MICROBIAL RESISTANCE AND GOOD ANTIBIOTICS PRESCRIBING

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Topics

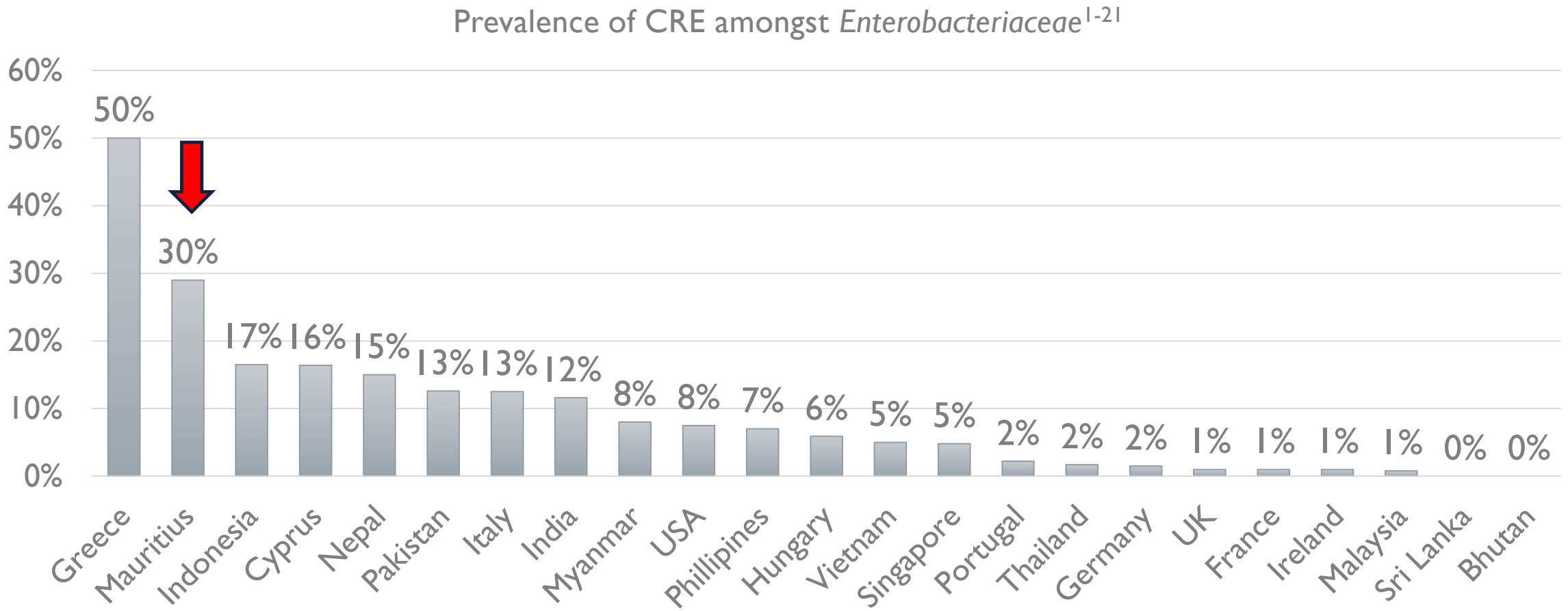
- The problem that we are facing
- Barriers that prevent proper antibiotic prescription
- General principles of antimicrobial therapy
- Recent paradigm shifts
- Solutions to prevent the abuse of antibiotics

THE PROBLEM THAT WE ARE FACING

IMPROPER PRESCRIPTION OF ANTIBIOTICS IS ONE OF THE LINKS TO ANTIMICROBIAL RESISTANCE

- Prescribing antibiotics when not needed (not infectious or not a bacterial infection)
- Prescribing too low a dose or incorrect frequency
- Prescribing too long duration
- Wrong antibiotic given
- Excess use of broad-spectrum antibiotics

