 6/100 ventilated patients

• ***enteral feeding***,

a. did not alter gastric acidity
b. ***increased*** gastric colonization with *Enterobacteriaceae*
c. no change in oropharyngeal or tracheal colonization
d. confounding factor of ↑ ***gastric volume*** controlled

NB: ***gastric acidity*** influenced gastric colonization, bot ***not*** colonization of the upper respiratory tract or the incidence of VAP

Nosocomial Infections CDC

- ***Sources of Bacteraemia***

1. surgical wound, intra-abdominal ~ 35%
2. urinary tract ~ 17%
3. respiratory tract ~ 15%
4. IV catheter ~ 10%
5. skin, burns ~ 5%
6. other vascular lines < 3%

CDC Survey 1956-1979		
Pathogen	Hospital	
	Endemic	Epidemic
E. coli	19%	5%
Enterococci	10%	1%
Pseudomonas	9%	4%
Klebsiella	8%	3%
Proteus	8%	1%
Enterobacter	4%	7%
Serratia	2%	8%
Salmonella	-	11%
Staph. aureus	10%	12%
Strep. group A	2%	3%
Site		
Urinary tract	38%	10%
Surgical wound	27%	9%
Respiratory	16%	12%
Skin	6%	11%
Bacteraemia	4%	6%
GIT	-	17%
Liver	-	12%
Meninges	-	5%

EPIGLOTTITIS - ADULT

a. *H. influenzae* type B, *H. parainfluenzae*
b. *Strep. pneumoniae, Strep. pyogenes*
c. other bacteria - Staph., Fusobacterium, Pseudomonas ?? commensals
d. viruses

• differences from childhood illness,

1. more often culture (-)'ve ~ 70% vs. 20%
2. higher mortality ~ 7% vs. < 1%
3. rapid or insidious course → diagnostic delay
4. underlying pathology - hypertrophied mucosa
   - carcinoma
5. occasionally recurrent

■ ***Frantz et al. JAMA 1994***

• case analysis of 129 patients aged > 18 years with laryngoscopically confirmed epiglottitis

a. mean age ~ 47 years
b. most common symptoms
   i. sore throat ~ 95%
   ii. odynophagia ~ 94%
   iii. muffled voice ~ 54%
c. microbiology
   i. blood cultures ~ 15% (8/52 tested +'ve)
      • *H. influenzae* (6)
      • *S. aureus* (2)
   ii. pharyngeal swab ~ 18% (9/48)
d. management
   i. artificial airway ~ **15%** (19/129)
   ii. 2nd/3rd cephalosporin ~ 75%
   iii. ***corticosteroids*** ~ 73% (94/129)
   iv. mean hospital stay ~ 4.1 days
e. outcome
   i. major complications ~ 5% (6)
   ii. ***motrality*** - nil

NB: concluded that ***conservative management*** of adult epiglottitis is safe and effective

- ***Acute Upper Airway Obstruction***

a. anaphylaxis | anaphylactoid reaction

b. angioneurotic oedema

c. abscess - peritonsillar
- retropharyngeal

d. carcinoma ± oedema

e. foreign body

f. trauma - laryngeal
- facial

g. hypocalcaemia

Gonnococcal Infections

Def'n: gram negative intracellular diplococci

- ***Clinical Presentation***

1. gonnococcal urethritis
2. epididymitis
3. acute salpingitis, pelvic inflammatory disease
4. bilateral Bartholin's gland abscesses
5. cystitis
6. conjunctivitis (children)
7. disseminated gonococcal septicaemia $\equiv^{t}$ ***meningococcaemia***
   → - fever, rash
   - petechiae, purpura, skin necrosis
   - polyarthralgia
8. septic arthritis, acute polyarthritis - arthritis-dermatitis syndrome
   *most common septic arthritis worldwide
9. myopericarditis, endocarditis
10. meningitis
11. perihepatitis - Fitz-Hugh-Curtis syndrome
    • salpingitis → RUQ tenderness, pain, friction rub
12. "toxic" hepatitis
13. purpura fulminans

- ***Treatment***

1. 3rd generation cephalosporin - ceftriaxone
   - ***cefotaxime***
2. spectinomycin

NB: also Rx non-gonococcal urethritis - ***doxycycline***

HEPATITIS

Aetiology

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

HEPATITIS				
Parameter	**A**	**B**	**C**	**Delta**
Virus	27 nm	42 nm, DNA	togavirus, RNA	defective RNA
Incubation	2-6 wks (~ 4)	6-24 wks (~ 10)	2-24 wks (~ 7)	
Onset	acute	insidious	insidious	
Seasonal	winter	no	no	
Age	children, young adults	any	adults	IV drug users
Transmission	faecal/oral	haematogenous, percutaneous, placental, STD	haematogenous percutaneous	coinfection, or superinfection with HBV
Severity	mild	often severe	mod-severe	
Prognosis	good	B&C worse with ***age & debility***		poor
Chronicity	rare	occasional ~ 5-10%	common ~ 10-50%	common
IgG-Ab	good	needle stick	none	none
Carrier	rare	0.1-1.0% (< 30% O/S)	~ 1.0%	common
Mortality	rare	~ 1%	?	~ 2%
Diagnosis	IgM/anti-HAV	HBsAg anti-HBs,c,e	anti-HCV	anti-HDV

- ***Complications of Hepatitis B***

a. cirrhosis with portal hypertension ~ 15-30%
   - probably less than this, some of these were HCV in the past

b. carrier state (HBsAg / HBcAb) ~ 5%

c. chronic active hepatitis ~ 3-5%

d. massive hepatic necrosis ± encephalopathy

e. primary hepatic carcinoma

f. immune complex syndromes
   - serum sickness
   - polyarteritis
   - glomerulonephritis
   - urticaria

