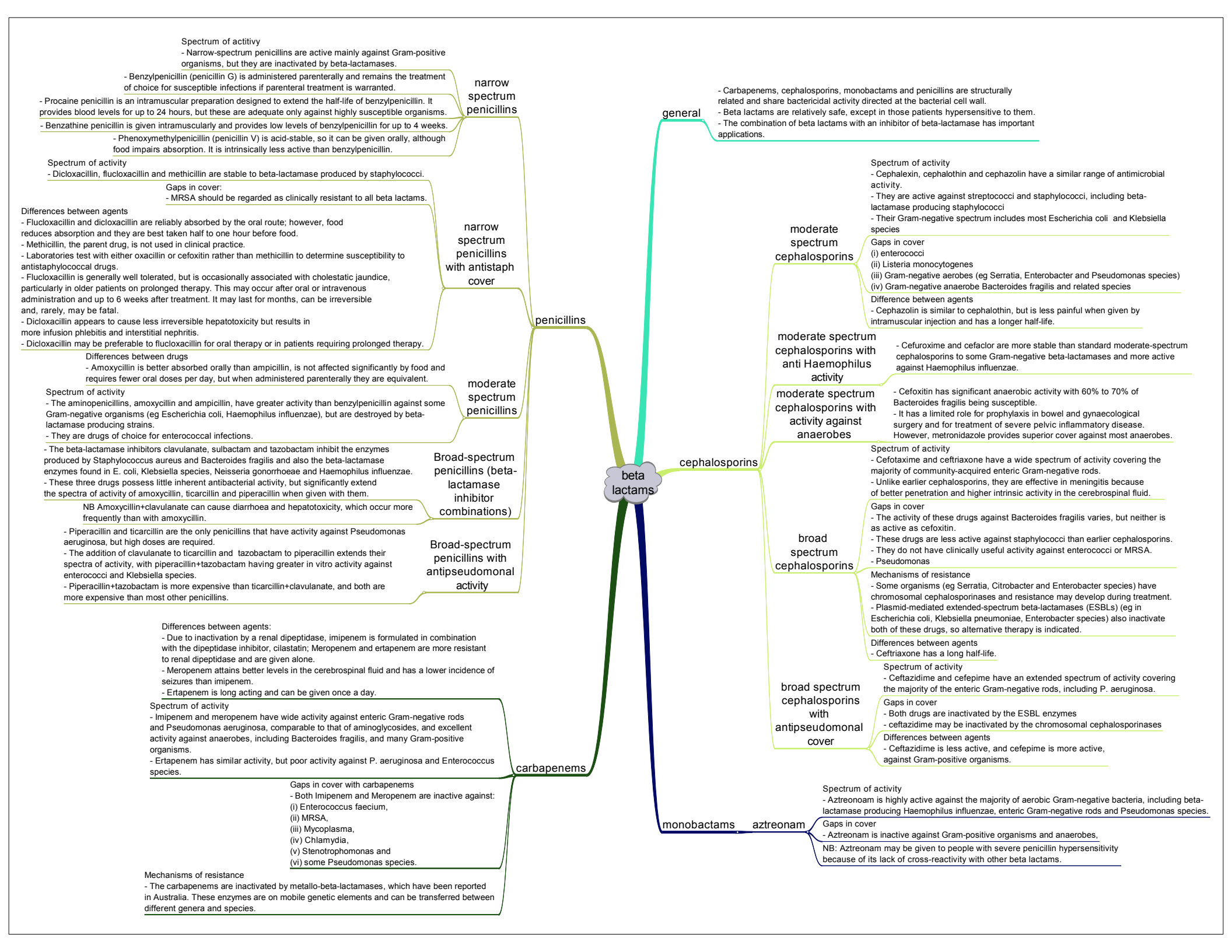
beta lactams
general
- Carbapenems, cephalosporins, monobactams and penicillins are structurally related and share bactericidal activity directed at the bacterial cell wall.
- Beta lactams are relatively safe, except in those patients hypersensitive to them.
