PRESCRIBING ANTIBIOTICS

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Conflicts of interest

- none

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Case: Male Dutch tourist 72 years old
Summer 2022

- Arrives on Saturday night at the ER because of *high fever and cough*
- Previous history: Hypertension (R/ACE inh)
- Yearly Flu vaccine, recent Pneumovax and COVID Pfizer vaccine booster March 2022
- Smokes 10 cigars per day
- 6 units alcohol per day
- No previous antibiotic exposure
- No exposure to Livestock/animals

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Case: Male Dutch tourist 72 years old
Summer 2022

- No problems until this morning
- After breakfast chills and rigors, temperature rise >39.9°
- Cough, no sputum
- Slight R-sided chest pain
- Feels ill
- Took paracetamol 500 mg
- Covid-19 antigen self test negative.

- Further history not remarkable

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Case: Male Dutch tourist 72 years old
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- **Physical exam:**
  - Dyspnea & tachypnea (32/min)
  - BP 88/58, pulse rate 100
  - Temp 39.5°
  - Small herpes labialis lesion
  - Dull percussion over right lower part of thorax
  - Ausc: Bronchial breathing with crepitations

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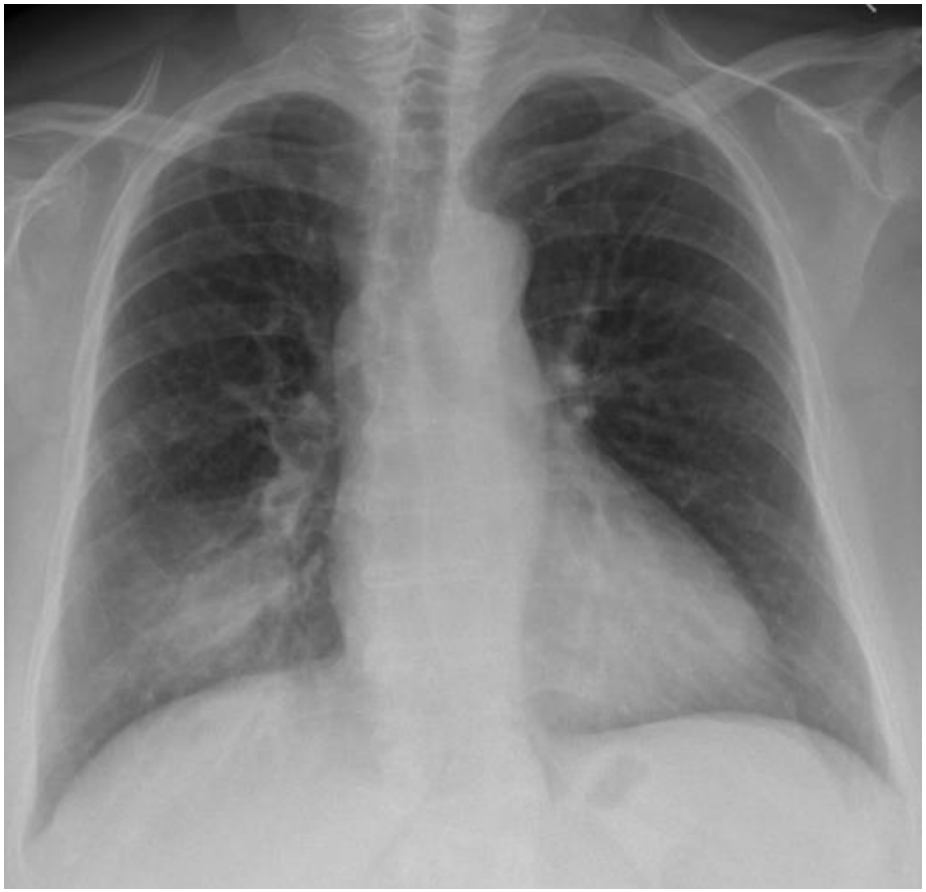

- **Lab:**
  - **CRP 80**
  - **Leukocytes 13.8**
  - **Hb 8 mmol/l**
  - **creat 100 µmol/l**
  - **BUN 6 mmol/l**
  - **Bilirubin slightly elevated**
  - **Sodium 129 mmol/l**
  - **pH 7.2; PO_2 8.1 kP**

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Case: Male Dutch tourist 72 years old
Summer 2022

- What is your differential diagnosis now?

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- What is your differential diagnosis now?
  - CAP
    - Lobar pneumonia probably pneumococcal
    - Other causes?
      - Legionella (male, smoker, alcohol, hotel)
      - Aspiration pneumonia (male, smoker, alcohol)
      - Other causes of pneumonia unlikely (Staph/Gram-negative/Mycoplasma/Qfever/Chlamydia psittaci or C. pneumoniae/ viral*)

* SARS CoV2? → antigen test and PCR negative

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Case: Male Dutch tourist 72 years old
Summer 2022

- What is your assesment of severity?