Hepatitis D - Delta Hepatitis

- 35 nm, double shelled external coat of HBsAg
- inside is the HDV-Ag and HDV-RNA
- ***always*** occurs in association with HBV, may be either acute or chronic,

1. ***coinfection*** - HBV-IgM (acute infection) + HDV-Ag
   - usually ***self limiting***
2. ***superinfection*** - HBsAg (carrier) + HDV-Ag
   i. of acute cases ~ 80% → chronic hepatitis
   ii. of chronic infection ~ 70-80% → ***cirrhosis***

- diagnosis is by clinical examination and radioimmunoassay of ***anti-HDV Ab***
- titres > 1:100 are found in chronic infection

■ ***Epidemiology***

a. endemic in HBsAg carriers
b. occasionally epidemic in HBsAg carriers
c. isolated cases in high risk groups - drug users
   - haemophiliacs, etc.
d. commoner in Mediterranean & Middle eastern peoples

- treatment is with ***interferon A***
- actual benefit derived from interferon is not precisely determined, cf. HCV

HIV INFECTION AIDS

Def'n: infection with HIV virus, usually with (+)'ve anti-HIV Ab

- HTLV III, or **HIV** is a 100nm ***RNA retrovirus*** (lentivirus) with ***reverse transcriptase***
- highly ***mutagenic*** during the course of infection, ∴ immunisation impracticable
- other retroviruses of the group,

1. HTLV I
   - endemic in Japan, Brazil and Carribbean, also IV users in USA
   - modes of transmission identical to HIV
   - longer incubation period ~ 20 years
   - implicated in 2 distinct disease entities

   i. adult ***T-cell lymphoma*** - aggressive T_4-cell NHL
   - survival usually < 1 year

   ii. tropical spastic paraparesis - neurologically similar to MS

2. HTLV II
   - indistinguishable from HTLV-I by ELISA or Western Blot
   - associated with ***hairy cell leukaemia***

3. HTLV-III → **HIV type 1**

4. HTLV-IV → HIV type 2
   - is a second cause of AIDS, though may be a milder form of the disease
   - same modes of transmission and possible to have ***dual infection***
   - base sequence homology between HIV-1 / HIV-2 ~ 40%
   - more closely resembles Simian T-lymphotrophic virus STLV
   - predominantly found in Western Africa

■ ***Modes of Spread***

1. sexual contact
   i. homosexual/bisexual contacts **~ 60%**
   ii. heterosexual contacts ~ 4%
2. parenteral exposure
   i. drug addicts, shared instruments **~ 20%**
   - both IV users and homosexual ~ 7%

   ii. blood transfusion, haemophiliacs ~ 1%
   iii. recipients of infected tissue
   iv. accidental, needle stick injury
3. perinatal infection
   - may occur prenatally, during birth, or by breast feeding
4. undetermined ~ 3%
   - many of this group when re-questioned actually fall into 1-2 above

- ***High Risk Groups***

a. homosexual, bisexual males
b. IV drug users
c. haemophiliacs
d. Haitians, people of central African origin
e. children of infected mothers
f. sexual partners of carriers

- ***Non-Transmission Modes***

• HIV has been isolated from tears, saliva, urine and CSF, however these ***have not*** been implicated in transmission of HIV
• modes not at risk of infection include,

1. non-sexual household contacts
2. mosquito bites
3. human bites

- ***Classification***

1. Group I - acute infection
   - may be subclinical or influenza-like illness
2. Group II - asymptomatic, anti-HIV (+)'ve
3. Group III - persistent generalized lymphadenopathy
4. Group IV - other disease
   i. subgroup A - constitutional disease
   ii. subgroup B - neurological disease
   iii. subgroup C - secondary infectious disease
      • category C_1 - specific secondary infectious diseases listed by the CDC
      • category C_2 - other non-specific secondary infectious diseases
   iv. subgroup D - secondary malignancies
   v. subgroup E - other conditions

NB: classification has neither ***prognostic*** significance, nor does it signify ***severity***

it is ***hierarchial***, in that once categorised at a level, patients should not be reclassified if clinical imrovement occurs, as this may ***not*** reflect change in the underlying disease severity

- ***Associated Diseases***

a.	viral infections	- disseminated CMV - chronic mucocutaneous herpes - papova-virus progressive multifocal encephalopathy
b.	bacterial	- disseminated TB - disseminated *Mycobacterium avium-intracellulare* - *Salmonella* spp.
c.	fungi	- oesophageal / disseminated *Candida* spp. - meningeal / extrapulmonary *Cryptococcus neoformans*
d.	protozoa	- *Pneumocystis carinii* pneumonia - cryptosporidial gastroenteritis - strongyloides pneumonia - toxoplasmosis, disseminated / encephalitis
e.	malignancies	- Kaposi's sarcoma, often multicentric - Non-Hodgkin's lymphoma, high grade, ± CNS

- ***Pathogenesis***

a. viral gp120 envelope → **CD-4 *receptor cells***, mainly T-lymphocytes
   - other cells can also be infected, but mechanism uncertain

b. CD-4 T-lymphocytes (helper cells) are progressively depleted during infection
   - there is also evidence for defective function of remaining cells
   - CD-4 counts < **200 / mm^3** → ↑ risk of opportunistic infection

c. monocytes / macrophages
   - infected either by CD-4 receptor or by phagocytosis of mature virion
   - serve as both a haven and as a ***reservoir*** for ongoing infection
   - may introduce virion into the brain, contributing to AIDS dementia complex
   - glial cells may either be activated, or infected

d. bone marrow cells
   - HIV infects myeloid monocyte progenitor cells, ? mechanism
   - contributes to pancytopenia

e. B-cells
   - demonstrate impaired function, however, direct infection has not been demonstrated
   - coinfection with EBV or CMV may contribute to this