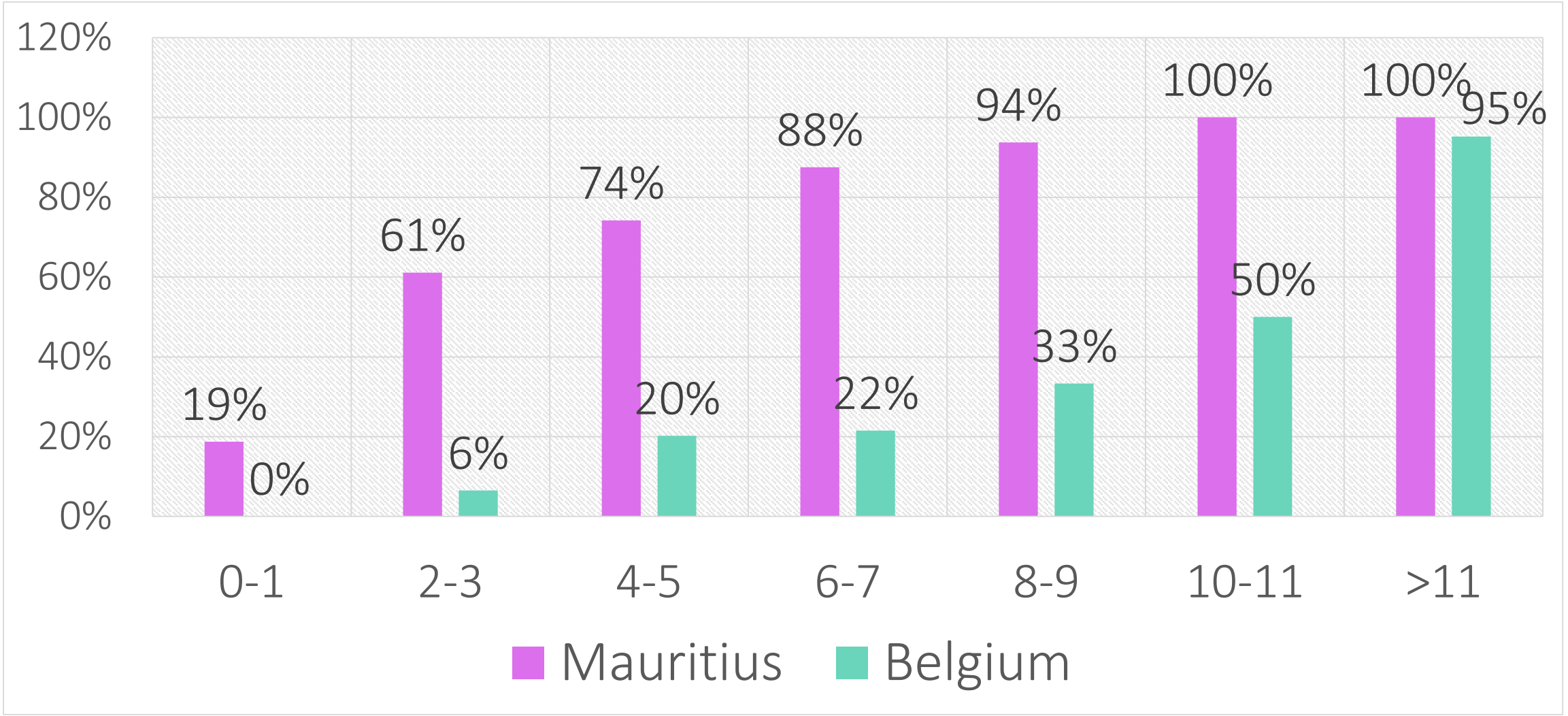
PREVALENCE OF CRE IN THE ICU



ANTIBIOTICS ARE LESS EFFECTIVE

- We don’t have many new molecules in the pipeline anymore

Mortality adjusted by SOFA score: Compared with Belgium



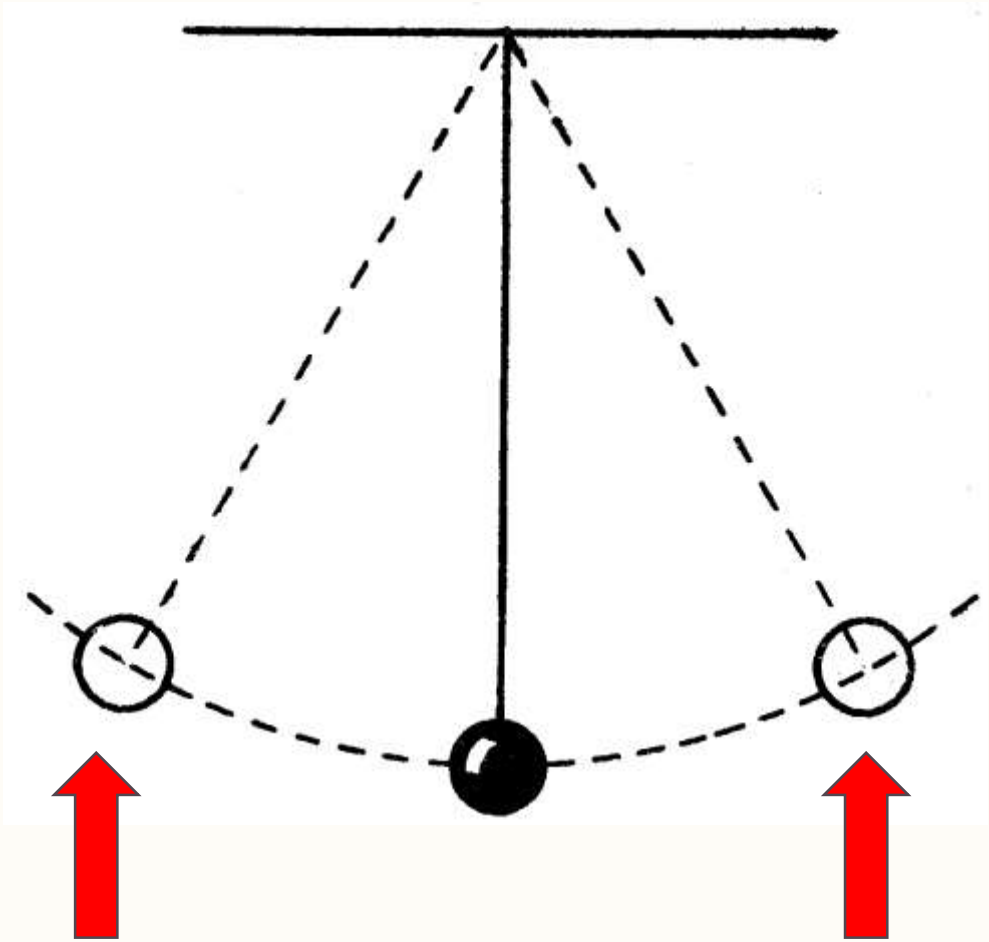
Barriers that prevent proper antibiotic prescription[23]

Sample case

- An 18-year-old girl presents with a sore throat, cough, chest pain and mild weakness.
- No fever
- Do you give antibiotics?

No antibiotic was given

- She was sent home with a diagnosis of upper respiratory tract infection and musculoskeletal pain
- A few days later, she was drowsy and hallucinating
- She died!
- Actual case in Scotland in 2013[22]



Overuse of antibiotics

Under-use of antibiotics

Barrier 1: Poor access

- Under-use of antibiotics is also bad!
- More people die from under-use of antibiotics than from over-use each year in the world
- Every hour by which an antibiotic is delayed for the treatment of sepsis increases mortality

Barrier 2: Fear of outcomes

- Medico-legal problems
- Better safe than sorry
- Let’s start an antibiotic “just in case” there’s an infection
- The consequences for missing an infection are usually worse than the consequences of over-treatment

