Meningitis and Brain Abscess

PRESEN	TING SYMPTOMS:	Sub-Acute (days) or	Acute (hours)
CLASSICAL TRIAD OF SYMPTOMS for MENINGITIS	 FEVER from infectious proce WORSENING HEADACH STIFF NECK from meninge PHOTOPHOBIA (rarely the pr ALTERED CONSCIOUSNESS FOCAL NEURO SIGNS from NAUSEA AND VOMITING fro 	ess ← IE from increased ICP ← eal irritation (PATHOGNOMIC) resenting symptom) S from increased ICP nerve pressure or irritation ← m increased ICP ←	ABSCESS SYMPTOMS
	Discout and the second	a second	

- Plus there is a characteristic petechial rash from meningococcal meningitis

Differential Diagnoses

The moment you hear "...fever headache and stiff neck..." you should think <u>MENINGITIS</u> Would hate to miss it in a child, because the disease progression is often very rapid. Thus, its CNS infection until proven otherwise

OTHERWISE ...

The ICP increase and its retinue of symptoms could be from

- Space-occupying Lesion eg. Primary Brain Lymphoma (! Also causes fever !)
 - Encephalitis
 - Viral meningitis
 - Aseptic Meningitis (i.e non-infectious causes, eg. myelogram gone wrong)
 - Cytotoxic oedema from a HUGE infarct (hard to tell if the patient is unconscious)
- Intracranial Hematoma (sub/epidural, subarachnoid or intracerebral)

The fever could be an unrelated infection

The stiff neck might be infected or a case of ANKYLOSING SPONDYLITIS (although not in kids)

TISIULY ! Assess consciousness 1°	Paediatric Coma Scale
Then, the key is to figure out the potential pathogens fr	om history and Eyes open
to exclude cancer and trauma	Spontaneously 4
THUS: ASK ABOUT	To speech 3
 Chronology of current symptoms 	To pain 2
something chronic will point towards can	er Not at all 1
BLIT something acute could be traumatic eq	Best verbal response
opidural (arterial) homotoma	Orientated 5
epicural (arterial) hematolia	Words 4
and something sub-acute could be a	Vocal sounds 3
subdural (venous) hematoma	Cries 2
 Any Recent Trauma to rule out hematoma 	None 1
 Most recent infections to get some idea of where the 	e pathogen Best motor response
migrated from	Obeys commands 5
! PNEUMONIA AND OTITIS MEDIA IN P	ARTICULAR ! Localizes pain 4
- Cardio History to see if there might be a ventricular s	eptal defect Flexion to pain 3
sending clots into the brain	Extension to pain 2
- Vaccination history to rule out a few nathogens	None 1
Trough biotory (con time of year) it may be someth	Normal aggregate score
- Traver history (esp. time of year,) it may be sometin	Birth to 6 months 9
- Sexual history and/or hiv status: as above	6-12 months 11
	1-2 years 12
The child younger than 3 months may have very nonspecific syr	ptoms, including 2-5 years 13
nypertnermia or nypotnermia, change in sleeping or eating	napits, Over 5 years 14

irritability or lethargy, vomiting, high pitched cry, or seizures

Examination: Assess airway, breathing pattern and circulation!

VITALS: expecting a high temperature

General: looking for signs of previous infection which could have migrated to the brain:

THUS: **Otoscopy** for otitis media;

Lung percussion/auscultation to look for bronchitis or pneumonia

Look for areas of tenderness over the scalp and neck

(looking for potential fracture or infectious process)

look for neck LYMPH NODES (drain from the meninges)

NEURO EXAM: Look for Cranial nerve lesions; try to trace them to one lesion (Occam's Razor)

- CN 6 and 4 may give FALSE LOCALISING SIGNS

Look also for cerebellar and brainstem signs eg. ataxia, proprioceptive loss, <u>decerebrate posturing (</u>i.e rigid extension of the arms and legs, downward pointing of the toes, and backward arching of the head)

Tests and Investigations

FBC

- Looking for INCREASED NEUTROPHILS (bacterial meningitis or abscess)
 - Or INCREASED
 - LYMPHOCYTES(viral meningitis)

Plus haemoglobin may be low, which is typical of infection.