Clinical Features

- ***Acute Primary Infection***

a. sudden onset of infectious mononucleosis type syndrome

b. incubation period ~ 1-12 weeks (mean 2-4/52)

c. duration of illness ~ 3-14 days (range 3-49/7)

d. signs / symptoms * non-specific
   i. fever, sweats, lethargy, malaise, photophobia, arthralgia, myalgia
   ii. truncal maculopapular rash
   iii. oral aphthous ulcers, or diffuse enanthema of the oral cavity
   iv. lymphadenopathy
   v. neurological manifestations - meningoencephalitis
      - peripheral neuropathy, GBS

e. laboratory investigation
   i. lymphopenia
   ii. ↑ ESR
   iii. ↑ ALP, AST / ALT
   iv. post-infection, may have atypical lymphocytosis, with inversion T_4/T_8 ratio
      • this is due to an eleveted T_8 count, the T_4 count is ***normal***
   v. ***seroconversion***
      • ***HIV-Ab*** usually detected within ***2 months***
      • conversion as early as 2 weeks has been documented
      • prolonged Ag-positive / Ab-negative states well documented
      • ***core*** **p24 Ag** detectable in serum & CSF within 2 weeks

- ***Asymptomatic HIV Infection***

• frequency unable to be determined
• estimated > 1,000,000 cases in USA

• approximates ***rates of progression,***

a. 3 years ~ 80-90% develop some degree of immune dysfunction

b. 7 years ~ 36% progress to AIDS
   ~ 40% have manifestations of infection (ARC - see over)

NB: thus, by 7 years ~ 75% of persons develop some symptoms of disease,
currently thought that ***all*** infected persons will develop progressive disease

- ***Persistent Generalised Lymphadenopathy***

a. definition ≥ 2 ***extrainguinal*** sites
> 1.0 cm diameter
> 3 months duration
- ***not*** attributable to other causes
- ***not*** associated with constitutional symptoms

b. incidence ~ 5-70% of HIV infected persons

c. pain & tenderness are uncommon

d. mediastinal & hilar adenopathy are unusual

e. mesenteric & retroperitoneal sites are common

f. histology shows nonspecific ***follicular hyperplasia***
- associated with T_8 cell proliferation
- cf. patients with severe disease (AIDS) have follicular depletion

- ***AIDS Related Complex***

NB: obsolete term → Group III, Group IV.A, Group IV.B

1. fever, weight loss, fatigue, sweats, diarrhoea
2. unexplained generalized lymphadenopathy
3. thrombocytopaenia
4. oral candidiasis
5. herpes zoster infection
6. constitutional wasting syndrome

- ***Haematological Abnormalities***

a. marrow depression - reduction in 1 or more elements
i. normochromic, normocytic anaemia
ii. neutropaenia
iii. lymphopaenia
iv. thrombocytopaenia

b. immune thrombocytopaenic purpura
- usually asymptomatic when platelets > 50,000
- similar to classical ITP, ***no splenomegaly*** & hyperplastic marrow suggesting ***peripheral destruction***
- AZT may produce anaemia & leukopaenia, but rarely thrombocytopaenia

c. thrombotic thrombocytopaenic purpura

AIDS

- only a small number of those infected actually have AIDS - Groups IV.C-1 and IV.D
- defined by the various opportunistic ***infections*** and ***neoplasms*** characteristic of AIDS
- CDC divides these diseases into 3 groups, and subclassifies AIDS accordingly

Neurological Disease

a. AIDS dementia complex ~ 40-60% of patients
b. peripheral neuropathy, myelopathy
c. cryptococcal meningitis, CNS toxoplasmosis
d. primary CNS lymphoma
e. progressive multifocal leucoencephalopathy
f. CMV
g. aseptic meningitis

Neoplasms

1. Kaposi's sarcoma
   - occurs in ~ 30% of AIDS patients
   - may present as multifocal vascular nodules in skin and viscera
   - may involve the lung with interstitial opacities, or rarely massive haemorrhage
   - like neurological disease, tends to occur ***before*** the onset of immunosuppression
2. non-Hodgkin's lymphoma
   - may involve brain, lymphoid tissue, GIT, skin, or bone marrow
   - usually aggressive with high mortality

Laboratory Features

a. T-cells - ***anergy***
   - ↓ total T_4 count ~ 700/µl
   - ↓ T_4 helper cells < 300/µl
   - ↓ T_4:T_8 ratio < 0.9 (N > 1.5)
   - ↓ T-cell proliferation, cytotoxicity
   - ↓ cytokine response (IL_2, interferon, lymphokines)

b. B-cells - ***polyclonal activation***
   - ↑ Ig's (viral Ab's, auto-Ab's, immune complexes)
   - impaired 1° Ab response

c. other - ↑ α-interferon, thymosin-a_1 and β_2-microglobulin
   - production of serum "IL_2 inhibitor"
   - impaired natural killer cell function

- ***HIV Screening Tests***

a. ELISA
- screening, result in hours
- false (+) ~ 0.04-0.15% of normal population
- positive to other HTLV viruses

b. Western blot
- confirmatory, research, expensive
- result in days
- false (-) in "window period" & terminally

• combining (a) & (b) → ***false positive*** ~ 1:135,000

c. HIV Ag tests

i. free virus - can be cultured in newly infected patients & in advanced disease

ii. core p24
- appears in acute infection & with advanced disease
- can be used in the ***individual*** to track response to therapy
- interpatient variability makes it unreliable as a disease marker

iii. PCR
- direct detection of viral Ag using gene amplification
- may be useful in "window period" for blood screening

- ***Treatment***

1. azidothymidine AZT
   - nucleoside analogue
   - readily crosses the BBB, with CSF levels ~ 50-60% of plasma
   - side effects
     - bone marrow suppression
     - myositis
     - headaches
     - N&V
2. specific therapy of opportunistic infections
3. radiotherapy for Kaposi's sarcoma

Infectious Mononucleosis

Def'n: an acute, self-limiting infectious disease of children and young adults resulting from ***Epstein-Barr virus*** (double-stranded DNA ***herpesvirus***);
producing the classical features