Barrier 3: Inadequate communication

- Lack of time – too much workload and it takes too much time to explain treatment options
- Fear of conflict with patient due to dissatisfaction and subsequent loss of the patient to the practice.
- Antibiotic-seeking behaviour of patients
- Need to maintain good patient-doctor relationship

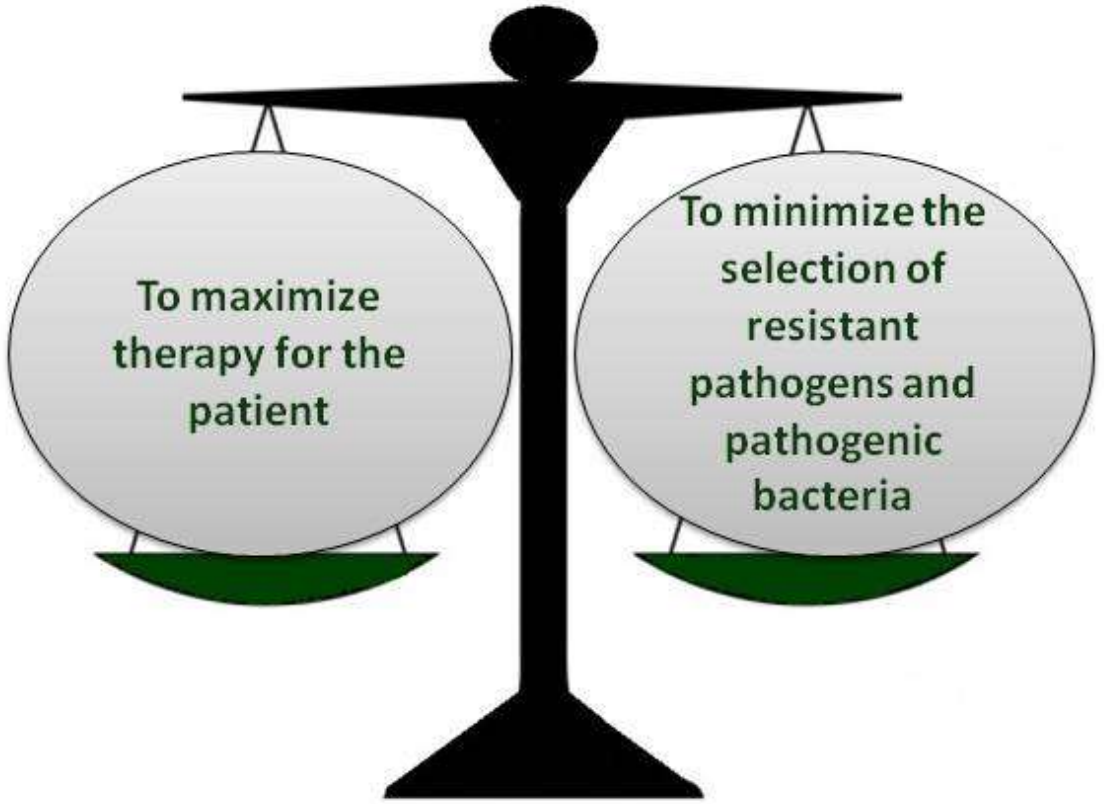
Barrier 4: Inadequate diagnostics

- Lab cultures take too long to be available
- Serological tests are too inaccurate
- Some tests are too expensive, and patients or hospitals cannot afford them

Barrier 5: Lack of consensus

- Sometimes there are no guidelines
- Conflicting guidelines - confusion caused by different treatment patterns by different clinicians
- Are the guidelines relevant to your patient?

Antibiotics use: finding the right balance



On one hand clinicians should offer optimal therapy for the individual patient under their care; on the other hand they should limit the impact of the antibiotic in order to prevent the selection of resistant pathogens and pathogenic bacteria such as *C. difficile*.