- The combination of beta lactams with an inhibitor of beta-lactamase has important applications.
penicillins
narrow spectrum penicillins
Spectrum of actitivy
- Narrow-spectrum penicillins are active mainly against Gram-positive organisms, but they are inactivated by beta-lactamases.
- Benzylpenicillin (penicillin G) is administered parenterally and remains the treatment of choice for susceptible infections if parenteral treatment is warranted.
- Procaine penicillin is an intramuscular preparation designed to extend the half-life of benzylpenicillin. It provides blood levels for up to 24 hours, but these are adequate only against highly susceptible organisms.
- Benzathine penicillin is given intramuscularly and provides low levels of benzylpenicillin for up to 4 weeks.
- Phenoxymethylpenicillin (penicillin V) is acid-stable, so it can be given orally, although food impairs absorption. It is intrinsically less active than benzylpenicillin.
narrow spectrum penicillins with antistaph cover
Spectrum of activity
- Dicloxacillin, flucloxacillin and methicillin are stable to beta-lactamase produced by staphylococci.
Gaps in cover:
- MRSA should be regarded as clinically resistant to all beta lactams.
Differences between agents
- Flucloxacillin and dicloxacillin are reliably absorbed by the oral route; however, food reduces absorption and they are best taken half to one hour before food.
- Methicillin, the parent drug, is not used in clinical practice.
- Laboratories test with either oxacillin or cefoxitin rather than methicillin to determine susceptibility to antistaphylococcal drugs.
- Flucloxacillin is generally well tolerated, but is occasionally associated with cholestatic jaundice, particularly in older patients on prolonged therapy. This may occur after oral or intravenous administration and up to 6 weeks after treatment. It may last for months, can be irreversible and, rarely, may be fatal.
- Dicloxacillin appears to cause less irreversible hepatotoxicity but results in more infusion phlebitis and interstitial nephritis.
- Dicloxacillin may be preferable to flucloxacillin for oral therapy or in patients requiring prolonged therapy.
moderate spectrum penicillins
Differences between drugs
- Amoxycillin is better absorbed orally than ampicillin, is not affected significantly by food and requires fewer oral doses per day, but when administered parenterally they are equivalent.
Spectrum of activity
- The aminopenicillins, amoxycillin and ampicillin, have greater activity than benzylpenicillin against some Gram-negative organisms (eg Escherichia coli, Haemophilus influenzae), but are destroyed by beta-lactamase producing strains.
- They are drugs of choice for enterococcal infections.
Broad-spectrum penicillins (beta-lactamase inhibitor combinations)
- The beta-lactamase inhibitors clavulanate, sulbactam and tazobactam inhibit the enzymes produced by Staphylococcus aureus and Bacteroides fragilis and also the beta-lactamase enzymes found in E. coli, Klebsiella species, Neisseria gonorrhoeae and Haemophilus influenzae.
- These three drugs possess little inherent antibacterial activity, but significantly extend the spectra of activity of amoxycillin, ticarcillin and piperacillin when given with them.
NB Amoxycillin+clavulanate can cause diarrhoea and hepatotoxicity, which occur more frequently than with amoxycillin.
Broad-spectrum penicillins with antipseudomonal activity
- Piperacillin and ticarcillin are the only penicillins that have activity against Pseudomonas aeruginosa, but high doses are required.
- The addition of clavulanate to ticarcillin and tazobactam to piperacillin extends their spectra of activity, with piperacillin+tazobactam having greater in vitro activity against enterococci and Klebsiella species.
- Piperacillin+tazobactam is more expensive than ticarcillin+clavulanate, and both are more expensive than most other penicillins.
carbapenems
Differences between agents:
- Due to inactivation by a renal dipeptidase, imipenem is formulated in combination with the dipeptidase inhibitor, cilastatin; Meropenem and ertapenem are more resistant to renal dipeptidase and are given alone.
- Meropenem attains better levels in the cerebrospinal fluid and has a lower incidence of seizures than imipenem.
- Ertapenem is long acting and can be given once a day.