1. fever & sore throat
2. lymphadenopathy, splenomegaly
3. lymphocytosis, with "atypical" changes in mononuclear elements
4. presence of ***heterophil antibodies*** in peripheral blood
   - agglutinates sheep (Paul-Bunnell) or horse (monospot) rbc's
   - nonspecific serological test
   - Ab levels may take 3 weeks to rise & remain high for 3-6 months

Typical Clinical Features

1.	exudative tonsillitis & pharyngeal inflammation	
2.	lymphadenopathy	- predominantly posterior cervical
3.	splenomegaly	~ 75% of cases - associated with spontaneous rupture
4.	hepatomegaly	~ 50% ~ 80% show abnormal LFT's
5.	maculopapular rash	~ 5% *virtually all if given ***amoxicillin***
6.	petechial exanthem on the soft palate	

Heterophil Negative IM

1.	CMV	
2.	viral hepatitis	- HAV, HBV, HIV
3.	*T. gondii*	
4.	leptospirosis	
5.	rubella	
6.	lymphoma / leukaemia	
7.	drugs	- phenytoin, PAS, isoniazid

- ***Life Threatening / Rare Complications***

a. hepatitis, massive hepatic necrosis ± encephalopathy

b. splenomegaly & spontaneous / traumatic rupture

c. GBS[§]

d. viral myositis[§] [§]respiratory failure ± bulbar palsy

e. glomerulonephritis - acute/chronic renal failure

f. myocarditis, pericarditis

g. encephalitis, meningitis

h. thrombocytopaenia

i. overwhelming 2° bacterial infections / septicaemia
   - depressed CMI and lymphocyte function

j. association with Burkitt's lymphoma & other tumours

k. concurrent Streptococcal infection ~ 20%
   - possibility of rheumatic fever, scarlet fever, Sydenham's chorea, etc.

l. chronic mononucleosis syndrome

CMV Infection

NB: member of the *Herpesvirus* group
large intracellular inclusion bodies in infected cells

- ***Clinical Manifestations***

a. congenital CMV
b. acquired subclinical infection in children
→ **~ 30-80%** of the adult population are CMV Ab (+)'ve
c. acquired clinical CMV
d. reactivated CMV infection
e. disseminated CMV in immunocompromised patients

- ***Congenital CMV***

• occurs with an incidence ~ 0.5%
• complication rate ~ 10-15%, especially neurological involvement
• presentation,

a. failure to thrive
b. hepatitis
c. pneumonitis
d. encephalitis
e. haemolysis
f. chorio-retinitis
g. purpura
h. pathological fractures

- ***Acquired Infection - Children & Adults***

a. asymptomatic, or "flu-like" illness
b. pneumonia
c. hepatitis
d. encephalitis
e. GBS ?? ~ 30% of GBS occurs post-CMV infection
f. thyroiditis
g. ulcerative GIT disease
h. thrombocytopaenic purpura

- ***CMV - Mononucleosis Syndrome***

  a. spontaneous, or following blood transfusion

  b. acute febrile illness with - lymphocytosis
     - atypical lymphocytes

  c. "flu-like" symptoms - rashes
     - arthralgias and myalgia

  d. viral hepatitic picture ± hepatomegaly

  e. splenomegaly

  f. ulcerative involvement of the intestinal mucosa

  g. haematological involvement - haemolytic anaemia
     - thrombocytopaenia

  h. pneumonitis

  i. pericarditis

- ***Disseminated CMV - Immunocompromised***

  a. similar to CMV mononucleosis but severe & often fatal

  b. atypical lymphocytosis usually ***not*** a prominent feature

  c. common organ involvement - liver & GIT
     - lungs
     - CNS
     - eyes

- ***CMV - Transplant Recipients***

  a. potential sources → ~ 60% 1° infection
     ~ 30% superinfection

     i. transplant
     ii. transfusion
     iii. reactivation - very low

  b. graft reactions may - intensify 1° infection
     - reactivate latent infection

  c. sero(+) donor / sero(-) recipient → greatest risk

  d. sero(+) donor / sero(+) recipient → ~ 30%

  e. sero(-) donor / sero(+) recipient → very low %

  f. ***bone marrow*** recipients at higher risk, even if sero (+'ve)

g. clinical manifestations
   i. severe progressive pneumonitis
   ii. hepatitis - fever
   - elevated LFT's
   iii. ulcerative GIT disease
   iv. marrow suppression
   v. disseminated CMV ~ 100% mortality
   vi. graft rejection
   vii. CMV mononucleosis syndrome

h. accounts for ~ 50% of ***interstitial pneumonias*** in transplant patients

i. incidence rises in the first 15 weeks ~ 0.2% per patient day
   ~ 25% mortality ?

Transplant type	Seroconversion	Clinical infection
cardiac	100%	30%
bone marrow	100%	15%
renal	60%	15%

• problems associated with CMV for the transplant recipient,

1. CMV infection *per se*
2. transplant rejection
3. immunosuppression
4. superinfection

■ ***Diagnosis CMV***

a. serology - C' fixation Ab rise > 4-fold
b. indirect fluorescent Ab - to surface Ag of CMV infected cells > 4-fold rise
c. immunoflourescence - IgM-Ab to CMV titre > 1:16
d. culture

NB: heterophil (P-B) & monospot tests will be ***negative***

• prophylactic measures for transplant recipients,

1. seronegative organ donor
2. improved, more specific immunosuppressive therapy → cyclosporin A
3. reduce blood sources - seronegative blood donor
   - WC filters

- ***Complications***

NB: uncommon in normal hosts, but the following have been reported

1. hepatitis - occasionally with clinical jaundice
2. interstitial pneumonitis
3. corioretinitis
4. immune phenomena
   i. amoxicillin-induced rash
   ii. haemolytic anaemia
   iii. thrombocytopaenia
5. neurological syndromes
   i. GBS
   ii. polyneuritis
   iii. aseptic meningitis, encephalitis