Chest X-ray

- This may point out a source of infection and narrow the range of potential pathogens;

CT scan with contrast →

 Blood brain barrier is breached in infectious CNS diseases, especially abscesses, so this will show up nicely

Culture of Discharge and Blood Culture

If it is bacterial infection, the culture should provide an accurate idea of what the pathogen is, as well as its resistance to antibiotics

CSF sample analysis and culture

- This is the BEST DIAGNOSTIC TEST to determine what the pathogen is;
- HOWEVER:



NEVER PERFORM A LUMBAR PUNCTURE ON SOMEONE WITH INCREASED INTRACRANIAL PRESSURE! ...Or you may change the pressure gradient in the brain

and suck the brainstem through the foramen magnum.

SO DON'T TAKE TOO MUCH!!

~3.5 mL of CSF is sufficient to obtain a cell count (1.0 mL), glucose and protein concentrations (1.0 mL), latex particle agglutination (LA) tests (0.5 mL), and Gram's stain and bacterial cultures (1.0 mL) CSF SAMPLE:

- The classic <u>CSF</u> abnormalities in bacterial meningitis are:
- (1) polymorphonuclear leukocytosis (>100 cells per microliter in 90%),
- (2) decreased glucose concentration [<2.2 mmol/L (<40 mg/dL) '
- and/or CSF/serum glucose ratio of <0.4 in ~60%],
- (3) increased protein concentration [>0.45 g/L (>45 mg/dL) in 90%], and
- (4) increased opening pressure (>180 mmH₂O in 90%).

CSF bacterial cultures are positive in >80% of patients, and CSF

Gram stain is high specific but only about 80% sensitive,

...depending on the number of organisms present in a given volume of CSF **VIRAL MENINGITIS:**

The classic CSF profile in patients with viral CNS infections is

a lymphocytic pleocytosis with a normal glucose concentration,

as contrasted with the PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis.

Disease Definition

Meningitis:... is an acute purulent infection within the subarachnoid space

Abscess: ... is a focal, suppurative process within the brain parenchyma; it begins in an area of devitalized brain tissue as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule.

Management

Immediate:

Treat empirically; give broad-spectrum 3rd generation antibiotics INTRAMUSCULARLY eq. cephalosporin

After investigations:

Use antibiotics for which there is no resistance and which penetrate the blood brain barrier, INTRAVENOUS OR INTRAMUSCULAR

Eg. Chloramphenicol, Bactrim, Ciprofloxacin

!! B-Lactam AB.concentration in the CSF should exceed the **Minimum Inhibitory Concentration of the bacterium** for 40% of the dosing interval

Cefotaxime, sulphonamides, beta-lactams (penicillins), anti-TB drugs (eg. isoniazid, rifampicin)

PLUS: you can give dexamethasone to reduce ICP and inflammation (because the antibioticmediated lysis of bacterial cell walls will release polysaccharides, thus aggravating the inflammation

Prognosis is related to the delay before therapy

- prognosis is worse for patients at the extremes of age (ie, <2 y, >60 y) and those with significant comorbidities and underlying immunodeficiency.
- Meningitis caused by S pneumoniae. L monocytogenes, and gram-negative bacilli has a higher case-fatality rate compared to meningitis caused by other bacterial agents.
- Seizures = poor prognosis **VIRAL MENINGITIS = GOOD PROGNOSIS**
- If you're in a coma at the moment of presentation, you're most likely to die.

The overall mortality for bacterial meningitis is 5-10%

(varies with causative organism and age.)

Neonatal meningitis has a mortality rate of 15-20%.

In older children, the mortality rate is 3-10%.