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CURB-65

- Confusion — No: 0 Yes: +1
- BUN >7 mmol/l — No: 0 Yes: +1
- Resp rate ≥ 30 — No: 0 Yes: +1
- Syst BP < 90 or Diast BP ≤ 60 — No: 0 Yes: +1
- Age ≥ 65 — No: 0 Yes: +1

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CURB-65

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- Age ≥ 65 — No: 0 Yes: +1

3 points: 14% 30-day mortality
→ ward admission

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Case: Male Dutch tourist 72 years old
Summer 2022

- What about antibiotics?

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Case: Male Dutch tourist 72 years old Summer 2022

- What about antibiotics?
  - Follow the guidelines…
    - Which guidelines?
  - Think!

(or do both!)

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This is not what I mean:

This is not what I mean either:

Guidelines are for beginners!

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Prescribing antibiotics

- Is there an infection?
- If so, is it likely to be bacterial?
- If so, which bacterium?
- If so, is antibiotic treatment beneficial?*

* e.g., acute bronchitis, acute otitis media, sinusitis → antibiotics rarely indicated

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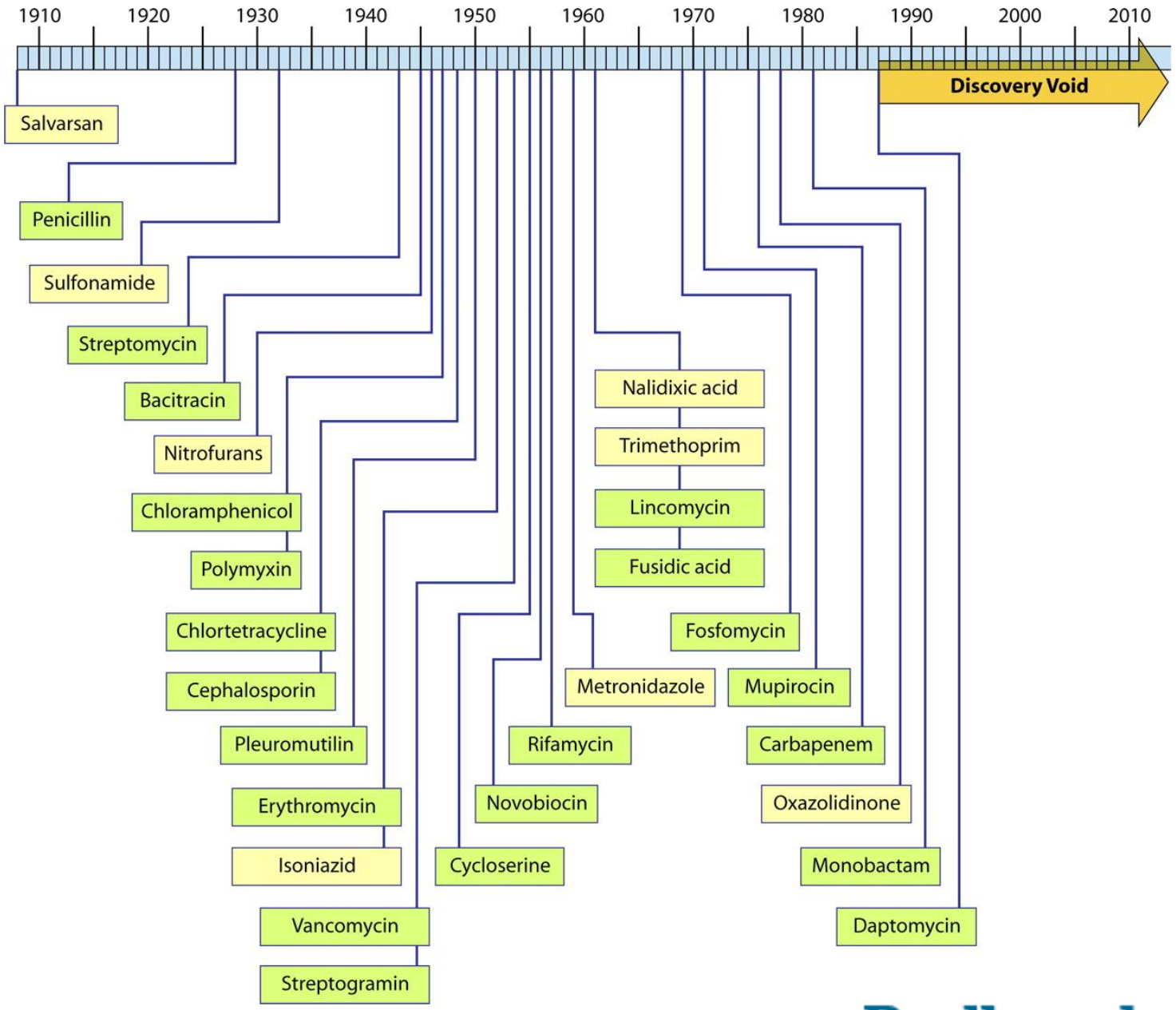
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
Discovery Void
Salvarsan
Penicillin
Sulfonamide
Streptomycin
Bacitracin
Nitrofurans
Chloramphenicol
Polymyxin
Chlortetracycline
Cephalosporin
Pleuromutilin
Erythromycin
Isoniazid
Vancomycin
Streptogramin
Cycloserine
Novobiocin
Rifamycin
Metronidazole
Nalidixic acid
Trimethoprim
Lincomycin
Fusidic acid
Fosfomycin
Mupirocin
Carbapenem
Oxazolidinone
Monobactam
Daptomycin