Spectrum of activity
- Imipenem and meropenem have wide activity against enteric Gram-negative rods and Pseudomonas aeruginosa, comparable to that of aminoglycosides, and excellent activity against anaerobes, including Bacteroides fragilis, and many Gram-positive organisms.
- Ertapenem has similar activity, but poor activity against P. aeruginosa and Enterococcus species.
Gaps in cover with carbapenems
- Both Imipenem and Meropenem are inactive against:
(i) Enterococcus faecium,
(ii) MRSA,
(iii) Mycoplasma,
(iv) Chlamydia,
(v) Stenotrophomonas and
(vi) some Pseudomonas species.
Mechanisms of resistance
- The carbapenems are inactivated by metallo-beta-lactamases, which have been reported in Australia. These enzymes are on mobile genetic elements and can be transferred between different genera and species.
cephalosporins
moderate spectrum cephalosporins
Spectrum of activity
- Cephalexin, cephalothin and cephazolin have a similar range of antimicrobial activity.
- They are active against streptococci and staphylococci, including beta-lactamase producing staphylococci
- Their Gram-negative spectrum includes most Escherichia coli and Klebsiella species
Gaps in cover
(i) enterococci
(ii) Listeria monocytogenes
(iii) Gram-negative aerobes (eg Serratia, Enterobacter and Pseudomonas species)
(iv) Gram-negative anaerobe Bacteroides fragilis and related species
Difference between agents
- Cephazolin is similar to cephalothin, but is less painful when given by intramuscular injection and has a longer half-life.
moderate spectrum cephalosporins with anti Haemophilus activity
- Cefuroxime and cefaclor are more stable than standard moderate-spectrum cephalosporins to some Gram-negative beta-lactamases and more active against Haemophilus influenzae.
moderate spectrum cephalosporins with activity against anaerobes
- Cefoxitin has significant anaerobic activity with 60% to 70% of Bacteroides fragilis being susceptible.
- It has a limited role for prophylaxis in bowel and gynaecological surgery and for treatment of severe pelvic inflammatory disease. However, metronidazole provides superior cover against most anaerobes.
broad spectrum cephalosporins
Spectrum of activity
- Cefotaxime and ceftriaxone have a wide spectrum of activity covering the majority of community-acquired enteric Gram-negative rods.
- Unlike earlier cephalosporins, they are effective in meningitis because of better penetration and higher intrinsic activity in the cerebrospinal fluid.
Gaps in cover
- The activity of these drugs against Bacteroides fragilis varies, but neither is as active as cefoxitin.
- These drugs are less active against staphylococci than earlier cephalosporins.
- They do not have clinically useful activity against enterococci or MRSA.
- Pseudomonas
Mechanisms of resistance
- Some organisms (eg Serratia, Citrobacter and Enterobacter species) have chromosomal cephalosporinases and resistance may develop during treatment.
- Plasmid-mediated extended-spectrum beta-lactamases (ESBLs) (eg in Escherichia coli, Klebsiella pneumoniae, Enterobacter species) also inactivate both of these drugs, so alternative therapy is indicated.
Differences between agents
- Ceftriaxone has a long half-life.
broad spectrum cephalosporins with antipseudomonal cover
Spectrum of activity
- Ceftazidime and cefepime have an extended spectrum of activity covering the majority of the enteric Gram-negative rods, including P. aeruginosa.
Gaps in cover
- Both drugs are inactivated by the ESBL enzymes
- ceftazidime may be inactivated by the chromosomal cephalosporinases
Differences between agents
- Ceftazidime is less active, and cefepime is more active, against Gram-positive organisms.
monobactams
aztreonam
Spectrum of activity
- Aztreonoam is highly active against the majority of aerobic Gram-negative bacteria, including beta-lactamase producing Haemophilus influenzae, enteric Gram-negative rods and Pseudomonas species.
Gaps in cover
- Aztreonam is inactive against Gram-positive organisms and anaerobes,
NB: Aztreonam may be given to people with severe penicillin hypersensitivity because of its lack of cross-reactivity with other beta lactams.