Meningitis from S pneumoniae and Listeria has the highest mortality rate N meningitidis has the lowest mortality rate **!!! HIGH RISK OF DEAFNESS !!! most common of long-term sequelae**

Epidemiology

Organism	no.(%)Incidence		<u>case fatality</u> (cases / 100.000		
<i>H.influenzae</i> B	45%	2.9	3%		
5.pneumoniae	18%	1.1	19%		
N.meningitidis	14%	0.9	13%		
Group B Strep	5%	0.4	12%		
Listeria	3%	0.2	22%		
Others:	15%	1.0	18%		
(Streptococcu	is sp, Staph o	ureus, Stap	h epidermidis		
Gram negative	s - E.coli, Kle	ebsiella, Seri	ratia, Acinetobacter,		

Rogues Gallery: most common pathogens Neonatal Meningitis (0-3 months of age)

Bacteria are acquired from the birth canal before the baby acquires its protective layer of Normal Flora. Common pathogens are

- Escherichia coli,
- Listeria monocytogenes
- Streptococcus agalactiae (= Beta-haemolytic Streptococcus Lancefield Group B = "Group B Strep").

Childhood Meningitis (4 months to 14 years)

Common pathogens are

- Haemophilus influenzae type b (Hib), now becoming rare because of immunisation,
- Streptococcus pneumoniae (SP)
- Neisseria meningitidis (NM). All may also occasionally cause neonatal meningitis.

Adult Meningitis

	BY AGE (SROUPS	- USA	1986	(%)	
AGE	GBS	List	HiB	<u>Pn</u>	Mn	Other
0-1 month	49	9	5	3	1	33
2mo - 4yrs	s 2		70	10	13	5
5 - 29yrs	2	2	8	17	42	29
30 - 59yrs	s 4	6	5	37	10	38
>60yrs	3	14	4	48	3	28

 Π

Actiology of adult meningitis

•	5.pneumoniae	30-50%

- 10-35% N.meningitidis
- 1-10% • G -ve bacilli

5%

- 1-3% H.influenzae
- Listeria
- 5% Streptococci
- 5-15% Staphylococci

0-1 month	49	9	5	3	1
2mo - 4yrs	2		70	10	13
5 - 29yrs	2	2	8	17	42
30 - 59yrs	4	6	5	37	10
>60vrs	3	14	4	48	3

N.meningitidis (particularly 15 - 25 years) and S.pneumoniae (particularly the elderly). MECHANISM OF PATHOGENESIS



Basic Sciences : Relevant anatomy

Clinical Anatomy of the Meninges

The brain is suspended in cerebrospinal fluid (CSF); It is surrounded by 3 layers which together make up the meninges:

- the pia
 - covers the external surface of the brain
- the arachnoid

more loose and filled with CSF
 (pia + arachnoid = leptomeninges)

• the dura

- attached to the periosteum of the skull, except where it forms **4 rigid septa**

- falx cerebri,
- falx cerebelli,
- tentorium cerebelli and
- diaphragma selli



Location of infection: Purulent collections in relation to the meninges:

- Subarachnoid space infection of CSF, spreads over the entire leptomeninges = meningitis
- Subdural space potential space between arachnoid and the dura.
 - Infection spreads rapidly because the arachnoid and dura are attached at few points (subdural empyaema)
- Epidural space infection confined by attachment of dura to bone (epidural empyaema)
- Adjacent structures and spread of infection intracranially:
 - Sinuses infection in the frontal or ethmoid spreads to anterior cranial fossa
 - Infection in sphenoid to middle cranial fossa, spreads to cavernous sinus (!! Death !!)
 - Middle ear and mastoid infection tracks to middle cranial fossa (temporal lobe, cerebellum)

Increased intracranial pressure (ICP) and displacement of intracranial structures:

• Leptomeningitis: pressure spreads evenly and no displacement unless severe ICP rise

• Focal collection: subdural, epidural or in brain - uneven pressure causes displacement early

- The brain herniates across the dural septa, in particular the temporal lobe over the tentorium, causing
- compression and paresis of the third cranial nerve (oculomotor),
- followed by ipsilateral corticospinal tract signs as the contralateral cerebral peduncle is compressed against the tentorium,
- and coma (the characteristic signs of coning).

Cranial nerves and meningitis

- All exit through the meninges at the base of the brain and are thus affected by basilar meningitis
- Third cranial nerve (oculomotor) close relationship to the tentorium
- Sixth cranial nerve (abducens) <u>longest intracranial course</u> may be involved directly or with increased ICP (false localising sign)



Functional Anatomy of the Cranial Nerves



NUCLEI: MOTOR = MEPIAL, SENSORY = LATERAL

Vestibular Anatomy and Function

Vestibular receptor cells are force detectors. the semicircular canals detect angular forces (from head rotation) the otoliths detect linear forces (from head tilts or translations).