Is it possible to achieve the right balance?

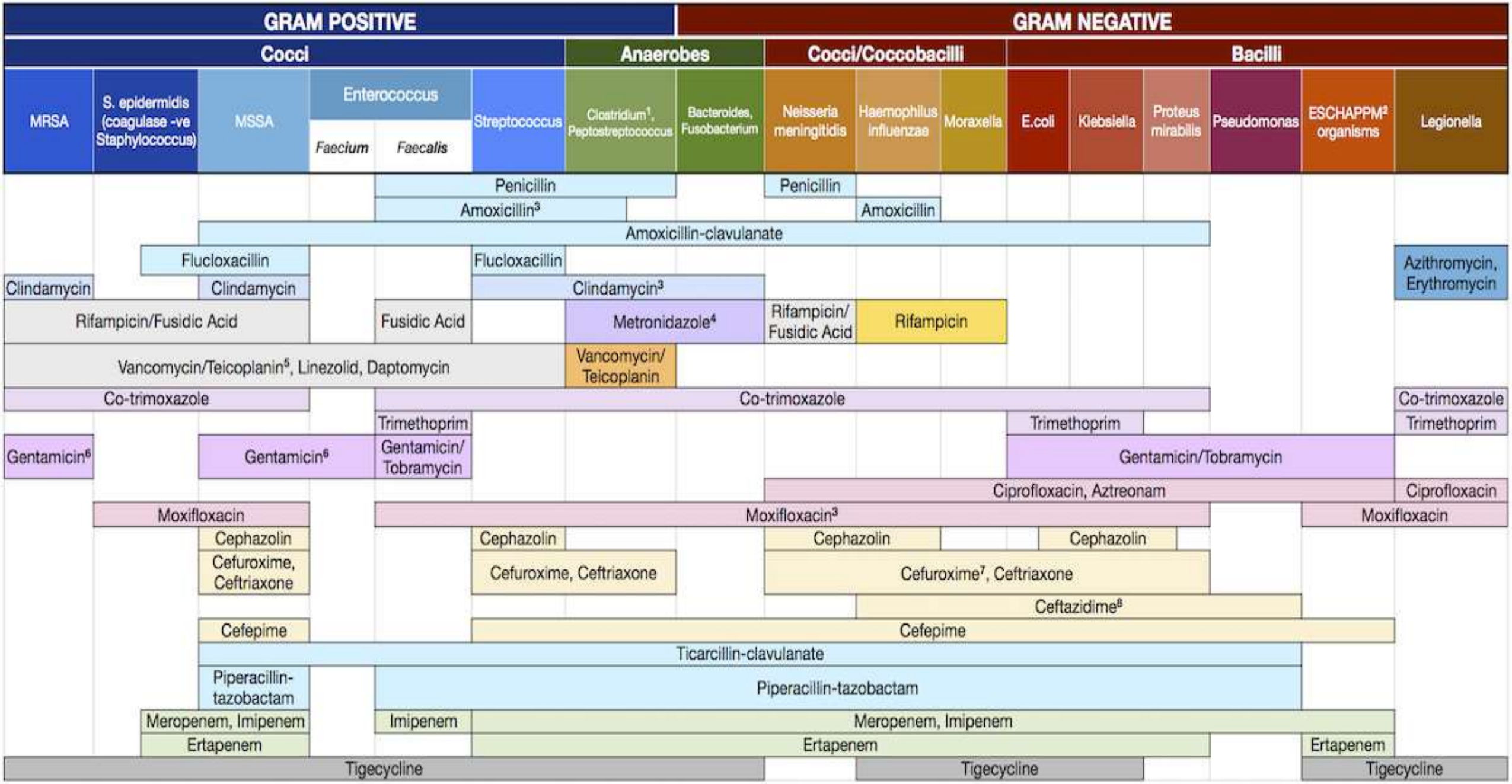
General Principles of Antimicrobial Therapy[24]

Factor 1: Is there an infection?