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How to choose an antibiotic?

The preferred antibiotic:

- Is effective against the (presumed) causative bacterium
- Attains effective concentrations at the site of infection
- Does lead to the least development of antimicrobial resistance
  - Of the causative micro-organism
  - Of the colonizing microflora
  - Of the micro-organisms in the environment
- Is (relatively) non toxic
- Can be administered in the most preferable way
- Is not more expensive than an equivalent

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How do we know this?

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How to choose an antibiotic?

The preferred antibiotic:

- **Is effective against the (presumed) causative bacterium**

How do we know this?

1. ***In-vitro susceptibility studies***
   - ***MIC***
   - ***Time-kill curves***
2. ***In-vivo studies***
   - ***In experimental animals***
   - ***In patients***

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In-vitro susceptibility studies

Minimal inhibitory concentration

- **Is a better indicator for resistance than for susceptibility**
- **performs better to compare the effect of one antibiotic on different bacteria (pneumococci are more sensitive than enterococci to benzylpenicillin) than the effect of different antibiotics to the same bacterium (pneumococci are more sensitive to benzylpenicillin than to amoxicillin)**
- **The translation to the in-vivo situation is difficult, because:**

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In-vitro susceptibility studies

Minimal inhibitory concentration

- **The in-vitro conditions differ greatly from in vivo:**
  - **Culture medium does not resemble the conditions in tissues and body fluids**
  - **The bacterium is exposed to a constant antibiotic concentration in vitro**
  - **Overnight incubation is not relevant in vivo**
  - **Protein binding is often not taken into account**
  - **Judgement of the in-vitro effect is visible growth**
- **Direct quantitive translation of MIC to in-vivo concentrations is unscientific.**

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How do we know this?

1. ***In-vitro susceptibility studies***
   - ***MIC***
   - ***Time-kill curves***
2. ***In-vivo studies***
   - ***In experimental animals***
   - ***In patients***

} **Teach us about pharmacokinetics:**
- **Time dependent killing**
- **Concentration-dependent killing**

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How to choose an antibiotic?

The preferred antibiotic:

- **Is effective against the (presumed) causative bacterium**

So we need good RCTs to know the real effectiveness of antibiotics!

Note of caution:

The older antibiotics have not been tested in modern-type RCTs!

Most RCTs have been performed with quinolones…

So there is a strong bias with regard to type A evidence!

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How to choose an antibiotic?

The preferred antibiotic:

- Is effective against the (presumed) causative bacterium
- Attains effective concentrations at the site of infection

  For most infections, this is not a problem.
  It is a problem for sites such as:
  - Prostatitis
  - Eye
  - Meningeal space and brain
  and for
  - abscesses
  - foreign bodies (such as prostheses)
  - empyema
  - bone sequesters

Here again time-dependent versus dose dependent killing is important!

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Development of antimicrobial resistance

- *Various mechanisms*
- *Antibiotics vary in their capacity to induce resistance*
- *Microorganisms vary in their capacity to become resistant*

- Of the causative micro-organism → rare
- Of the colonizing microflora → dependent on the effect of the antibiotic on commensals
- Of the micro-organisms in the environment
  → dependent on (urinary) excretion of the drug and its stability

