Side effects & complications of antibiotic therapy

PRESENTER: BOITUMELO PHAKATHI
Bactericidal agents

INTERFERES WITH THE SYNTHESIS & PROMOTE LYSIS OF BACTERIAL CELL WALLS
Penicillins

• Allergic reaction
  ❖ 10% of patients, with a fatal reaction occurring in 0.002% of patients
  ❖ Symptoms: erythema, pruritis, urticaria, morbiliform rash, angioedema, wheezing, hypotension or shock
  ❖ Divided into:
    ❖ Immediate allergic reaction: within 2-30 mins of penicillin administration
    ❖ Accelerated allergic reaction: within 1-72 hrs. not life-threatening as reaction is modified by IgG, unless laryngeal edema present
    ❖ Late allergic reaction: > 72 hrs. frequent type & is often seen in pts with leukemia, lymphomas, infectious mononucleosis, renal failure & those on allopurinol
    ❖ Less common allergic reactions: immune hemolytic anemia, interstitial nephritis, drug-induced SLE
  ❖ Symptoms- histamine & other vasoactive amines release from IgE sensitised mast cells & basophils
  ❖ Cross- reactions: cephalosporins, imipenem
Penicillins

- Eosinophilia
  - Discontinue the drug if levels > 15% of peripheral WBC & investigate for evidence of interstitial nephritis
- Interstitial nephritis: relatively uncommon and dose-related
- CNS toxicity
  - Early sign- myoclonic jerks
  - Very high blood levels- seizures (prevented by using < 30mU/d if normal renal function and adjust in renal failure patients)
Beta-lactamase inhibitor combinations

- E.g augmentin (amoxicillin + clavulanic acid), tazocin (tazobactam + piperacillin)
- Augmentin
  - GI disturbance: diarrhea, N/V, abdominal discomforts (minimised by taking with meals)
  - Hepatitis & cholestatic jaundice - attributed to clavulanic acid & may occur up to 6 weeks after therapy
Beta-lactamase inhibitor combinations

- Tazocin
  - Side-effects profile as for penicillin
  - Piperacillin-high sodium content (water retention), bleeding diathesis (neutropenia, leucopenia, thrombocytopenia)
  - Thrombophlebitis
  - Cholestatic jaundice
  - Bloody diarrhea
  - Reversible renal impairment
Cephalosporins

- Phlebitis - common than with penicillins
- Allergic reactions
  - 1-5% incidence of primary allergic reactions
  - 1% of patients with penicillin-allergic reactions
  - Avoid cephalosporins in patients with a history of immediate reaction to penicillin
  - Delayed mild reaction to penicillin- cephalosporins may be used but with caution
- Nephrotoxicity
  - Infrequently cause significant renal impairment when used alone.
  - May potentiate nephrotoxicity caused by aminoglycosides
Cephalosporins

- Hematologic effects:
  - false positive coomb’s test, granulocytopenia, thrombocytopenia
- Neurotoxicity
  - Hallucinations, confusion, convulsion with high doses or renal failure
  - Common: headache, dizziness, vertigo
- GI disturbance
  - Less common than with penicillin
  - Pseudomembraneous enterocolitis
  - Transient elevation of liver enzymes
Carbapenems

- Side-effects are similar to those of other beta-lactams
- Hypersensitivity reaction (small risk of cross-reaction)
- Pseudomembranous colitis
- Transient renal impairment
- Seizures (imipenem)
- Erythema & thrombophlebitis
Aminoglycosides

- Side-effects depend on the particular aminoglycoside, dosage, frequency & duration of treatment
- Nephrotoxicity
  - Defined as an increase in serum creatinine of 0.5mg/dl or > 50% increase from the baseline, for 2 consecutive measurements
  - Direct toxic effects to proximal renal tubules
  - ATN reported in 5-15% of patients
  - Reversible when drug discontinued
  - Risk factors: older age group, females, use of other nephrotoxic drugs, previous course of aminoglycosides, pre-existing renal disease
Aminoglycosides

- Ototoxicity
  - Irreversible damage to CNVIII
  - Involves vestibular &/or cochlear division
  - Incidence: hearing loss - 20% of pts & loss of balance - 15% of patients
  
  - Results in bilateral sensorineural hearing loss, beginning as high frequency hearing loss or as a combination of vertigo, nausea, vomiting, nystagmus, ataxia

- Neomycin - most toxic, followed by gentamycin
- Amikacin & neomycin tend to be more cochleotoxic, while gentamycin & streptomycin vestibulotoxic
Vancomycin (glycopeptide antibacterials)

- Red man syndrome
  - Flushing of the face, neck or torso; intense pruritis, palpitations, hypotension following a rapid infusion of vancomycin
  - Due to non-immunologically mediated histamine release associated with rapid infusion
  - It's not an allergic response thus does not preclude continued administration of vancomycin
  - However, if bronchospasm & angioedema present, it suggest a true allergic reaction
  - Prevented by slow infusion, over at least 1 hr of well diluted drug
Vancomycin

