

PRESCRIBING ANTIBIOTICS

Jos WM van der Meer
Emeritus professor of Medicine
Radboud umc
Nijmegen NL

Conflicts of interest

- none

Case: Male Dutch tourist 72 years old Summer 2021

- 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 Spring 2021
- Smokes 10 cigars per day
- 6 units alcohol per day
- No previous antibiotic exposure
- No exposure to Livestock/animals

Case: Male Dutch tourist 72 years old Summer 2021

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

- Further history not remarkable

Case: Male Dutch tourist 72 years old Summer 2021

- **Physical exam:**
 - **Dyspnea & tachypnea (32/min)**
 - **BP 88/58, pulse rate 100, temp 39.9°**
 - **Temp 38.5°**
 - **Small herpes labialis lesion**
 - **Dull percussion over right lower part of thorax**
 - **Ausc: Bronchial breathing with crepitations**

Case: Male Dutch tourist 72 years old Summer 2021



- **Lab:**
 - CRP 80**
 - Leukocytes 13.8**
 - Hb 8 mmol/l**
 - creat 100 μ mol/l**
 - BUN 6 mmol/l**
 - Bilirubin slightly elevated**
 - Sodium 129 mmol/l**
 - pH 7.2; PO₂ 8.1 kP**

Case: Male Dutch tourist 72 years old Summer 2021

- What is your differential diagnosis now?

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- 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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- What is your assessment of severity?

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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- Age ≥ 65 No: 0 Yes: +1

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

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- What about antibiotics?

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- **What about antibiotics?**
 - Follow the guidelines...
 - Which guidelines?
 - Think!

(or do both!)

This is not what I mean:

Comply with
the guidelines,
that is good
for your
patient

To hell with
guidelines,
Your own
way is OK!



This is not what I mean either:

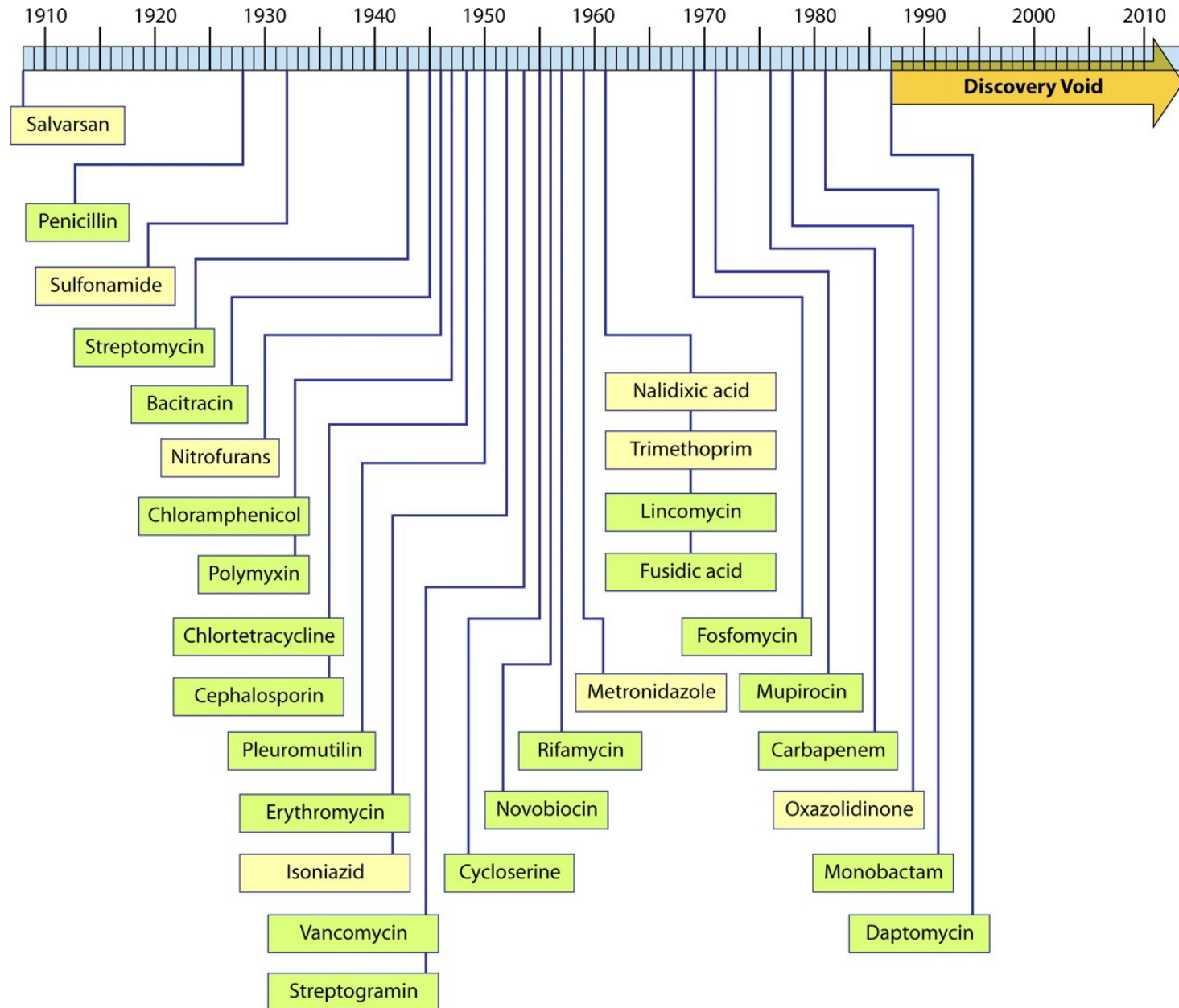
Guidelines are for beginners!



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



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

How to choose an antibiotic?

The preferred antibiotic:

- Is effective against the (presumed) causative bacterium

How do we know this?

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*

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:**

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 quantitative 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

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 sequestrs*

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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The preferred antibiotic:

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Toxicity

- **Allergy: especially penicillins**
- **Dose-dependent toxicity:**
 - Aminoglycosides
 - Polymyxins
 - Quinolones

How to choose an antibiotic?

The preferred antibiotic:

- Is effective against the (presumed) causative micro-organism
- Attains effective concentrations at the site of infection
- Does not lead to the least development of:
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- Classification
 - Curb-65 score +3**

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...

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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- Other causes?

- Legionella (male, smoke

- Aspiration pneumonia (r

- Other causes of pneumo
negative/Mycoplasma/Q
pneumoniae/ viral)

But this is classical
Pneumococcal
pneumonia!!



- Classification

- Curb-65 score +3

Case: Male Dutch tourist 72 years old Summer 2021

- 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?

Streamline!



Case: Male Dutch tourist 72 years old Summer 2021

- **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**