- ***Treatment***

a. ***Gancyclovir*** ~ 5 mg/kg / q12h for 2 weeks
+ anti-CMV IgG
→ **~ 52%** improve

b. anti-CMV IgG
→ ~ 15-20% improve (not very effective)

c. Acyclovir - most studies show ***no benefit***, even in high doses
- 2 studies show some benefit in bone marrow transplants

d. steroids

e. foscarnet

- ***Problems Gancyclovir/Acyclovir***

1. resistance with prolonged prophylaxis
2. reversible neutropaenia - esp. gancyclovir
3. CNS toxicity

Candida Infection

• numerous species, common agents C. *albicans*, C. *parapsilosis*
• ***commensal*** organism in the mouth, large bowel and vagina

- ***Common Sites***

  a. skin
  b. urinary tract
  c. mouth
  d. distal oesophagus
  e. endocarditis
  f. systemic candidaemia
  g. endophthalmitis

- ***Predisposing Factors***

  a. poor skin hygiene, obesity
  b. steroids | immunosuppressive therapy
  c. broad spectrum antibiotics
  d. indwelling catheters
     - urinary catheters
     - CVC, PA, IA catheters
     - PD catheters
  e. immunocompromised patients
     - diabetes mellitus
     - malignancy
     - renal failure
     * AIDS
  f. IV drug abusers

- ***Laboratory Diagnosis***

  a. wet prep - pseudohyphae
  b. culture - smooth, shiny colonies
     - hyphae, pseudohyphae on some media
  c. serology - Candida Ag (+)'ve
     - limited sensitivity / specificity for invasive infection

- ***Treatment Candidal Infection***

a. remove ± treat predisposing factors

b. antifungal therapy

i. topical - oral Nystatin
- antifungal creams

ii. Amphotericin bladder washouts ~ 50-100 mg/100 ml
- q8h with 30 min dwell time

iii. Amphotericin B ~ 0.5-0.7 mg/kg/day IV for 6 weeks

iv. Flucytosine ~ 25 mg/kg q6h
+ Amphotericin 0.3 mg/kg/day

- ***synergistic*** for most fungal infections
- don't use combined therapy in AIDS patients

v. Fluconazole ~ 200-400 mg/day IV

vi. Ketoconazole ~ 400 mg/day
- oesophageal disease
- resistant GUS infection

NB: criteria for treatment with systemic antifungal agents,

→ ***systemic inflammatory response syndrome***, plus

i. negative cultures for bacteria, plus
Candida grown from ***two*** different sites, or

ii. micro shows heavy growth with hyphae/pseudohyphae

ENDOCARDITIS

Non-Infective Endocarditis

- ***Causes***

1. rheumatic fever
2. SLE
3. non-bacterial, thrombotic endocarditis - 'merantic'

• found in ~ 1% of all autopsy specimens from patients with,

1. neoplastic disorders
2. DIC / sepsis
3. burns
4. central venous cannulae

• 50% have pulmonary emboli if right-sided endocarditis exists

Infective Endocarditis

Def'n: infection by micro-organisms of a platelet/fibrin vegetation on the endothelial surface of the heart

a. incidence ~ 1:200-6,000 hospital cases, or
~ 1:17,000 normal population

b. mortality

i.	overall	~ 20-30%	
ii.	elderly	~ 40-70%	↑ 2x
iii.	severe CCF	~ 100%	

NB: the later may be reduced to ~ 30% with surgery

Acute Bacterial Endocarditis

- rapid, severe, destructive infection often with virulent bacteria
- often occurs on ***normal valves*** and has a high associated mortality
- causative organisms include,
    a. *Staphylococcus aureus*
    b. *Strep. pneumoniae* & *Strep. pyogenes*
    c. *Neisseria gonorrhoeae*

- ***Causative Organisms SBE***

NB: = "just about any"

a.	Streptococci		**~ 60%**
	i.	*S. viridans*	~ 30%
	ii.	*S. faecalis*	~ 10%
	iii.	other	~ 15-30%
b.	Staphlococci		**~ 25-35%**
	i.	*S. aureus*	~ 20-30%
	ii.	*S. epidermidis*	~ 5%
c.	gram negatives		**~ 1.5-13%**
	i.	*E. coli*	
	ii.	*P. aeruoginosa*	
	iii.	*H. influenzae*	
d.	anaerobes		~ 4%
e.	fungi		**~ 4%**
	i.	Candida	
	ii.	Aspergillus	
f.	rickettsia		
	i.	Q-fever	

NB: in IV drug abusers,

	i.	Staphylococci	~ 60%
	ii.	Candida, and	
	iii.	gram negatives	→ more common

- ***Predisposing Factors***

a. none found ~ 20-40%

b. ***rheumatic*** valvular disease ~ 25-60%
   - used to be most frequent cause
   - more recent studies **≤ 15%**

c. ***mitral valve prolapse*** ~ 10%
   - up to 50% and most frequent cause in some studies

d. ***congenital*** valvular disease ~ 10-20%

e. ***prosthetic*** valves & cardiac surgery ~ 10-20%

f. other cardiac risk factors[§]

g. ***nosocomial*** endocarditis
   i. peripheral AV fistulae / chronic haemodialysis, prosthetic aortic grafts
   ii. pacemakers, IV or IA lines
   iii. postoperative wound infections
   iv. genitourinary manipulation

h. immunosuppression
   - therapeutic
   - IV drug abuse, severe burns, alcoholism

i. Marfan's syndrome

- ***Cardiac Risk Factors[§]***

1. ***high risk***
   i. prosthetic valves
   ii. mitral regurgitation - rheumatic
   iii. aortic valve disease - rheumatic or bicuspid
   iv. Fallot's tetralogy, other complex CHD
   v. patent ductus arteriosus, VSD, coarctation of the aorta
2. ***intermediate risk***
   i. mitral valve prolapse, isolated mitral stenosis
   ii. tricuspid / pulmonary valve disease
   iii. calcific aortic stenosis, idiopathic subaortic stenosis
   iv. right heart catheterisation
3. ***low risk***
   i. ASD
   ii. pacemakers
   iii. arteriosclerotic plaques, syhilitic aortitis