- Nephrotoxicity
  - Risk factors: trough levels > 15mcg/ml
    - black race
    - intermittent infusion
    - concomitant use of other nephrotoxic drugs
    - pre-existing renal failure
- Ototoxicity - relatively uncommon
- Hypersensitivity reactions
- Reversible neutropenia & eosinophilia
- Thrombophlebitis
- Intracranial pressure elevation
Polymixin (colistin)

- Nephrotoxicity
  - Mild & reversible
  - Risk factors: pre-existing renal failure, Hypertension, concomitant use of other nephrotoxic drugs
- Neuromuscular blockade
  - Effect potentiated with concomitant use of neuromuscular blocking agents
  - Paraesthesia, vertigo, dizziness, slurred speech, blurry vision, respiratory arrest
Fluoroquinolones

- **GI disturbance**
  - Abdominal pain, N/V, diarrhea
  - Pseudomembranous colitis rare
  - Increased liver enzymes, hepatic necrosis
- **CNS effects**
  - Headache, dizziness, restlessness, drowsiness, confusion, depression, hallucinations, seizures (rare but may occur in those with underlying CNS disease)
- **Hypersensitivity reaction**
- **QT prolongation**
- **Interstitial nephritis**
Bactericidal agents & AKI

- Experimental study
- Bactericidal agents temporarily increase inflammation & worsens AKI
  - IL-6 levels peaked in the antibiotic treated group & were significantly greater than placebo-treated animals
  - Serum creatinine peak observed 48hrs after peak of IL-6 concentration & recovered gradually (placebo treated animals- serum creatinine increased more slowly & remained elevated longer)
  - Increase in IL-6 is related to rapid bacterial cell death, resulting in endotoxin release
Bacteriostatic agents

INTERFERES WITH BACTERIAL PROTEIN SYNTHESIS THEREBY INHIBITING BACTERIAL GROWTH
Macrolides

- E.g. erythromycin, azithromycin, clarithromycin
- GI disturbance
  - abdominal pain/cramps, N/V, diarrhea (minimised when taken with meals)
  - hepatotoxicity - may take two forms
    - Elevation of serum transaminases
    - Cholestatic hepatitis - rare, usually affects adults, neonates & is related to dosage, duration of treatment & maybe immunologically mediated
Macrolides

- Transient deafness
  - Dose-related (>4g/d, ivi)
  - Common in elderly patients with renal failure
  - Resolves within 6-14 days after discontinuation
- Allergic reaction (rash, fever, eosinophilia)
  - Uncommon
- Pseudomembranous colitis - rare
Linezolid

- GI symptoms
  - Metallic taste, abdominal pains/ cramps, diarrhea, N/V
- headaches
Clindamycin

• GI problems
  - Pseudomembranous colitis
  - N/V, abdominal pains, flatulence, oesophagitis (minimised when taken with food)
  - Transient increase in liver enzymes, bilirubin
• Skin rash (morbiliform rash, erythema multiforme)
• Hematological signs
  - Transient leucopenia, agranulocytosis, thrombocytopenia, eosinophilia during prolonged use
Tetracyclines

- E.g. doxycycline, minocycline
- **Common side-effects**
  - N/V, diarrhea, flatulence, epigastric pain
  - Photosensitivity
  - Candida superinfection of the gut & vagina
  - Pseudomembranous enterocolitis
- **Rare side-effects - long term use**
  - Hepatotoxicity
  - Hypersensitivity reaction
Antibiotics associated diarrhea

- Common complication, especially with broad spectrum agents
- Common in elderly but can occur at any age
- Specific mechanisms unknown
- C. difficile: 20-25% of cases
  - Occasional constituent of normal flora
  - Abolition of resistance following broad-spectrum therapy
  - Antibiotic exposure can also stimulate toxin production
  - Symptoms range from diarrhea to pseudomembranous colitis
- C. perfringes, klebsiella oxytoca - not common
Conclusion

- Side-effects & complications on antibiotics depend on the dose, frequency & duration of treatment.
- Adjust treatment in high-risk patients: elderly & those with co-morbidities (renal failure, HPT).
- Beware of drug interactions when multiple drugs are used.
- Determine the type of allergic reaction in patients allergic to penicillin.
- Close drug-level, renal & liver function monitoring is crucial.
- Discontinue the offending drug as soon as there is a side-effect/complication noted.
References

- Reese E Richards: Handbook of antibiotics, 2nd edi.
- South African Medicine formulary, 9th edition
- Doshi NM, et al. Hum Pharm & Drug Ther. Dec 2011.31(12):1257-64