Almost every head movement results in a combination of both angular and linear forces.

The neural signals from the vestibular force detectors result in three major effects:

- Perception:
- If you close your eyes, you know whether you are moving or not and whether your head is upright or tilted.. Oculomotor responses:
- vestibular stimulation normally causes the eyes to move to compensate for head movement = the vestibulo-ocular response (VOR).
- Postural responses: some vestibular pathways project to the muscles of the neck and trunk, causing these muscles to react to
 compensate for head movement and to preserve postural stability.



Cell Biology: the BLOOD-BRAIN BARRIER

Unlike peripheral capillaries that allow relatively free exchange of substance across / between cells, the BBB strictly limits transport into the brain through both physical (tight junctions) and metabolic (enzymes) barriers.



Thus the BBB is often the rate-limiting factor in determining permeation of therapeutic drugs into the brain.

The periendothelial accessory structures of the **BBB** include

pericytes,

- astrocytes, plus a basal membrane.

The endothelial cells of the BBB are distributed along the length of the vessel and completely encircles the lumen. A thin basement membrane (i.e. basal lamina) supports the **ablumenal surface of the endothelium**. The basal lamina surrounds the endothelial cells and pericytes; the region between which is known as the **Virchow-Robin space.** Astrocytes are adjacent to the endothelial cell, with astrocytic end feet sharing the basal lamina (*Figure 1.2.1 & 1.2.2*).

Figure 1.21 A representative cross-section of a cerebral capillary of the BBB. Shown are the astrocytic end feet (AE), basal lamina (BL), endothelial cell (EC), nucleus (NU), pericyte (P), and tight junction (TJ).
Figure 1.2.2 A representative cross / longitudinal-section of a cerebral capillary of the BBB. Shown are the astrocytic end feet (AE), basal lamina (BL), and endothelial cell.(EC).

THUS: the 3 components of the BBB are: 1) Tight junctions of the endothelial cells 2) thick basal lamina 3) Astrocyte foot processes

Pericytes

in the periphery are flat, undifferentiated, contractile connective tissue cells, which develop around capillary walls. They are derived from microglia. Their function?

- Apparently, to regulate capillary endothelial cell proliferation and all aspects of angiogenesis

-THEY DO SO BY INHIBITION: lack of pericytes = vascular hyperplasia

ASTROCYTES

Astrocytes are glial cells which envelop > 99% of the BBB endothelium. Intercellular adhesion between astrocytes = gap junctions

Astrocytes serve as scaffolds, guiding neurons to their proper place during development and direct vessels of the BBB. The association of astrocytes to the cerebral microvasculature is underlined by the association of neurons to astrocytes.

The ~20 nm gap between adjacent astrocytes, which is readily diffusible by horseradish

peroxidase (Brightman and Reese, 1969), indicates that they most likely **do not contribute** to the physical barrier of the BBB.

BASAL LAMINA

consists of laminin, fibronectin, tenascin, collagens, and proteoglycan

- provides mechanical support for cell attachment,
 - serves as a substratum for cell migration,
 - separates adjacent tissue,
 - can act as a barrier to the passage of macromolecules.

Anatomy of the cerebral capillary

The surface area of the brain microvasculature is ~ 100 cm² · per gram of tissue, with the capillary volume and endothelial cell volume constituting approximately 1% and 0.1% of the tissue volume, respectively The mean intercapillary distance in the human brain is ~ 40micrometres

This short distance allows for near instantaneous solute equilibration throughout the brain interstitial space for small molecules, once the BBB has been overcome.

The microvasculature of the central nervous system (CNS) can be differentiated from the peripheral tissue endothelia in that it possess uniquely distinguishing characteristics:

- Tight junctions
- Cells of uniform thickness without fenestrations
- BBB endothelial cells are ~ 39% thinner than peripheral ones
- Greater number of mitochondria than in the peripheral vascular endothelium
- An active enzyme barrier (metabolism occurs in the cerebral endothelium)
- There is a difference in numbers of transmembrane protein receptors, between the lumen side and the astrocyte side of the endothelial cells in the BBB

Transport at the Blood Brain Barrier (BBB)

There are four basic mechanisms by which solute molecules move across membranes.