- ***Predisposition***

a.	*S. viridans*	- dental procedures ~ 20%
b.	*S. faecalis*	- GIT, bowel surgery ~ 50%
c.	Staphylococci	- skin lesions, IV drug abuse ~ 40%

- ***Causes of Culture Negative Endocarditis***

a.	usual organism	- false negative - prior treatment with antibiotics
b.	unusual organism	- *Coxiella burnetti* - *Clamydia psittaci* - pyridoxine requiring Streptococci - fungi

- ***Clinical Findings***

a.	murmur	**~ 90%**
	• changing murmur	~ 12%
	• acute valvular dysfunction / rupture	
b.	fever > 38°C	**~ 77%**
c.	embolic episodes	**~ 50%**
	• brain, spleen, kidney, heart	
	• mycotic aneurysms	
d.	skin changes	**~ 50%**
	• petechiae	~ 20%
	• splinter haemorrhages	~ 15%
	• Osler's nodes	~ 10%
	• Janeway lesions	~ 10%
	• jaundice	
e.	splenomegaly	~ 25%
f.	metastatic infection	~ 20%
g.	clubbing	~ 12%
h.	Roth spots	~ 5%
i.	***immune complex*** phenomenon	~ 15%
	• arthritis	
	• acute GN	
j.	negative cultures	~ 5-40%

- ***Laboratory Investigations***

a. FBE / ESR
   - normochromic, normocytic, low reticulocyte anaemia ~ 50%
   - ↑ ESR/CRP ~ **90%**
   - ↑ WCC ~ 75%

b. blood cultures x 1 ~ 80%
   x 3 ~ 90% sensitivity (ARD disc positive)
   - IV adequate, IA unnecessary ~ 10 ml/btl
   - sensitivities with MIC, MBC ***essential***

c. serology - Q fever, *Clamydia*, and *Mycoplasma*
   - 10% culture negative - more likely false negative than unusual organism

d. features of GN & renal involvement ~ **50%**
   - haematuria, proteinuria, RBC casts

e. echocardiography **~ 50%** sensitivity (LIGW says up to 80%, ? TEE)
   - may confirm diagnosis
   - most lesions need to be **> 5 mm** before reliably detected
   - assesses risk of emboli, degree of valvular dysfunction, LV function

Clinical Management

a. ***always*** consult microbiologist & cardiac surgeon

b. empirical therapy - ***all*** for 4/52
   i. penicillin - 1.2g IV q4h
      - penicillin 1.8g if MIC > 0.2 mg/l
   ii. flucloxacillin - 2.0g IV q4h
   iii. gentamicin - 1.5 mg/kg IV q8h
      - single daily dosage in SBE/synergistic roles not established

c. known organism - ***all*** for 4-6/52
   i. *Strep viridans* - penicillin & gentamicin
   ii. *Strep. faecalis* - amoxicillin 2g q6h & gentamicin
   iii. *Staph. aureus* - flucloxacillin & gentamicin
   iv. MRSA - vancomycin 1.0g IV q12h 6/52
   v. gram (-)'ve - cefotaxime 1-2g q6h & gentamicin
   vi. pseudomonas - timentin 3.1g q4h & tobramycin 1.5mg/kg q8h

d. patient allergic to penicillin → vancomycin

- persistence of ***fever*** beyond 4-7 days may represent myocardial or embolic abscess, or drug sensitivity
- monitor with serial CRP and echocardiography

Prophylaxis

1. dental, oral, or upper respiratory tract surgery
   i. standard regimen
      - oral penicillin V 2g prior & 1g 6 hrs post-procedure, or
      - IM or IV benzyl penicillin 2 MU 30 mins prior & 1 MU 6 hrs post-procedure

   ii. maximal therapy options
      - amoxicillin 2g & gentamicin 1.5 mg/kg IV/IM 30 min prior, & either penicillin V 1g orally or benzyl penicillin 1 MU 6 hrs post-procedure

   iii. penicillin allergy
      - oral - erythromycin 1g 1 hr prior & 500mg 6 hrs post-procedure
      - IV - vancomycin 1g over 60 minutes prior to procedure

2. gastrointestinal & genitourinary
   i. standard regimen
      - amoxicillin 2g & gentamicin 1.5 mg/kg 30 min prior & 8 hrs post-procedure

   ii. low risk procedure/patient
      - oral amoxicillin 3g 1 hr prior & 1.5g 6 hrs post-procedure

   iii. penicillin allergy
      - vancomycin 1g over 60 minutes & gentamicin 1.5 mg/kg prior to procedure
      - this may be repeated at 6-8 hrs post-procedure

3. prosthetic valve insertion
   - vancomycin 1g over 60 minutes prior & 500 mg q12h x2 doses post procedure

Indications for Valvular Surgery

1. native valve infection, plus
   i. acute valvular incompetence / worsening cardiac failure
   ii. fever > 6/52
   iii. persistent large vegetations
   iv. significant embolic phenomena

2. prosthetic valve infection, plus
   i. signs of valve dehiscence
   ii. continuing embolic manifestations
   iii. worsening cardiac failure

LEGIONNAIRE'S DISEASE

Def'n: acute respiratory infection caused by *Legionella pneumophila*

a. organism
- gram negative bacillus / rod
- intracellular, pleomorphic
- aerobic, fastidious, difficult to culture (best in 2.5-5% CO_2)
- several sero/subgroups with cross-reactivity
→ serological D_x requires multiple Ab's

b. epidemiology
- incubation period 2-10 days
- respiratory transmission
- all age groups but more common in middle & elderly persons
- high risk groups
  - elderly
  - smokers
  - immunosuppressed
  - renal failure
  - malignancy