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Toxicity

- Allergy: especially penicillins

- Dose-dependent toxicity:
  - Aminoglycosides
  - Polymyxins
  - Quinolones

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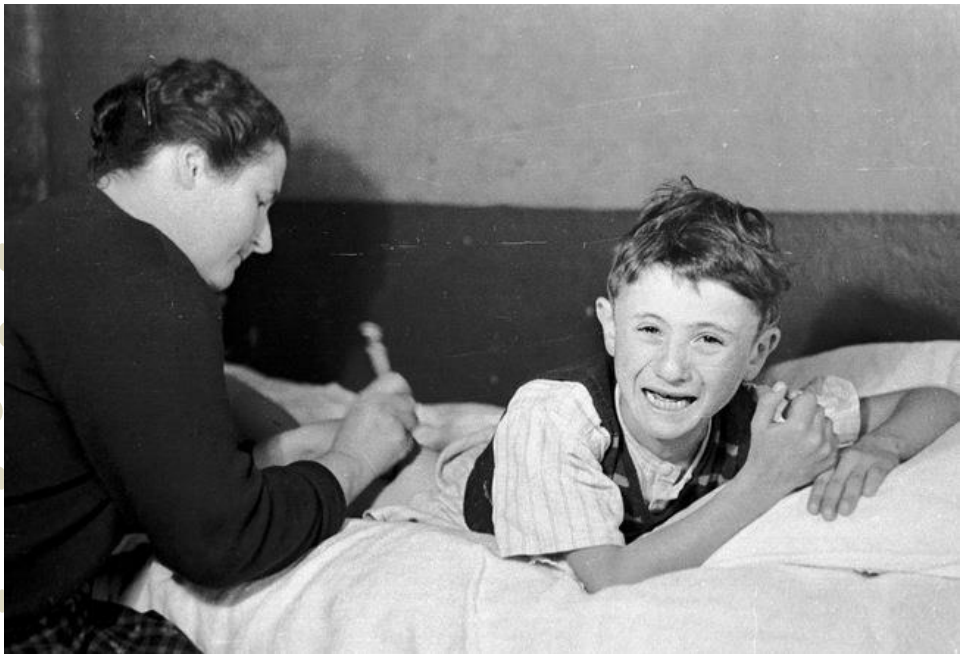
How to choose an antibiotic?

The preferred antibiotic:



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- Classification

  Curb-65 score +3

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What do guidelines say?

- **Dutch SWAB guideline**
  - **For CURB-65 score +3:**

  For patients with risk category III (severe CAP – ward admission; CURB-65: 3-5; PSI: 5; hospitalized on non-ICU ward) therapy should be started with a 2nd or 3rd generation cephalosporin. No empiric coverage for atypical microorganisms is given. A Legionella and pneumococcal urinary antigen test should be carried out as a routine procedure within 12-24 hours of admission.

  So let us choose for ceftriaxon…

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How to choose an antibiotic?

The preferred antibiotic: → ceftriaxon

Assuming pneumococcus/aspiration pneumonia

- Is effective against the (presumed) causative bacteria √
- Attains effective concentrations at the site of infection √
- Does lead to the least development of antimicrobial resistance
  - Of the causative micro-organism √
  - Of the colonizing microflora √
  - Of the micro-organisms in the environment √
- Is (relatively) non toxic √
- Can be administered in the most preferable way ← only IV
- Is not more expensive than an equivalent ← off patent

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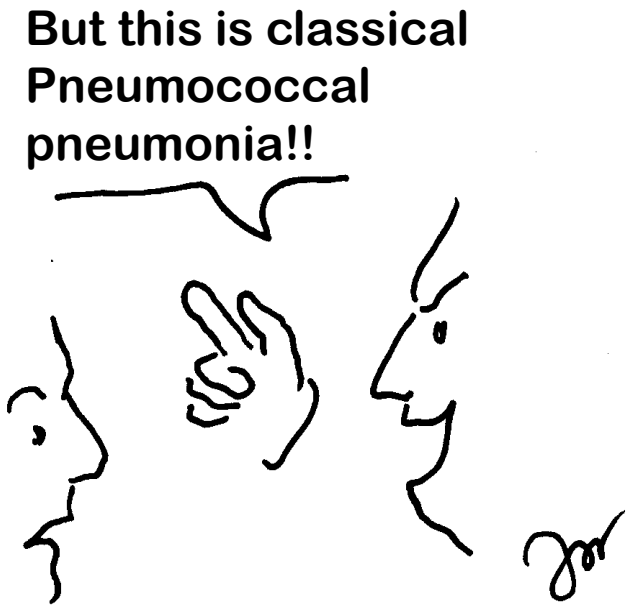

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Case: Male Dutch tourist 72 years old
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- We decide to start treatment with ceftriaxon and ciprofloxacin
- The next day the pneumococcal antigen test in urine is positive, the legionella antigen test is negative.
- The temperature has normalised

So what is the next step?

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Streamline!

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- We decide to start treatment with ceftriaxon and ciprofloxacin
- The next day the pneumococcal antigen test in urine is positive, the legionella antigen test is negative.
- The temperature has normalised

So what is the next step?

Stop ciprofloxacin

Switch to oral amoxicillin (5 days)

- Culture result sputum (day 2): penicillin-sensitive Pneumococcus

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