- **simple diffusion**, which proceeds from low to high concentrations.
- **facilitated diffusion**, a form of carrier-mediated endocytosis, in which solute molecules bind to specific membrane protein carriers, also from low to high concentration.
- simple diffusion through an aqueous channel, formed within the membrane.
- active transport through a protein carrier with a specific binding site that undergoes a change in affinity.



Transport mechanisms at the BBB.

- 1 = paracellular diffusion (sucrose),
- 2 = transcellular diffusion (ethanol),
- 3 = ion channel (K+ gated),
- 4 = ion-symport channel (Na+/K+/CI- cotransporter),
- 5 = ion-antiport channel (Na+/H+ exchange),
- 6 = facilitated diffusion (Glucose via GLUT-1),
- 7 = active efflux pump (P-glycoprotein),
- 8 = active-antiport transport (Na+/K+ ATPase),
- 9 = receptor mediated endocytosis (transferrin & insulin)

Behavioural science: kids in hospital

About one in every four children will be hospitalised at least once before reaching school age.

Impact on the Child

Most children respond to hospitalisation with **some level of overt distress and a deterioration in psychosocial function**ing.

Some children still show clinically significant behavioural/emotional disturbance 6 months after discharge.

GREATER RISK OF THIS:

- aged between 6 months and 4 years
- developmentally delayed
- individual characteristics that affect a child's ability to cope with adverse, stressful situations, such as personality (e.g. high trait anxiety), a coping style that is avoidant or an external locus of control
- a prolonged admission
- multiple admissions
- previous adverse experience of hospitalisation or procedures
- more severe trauma or illnesses, particularly those which result in pain or painful procedures
- inadequate or inappropriate preparation of the child and/or parents about the possible effects of hospitalisation and how they can be minimised or managed
- lack of training of medical, nursing and other staff as to how to minimise adverse effects
- especially in the younger child, lack of parental contact, or at least regular contact with someone with whom the child can form a supportive relationship
- parents who are highly anxious or respond poorly to stress
- a punishing parental style or tendency to reinforce dependency

Impact on the Family

- Factors associated with good family adjustment include a
- prior history of good coping,
- good quality of marital and family relationships,
- good support systems,
- religious or spiritual faith,
- a trusting relationship with medical staff.

Strategies which help parents cope include

- (1) obtaining as much information as possible about the child's medical condition,
- (2) establishing a social support system to help share the burden of the child's hospitalisation, and
- (3) attempting to integrate the child's illness into the mainstream of their everyday life.

Minimizing Adverse Effects

Hospital staff can minimimze the effects by

(1) providing timely information to parents and children,

(2) providing play therapy and modelling for younger children and teaching cognitive coping strategies to older children, and (3) providing facilities for parents to room-in and support which enables them to focus their attention on caring for their child.

Microbiology and Immunology

Site of infection:

The localisation of CNS infections is a function of both the causative agent and the host and may be generalised (meningitis, encephalitis) or specific –

- either for certain cell types (for example, polio virus and the anterior horn cell or rabies virus and neurones)
- or anatomic areas (for example, Herpes simplex virus with predilection for the temporal lobe, tuberculous meningitis which predominantly affects the meninges at the base of the brain and spread from adjacent structures as outlined above)

Exposure history:

Recent arrival from or travel to areas outside Australia will require consideration of a much wider range of infections, not present in Australia. For example, only two cases of rabies have been diagnosed in Australia, both acquired overseas and both diagnosed at post mortem. Cerebral malaria is a medical emergency and in contrast to rabies, treatable. Within Australia, specific exposures such as pig shooting (brucellosis) or caving (histoplasmosis) require careful history taking.

Host factors

Age

Susceptibility to and causes of CNS infection differ markedly with age. In previously well individuals in Australia, certain neurotropic viruses (enteroviruses, mumps, herpes simplex) and encapsulated bacteria are the most common causes of CNS infections. Viruses may cause meningitis or encephalitis, and while the incidence is higher in the neonatal period, the spectrum of viruses does not change greatly throughout life. In contrast, bacteria, including mycobacteria, largely cause meningitis and the likely causative agents vary considerably with age

Other foci of infection

Infection of the middle ear and sinuses is particularly associated with intracranial abscess, either

epidural, subdural or parenchymal. Chest lesions are commonly present when meningitis due to Cryptococcus neoformans occurs and miliary disease, including pulmonary disease, is usually present in tuberculous meningitis.