~ 15-50% *mortality*

c. diagnosis
- serological ~ 4x rise in Ab titre, or > 1:256 initial titre
- direct fluorescent Ab stain of sputum, Bx, BAL etc.
- Dieterle stain

■ ***Clinical Features***

- may be asymptomatic
- average duration 2/52

a. respiratory
   i. "influenza like" syndrome - fever, myalgias, headache
   ii. pneumonia
   - non-productive cough
   - high fever, tachypnoea, tachycardia
   - pleuritic pain
   ~ 20-30% respiratory failure
   ~ 20% haemoptysis, mucopurulent sputum

b. GIT ~ 25% have GIT symptoms, pain, N&V
- mild hepatitis, jaundice, infective hepatitis
* 2 recent reviews with 3-5 cases each but ***no*** GIT symptoms

c. CVS - hypotension, fever, tachycardia

d. acute reversible renal dysfunction

e. septic syndrome
- acute renal dysfunction
- liver dysfunction
- acute respiratory failure

f. CNS - confusion, agitation, obtundation
* ***not*** correlated with degree of hypoxaemia

- ***Investigations***

a. CXR
   - usually ***worse*** than clinical signs
   - diffuse patchy lobar infiltrates
   - poorly marginated rounded opacities
   - ~ 65% unilateral lobar involvement early, eventually bilateral in 75%
   - ~ 30% have pleural effusions

b. laboratory
   i. FBE - neutrophilia, toxic changes
      - high ESR
   ii. biochem - abnormal LFT's
      - renal impairment
   iii. AGA's - hypoxaemia with high $AaDO_2$

- ***Treatment***

NB: Erythromycin ~ 15 mg/kg (≤ 1g) q6h

• later generation macrolides may be equally/more effective
• some data to suggest ***quinolones*** equally effective

Meningococcal Infection

a. organism
- gram (-)'ve, intracellular diplococci, ***oxidase*** positive
- warm choc. agar at 37°C
- serological subgroups: A, B, C, D, & others
- most common epidemic subtypes → A, C & Y
- nasopharynx is ***only*** known habitat
- **~ 2-15%** of general population are ***carriers***
- carriage is transient & confers immunity

b. presentation
~ 20-40% meningitis alone
~ 30-50% meningococcaemia without meningitis
~ 5% other presentations

c. complications of ***meningococcaemia***

i. CNS - meningitis, acute diffuse encephalitis

ii. CVS - myocarditis, pericarditis, septic shock

iii. purpura fulminans - non-thrombocytopaenic
- limb & digit ischaemia (~ 10% requiring surgery)

iv. Waterhouse-Friedrichsen syndrome
→ meningococcaemia + septic shock + haemorrhagic ***adrenal necrosis***

v. septic arthritis ~ 2-10%

vi. chronic meningococcaemia - fever, rash, arthritis, splenomegaly

d. complications of meningococcal ***meningitis***
- cerebral oedema, obstructive hydrocephalus
- long-term neurological/psychological sequelae
- seizures, deafness
- thrombosis of cerebral venous sinus
- herpes labialis

Treatment

a. ABC - treat septic shock

b. Penicillin G ~ 2-4 MU q4h, or Ceftriaxone/Cefotaxime

c. dexamethazone ~ 0.15 mg/kg ? 2 or 4 days

d. unproven
- plasmapheresis, haemofiltration
- FFP, protein C concentrates, heparin/fragmin, tPA

e. contacts - Rifampicin 400mg bd for 4 days

f. Meningovax
- group A & C antigens, ∴not complete cover
- delayed effect & not 100% of population

g. ? role of cerebral oedema management & ICP monitoring
- if papilloedema or obtunded, no LP → CAT scan
- if CT evidence of hydrocephalus ± cerebral oedema → ICP monitoring

Normal Flora

a. **skin**

i.	aerobic	- Staph. aureus, epidermidis - Strep. pyogenes - Candida
ii.	anaerobic	- gram (+)'ve cocci - Eubacterium

b. **pharynx**

i.	aerobic	- Staph. aureus - Strep. viridans, pyogenes, pneumoniae - Haemophilus - Klebsiella - Candida - occ. gram (-)'ve bacilli
ii.	anaerobic	- gram (+)'ve cocci - Bacteroides melano - Fusobacterium - Actinomyces - Bifidobacterium - Eubacterium

c. **colon**

i.	anaerobic	- gram (+)'ve cocci, esp. Enterococci - Bacteroides melano, fragilis - Fusobacterium - Clostridia - Bifidobacterium - Eubacterium
ii.	aerobic	- gram (-)'ve coliform bacilli - Staphlococci - Strep. viridans - Pseudomonas

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 cause
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

PSEUDOMONAS INFECTIONS

a. ***pathogen***
- gram (-)'ve, motile, *aerobic* bacillus
- cryophilic, not gas producing
- common in soils and plants
- ~ 6-10% of population faecal carriers
- skin of some individuals (axillae, groin)
- high inpatient colonisation rate ~ ***normal flora***
- common contaminant in wounds and respiratory tract (esp. ETT + antibiotics)

b. ***bacterial factors***

i. propensity for moist environments
- patients, hands of staff, foodstuffs
- ventilators, nebulisers, humidifiers, etc.
- mops, sinks, soaps, buckets, vases, urinals
- endoscopes, antiseptic solutions, ophthalmic ointments

ii. development of bacterial resistance
- mutation, induction, plasmid formation

iii. ***exotoxin*** formation
- exotoxin A - inhibits protein synthesis
- phospholipase - surfactant breakdown
- antiphagocytic components
- lipid A - gram (-)'ve ***endotoxin***

iv. cryophilic

c. ***predisposing factors***

i. antibiotic use

ii. invasive procedures, catheters

iii. elderly, very young

iv. immunocompromised

v. immunosuppressants - steroids, cytotoxics

vi. endemic sources - aqueous environments
- sinks, circuits, etc.

d. ***sites of infection***

i.	skin	- wounds, burns
ii.	GUS	- catheter associated UTI
iii.	septicaemia	- haemorrhagic nodules - ***erythema gangrenosum**** - 1cm purple/black nodules in groin/axillae - rarely also green urine (verdoglobin)
iv.	bone	- abscess, penetrating wound
v.	meningitis	- instrumentation, LP, skull #
vi.	endocarditis	- prostheses
vii.	respiratory	- ETT, tracheostomy, IPPV, antibiotics - change in "normal" flora - bronchopneumonia
viii.	GIT	- bacterial ulcerative colitis

e. factors necessary for ***normal host defence***

i. Ab formation to cell wall and toxins
ii. complement activation
iii. neutrophil function

NB: cell mediated immunity less/not important

Treatment

a. remove predisposing factors

b. drain collections

c. antibiotics

- silver sulphadiazine
- aminoglycosides - gentamicin, tobramycin
- synthetic broad spectrum penicillins - ticarcillin, piperacillin
- 3rd generation cephalosporins - ceftazidime
- Imipenem, Ciprofloxacin, Aztreonam

d. hyperimmune gamma globulin (from vaccinated patient)

e. polyvalent vaccine

NB: from TQEH isolates ~ 40-50% ***timentin resistant***

TOXIC SHOCK SYNDROME

Def'n: syndrome due to the production, absorption and widespread distribution of a toxin, or toxins, from *Staphylococcus aureus* infection

1. ***menstrual TSS*** ~ 99% of cases
   - young menstruating women
2. ***nonmenstrual TSS*** ~ 1%

■ ***Diagnostic Criterea***

1. ***hypotension*** < 90 mmHg systolic, or 30% decrease
2. ***fever*** ≥ 38.9°C
3. erythematous rash, followed by ***desquamation***
4. involvement of ≥ 4 organ systems
5. absence of other known causes
   i. meningococcaemia
   ii. streptococcal scarlet fever
   iii. *Rickettsia*, leptospirosis
   iv. erythema multiforme
   v. scalded skin syndrome
   vi. Kawasaki's disease

■ ***Clinical Features***

a. sudden onset of marked ***pyrexia***
b. malaise, nausea, vomiting and watery diarrhoea
c. sore throat, or very tender mouth
d. headache, fatigue, irritability, disorientation
e. myalgia, muscle tenderness
f. abdominal distension & pain which may suggest peritonitis
g. erythematous ***rash***
h. ***desquamation*** occurs ~ 10 days following the disease onset
   • especially on the palms and soles
i. acute illness phase lasts ~ 4-5 days
j. convalescent phase lasts several weeks

NB: recurrence rate is ~ 30% in women who continue to use tampons

- ***Investigations***

a. FBE - neutrophilia

b. EC&U - ↑ creat/urea
- hypokalaemia, hyponatraemia, hyperglycaemia

c. LFT's - ↑ AST, ALT, bilirubin, lactate

d. ↑ CPK

e. MC&S

i. vagina ~ 98% are culture positive for *Staph aureus* ***prior*** to antibiotics
- most are negative, ie. treated prior to presentation

ii. throat / nasopharynx

- ***Management***

1. remove all foreign material
2. ABC
3. antibiotics
   - ***no improvement*** in outcome
   - reduction in recurrence rate

PANTON-VALANTINE TOXIN (PVL)

- first described in 1932 by Panton & Valentine
- present in only ~ 2% of *S. aureus* isolates
- encoded by mobile phage (ΦSLT) which can transfer PVL to other strains
- predisposition for young adults, often in clusters
- associated with:

1. furuniculosis
2. severe haemorrhagic pneumonia *poor prognosis

NB: clinical presentation of a young adult with recurrent boils & new onset pneumonia should raise suspicion & alert due to high mortality

Malaria

- ***Species***

1. *Plasmodium vivax*
2. *Plasmodium falciparum*
3. *Plasmodium ovale*
4. *Plasmodium malariae*

• transmitted by bite of female *Anopheles* mosquito
• initiation is via attachment to specific ***RBC receptors***
• most West Africans are resistant to *P. vivax*
• drug resistant *P. falciparum* is seen in S-E Asia, W. Pacific, Central America etc.
• ***parasitaemia*** is limited in,

a. sickle cell trait
b. thalassaemia
c. G6PD deficiency

- ***Clinical Features***

1. *P. vivax | P. ovale*
   - incubation period ~ 10-14 days
   - myalgia, fever, chills preceding rigors, sudden high fever & defeverescence
   - ***relapsing fever*** alternate days in synchronized infection
2. *P. malariae*
   - mildest & most chronic form
   - relapsing fever every 3rd day
   - may present with immune-complex nephropathy
3. *Plasmodium falciparum*
   - insidious onset with irregular fever
   - headache, confusion, ***encephalopathy***
   - hypotension, oedema
   - GI symptoms, splenomegaly
   - renal dysfunction
   - ***complications***,

   i. acute pulmonary insufficiency - 3-4th day of therapy
      - aspiration
   ii. blackwater fever
      - massive intravascular haemolysis & haemoglobinuria, ARF
   iii. cerebral malaria
   iv. hypoglycaemia

- ***Diagnosis***

1. FBE
   - ↓ WCC - may be normal
   - ↑ ESR
   - thin & thick blood smears
2. culture

- ***Management***

a. chloroquine

b. primaquine

c. severe *P. falciparum* infection
   i. ABC
   ii. exchange transfusion
   iii. steroids, mannitol & heparin should be ***avoided***