Immunosuppression

In a patient who has impaired immunity, the range of possible pathogens expands greatly and differs according to the part of the immune system affected (cellular, humoral or complement or multifactorial) and whether the defect is congenital or acquired.

Pathogenesis of meningitis and prevention by immunisation

Entry to the meninges

Haematogenous spread: Possession of a polysaccharide capsule is the common factor which

distinguishes the most common meningeal pathogens (Hib, SP and NM). *The polysaccharide capsule interferes with phagocytosis by complement, allowing invasion into the bloodstream and subsequently the meninges.* Antibody to polysaccharide(PS) acts with complement to protect against invasion.

Antibody develops naturally from the age of 2 years (probably by cross immunity from related organisms) which accounts for the age-related susceptibility to encapsulated organisms.

Under two years, PS must be conjugated (joined) to a protein to elicit an antibody response following immunisation (the principle used for Hib immunisation).

Over 2 years, antibody responses are elicited to PS alone. Meningococcal vaccines contain two PS, types A and C, while pneumococcal vaccines must contain 21 types in order to cover the most common stereotypes.

<u>Spread from adjacent structures</u>: This requires a defect in the barriers separating the meninges which puts the normal bacterial flora of adjacent anatomic structures (facial sinuses, nasal cavity or middle ear) in contact with the CSF.

Such defects may be

- traumatic (e.g. facial fracture)

or

- **congenital (**e.g. defect in the oval or round window of the middle ear).

Overall, meningitis from haematogenous spread is much more common.

Tissue Damage

• Tissue damage from bacterial meningitis is mediated both directly by microbial factors and by cytokines induced by them.

Paradoxically, antibiotic therapy leading to microbial lysis promotes release of bacterial cell wall components stimulating cytokine release. This has led to the suggestion that **corticosteroids** or other agents aimed at damping down the inflammatory response be used together with antibiotic therapy in bacterial meningitis.

Cefotaxime

Mechanism of Action

3rd generation **Cephalosporin**, mechanism of action as for other **Beta-lactams**; Crosses Brainblood barrier.

Dosage

2-6 g daily in divided doses

Other Uses

Infections due to susceptible organisms; Respiratory, UTI; Septicaemia; Intra-abdominal infections; Gonorrhoea; ENT infections; Soft tissue, bone, joint infections; Meningitis (combination therapy); Postop obstetric, biliary surgery;

Contraindication

Do not administer with lignocaine; Hypersensitivity to other beta-lactams; Renal or hepatic impairment; Fluid restriction; Side Effects Superinfection; Pseudomembranous colitis; GI upset; Hypersensitivity; Arhythmia; Neutropenia; **Risk in Pregnancy B1**

<u>Dexamethasone</u>

Mechanism of Action

Same as for Cortisol but more potent (30x antiinflammatory) and does not stimulate Na retention; i.e immune suppressant

Dosage

Initially 0.5-10 mg daily , then 0.5-1 mg daily Other Uses

Corticosteroid responsive disorders; Drug of choice for suppression of ACTH production;

Contraindication

Uncontrolled infections; Stress; Prolonged use; Live virus vaccinations; Hepatic impairment; Diabetes; Age; Side Effects As for other glucocorticoids, consult literature;

Risk in Pregnancy A

Pharmacology of ANTIBACTERIAL AGENTS: With loud thanks to Medical Pharmacology At A Glance, 1997 3rd ed. M.J. Neal

* GRAM STAIN:

Reflects important differences in cell wall structure:

Depending on retention or not of methyl violet after washing with acetone +ve = peptidoglycan slime

-ve = LPS and double-layered phospholipid wall

ANTIBIOTICS INHIBITING NUCLEIC ACID SYNTHESIS



SULFONAMIDES:

- Interfere with FOLIC ACID SYNTHESIS
- Are negated by presence of pus and some local anaesthetics eg. procaine.
- Concentrated in the urine (but may crystallise due to low solubility)
- NOW MAINLY USED TO TREAT Urinary Tract Infections.
- BACTERIOSTATIC

TRIMETHOPRIM:

- Mimicks FOLIC ACID;
- 50,000 more affinity for inhibiting bacterial dihidrofolate reductase than for the human enzyme.
- Synergistic with sulfonamides (particularly sulphamethoxazole)
- Excreted in the urine
- USED MAINLY vs. RESPIRATORY INFECTIONS and UTI (poor effect on pneumococcus and S.pyogenes)
- BACTERIOSTATIC

QUINOLONES:

- Inhibit DNA gyrase, thus no supercoiling of bacterial DNA. Eucariotic cells have no DNA gyrase.
- Good penetration into tissues, low toxicity, effective when given orally. BROAD SPECTRUM.
- Concentrated in the urine
- **BACTERIOSTATIC AND BACTERICIDAL**

5-NITROIMIDAZOLES:

- Upon entry into bacteria, Reduced into active intermediates which damage DNA and interfere with synthesis
- Effective vs. ANAEROBES and some PROTOZOA- BROAD SPECTRUM
- **BACTERIOSTATIC AND BACTERICIDAL**

ANTIBIOTICS INHIBITING BACTERIAL CELL WALL SYNTHESIS



- Often given with a beta-lactamase inhibitor
- POOR PENETRATION INTO THE BRAIN!
- Mainly excreted in the urine
- BACTERICIDAL

CEPHALOSPORINS: eg. what we used to treat 6.03

Very similar to penicillins in structure and action (i.e beta-lactam ring is primary active component)

- Mainly excreted in the urine
- BACTERICIDAL
- PENETRATE Blood-Brain Barrier THUS useful in meningitis

VANCOMYCIN:

Inhibits the release of building-block peptide from carrier molecule, thus halting the synthesis of peptidoglycans

- <u>NOT absorbed orally!</u>
- BACTERICIDAL

ANTIBIOTICS INHIBITING PROTEIN SYNTHESIS

..Are SELECTIVELY TOXIC TO BACTERIA: Bacterial ribosimes have a 50S subunit and 30S subunit, while mammal ribosomes have a 60S subunit and a 40S subunit



TETRACYCLINES

- Inhibit protein synthesis by competing with tRNA for the activation site (the 30S subunit) on the ribosome
- Absorbed well into macrophages therefore good for *Rickettsia* and *Chlamydia* and other intracellular pathogens
- !! Cause DISCOLOURATION OF NEW TEETH !! therefore not given to under 8 yr. olds
- BROAD SPECTRUM
- BACTERIOSTATIC AND BACTERICIDAL

AMINOGLYCOSIDES

- Interefere with protein synthesis by altering base-pairing properties of bacterial tRNA :
- THUS misreading of mRNA occurs: NON-FUNCTIONAL PROTEINS PRODUCED, which cause cell death
- ALL AMINOGLYCOSIDES are potentially TOXIC
- BACTERIOSTATIC AND BACTERICIDAL

CHLORAMPHENICOL

- Inhibits transfer of the new amino acid to the growing peptide (transpeptidation) at the 50S subunit
- Penetrates everywhere including the brain, thus VERY GOOD FOR Haemophilus Influenzae MENINGITIS
- SERIOUS SIDE EFFECTS: bone marrow aplasia, RBC + WBC suppression, encephalopathy, optic neuritis.
- → WILL ALMOST CERTAINLY KILL NEONATES who cant metabolise it ("grey baby syndrome")
- BACTERIOSTATIC AND BACTERICIDAL

MACROLIDES

- Inhibit translocation of the peptide chain from the active peptide-building (A) site to the waiting (P) site (50S)
- THUS: no new peptide is built because the old peptide is stuck at the A-site.
- Mainly Gram-POSITIVE bacteria, like the pennicillins.
- POOR PENETRATION OF BLOOD-BRAIN BARRIER
- UNLIKE PENICILLINS the macrolides are effective vs. WEIRD PATHOGENS eg. Mycoplasma and Legionella
- BACTERIOSTATIC AND BACTERICIDAL