- Contaminant (no infection)
  - Coagulase negative staphylococcus and diphtheroids in the blood (unless there's a foreign body) or from swabs
- Colonizer
  - Candida in urine cultures or sputum cultures
- Asymptomatic carrier and super-spreader
- Latent / dormant / inactive stage
- Subclinical
- Active infection (uncomplicated, sepsis, septic shock and multi-organ failure)

FACTOR 2: SPECTRUM OF ANTIBIOTICS

- When offering empiric therapy, the likely organisms causing the infection should match the spectrum of the antibiotic/s being used


GRAM POSITIVE
GRAM NEGATIVE
Cocci
Anaerobes
Cocci/Coccobacilli
Bacilli
MRSA
S. epidermidis (coagulase -ve Staphylococcus)
MSSA
Enterococcus
Faecium
Faecalis
Streptococcus
Clostridium[1], Peptostreptococcus
Bacteroides, Fusobacterium
Neisseria meningitidis
Haemophilus influenzae
Moraxella
E.coli
Klebsiella
Proteus mirabilis
Pseudomonas
ESCHAPPM[2] organisms
Legionella
Penicillin
Penicillin
Amoxicillin[3]
Amoxicillin
Amoxicillin-clavulanate
Flucloxacillin
Flucloxacillin
Azithromycin, Erythromycin
Clindamycin
Clindamycin
Clindamycin[3]
Rifampicin/Fusidic Acid
Fusidic Acid
Metronidazole[4]
Rifampicin/ Fusidic Acid
Rifampicin
Vancomycin/Teicoplanin[5], Linezolid, Daptomycin
Vancomycin/ Teicoplanin
Co-trimoxazole
Co-trimoxazole
Co-trimoxazole
Trimethoprim
Trimethoprim
Trimethoprim
Gentamicin[6]
Gentamicin[6]
Gentamicin/ Tobramycin
Gentamicin/Tobramycin
Ciprofloxacin, Aztreonam
Ciprofloxacin
Moxifloxacin
Moxifloxacin[3]
Moxifloxacin
Cephazolin
Cephazolin
Cephazolin
Cephazolin
Cefuroxime, Ceftriaxone
Cefuroxime, Ceftriaxone
Cefuroxime[7], Ceftriaxone
Ceftazidime[8]
Cefepime
Cefepime
Ticarcillin-clavulanate
Piperacillin-tazobactam
Piperacillin-tazobactam
Meropenem, Imipenem
Imipenem
Meropenem, Imipenem
Ertapenem
Ertapenem
Ertapenem
Tigecycline
Tigecycline
Tigecycline

IDENTIFY THE MISTAKE

- Amoxicillin/clavulanate + metronidazole

- Same with meropenem + metronidazole OR piperacillin-tazobactam + metronidazole

IDENTIFY THE MISTAKE

- Amoxicillin/clavulanate + ceftriaxone

- Same with amoxicillin/clavulanate + flucloxacillin OR meropenem + ceftriaxone

Factor 3: Know which organisms are likely to cause the infection

- Pneumonia: Cover *Streptococcus pneumoniae*
  - Ciprofloxacin does not
- Abscess: Cover *Staphylococcus aureus*
- Gastrointestinal infections: Cover gram negatives and anaerobes

Factor 4: Cost-effectiveness

- If 2 antibiotics likely have the same efficacy, use the cheapest one, for the shortest duration and use the oral formulation preferably

Example

- An *Escherichia coli* that is pan-susceptible should be treated with ampicillin or amoxicillin instead of ceftriaxone

- A *Klebsiella pneumoniae* that is susceptible to both ceftriaxone and meropenem should be treated with ceftriaxone

Factor 5: Host characteristics

- Renal failure – need to adjust doses

- Weight – more complicated than expected
  - For vancomycin, use the total body weight.
  - For gentamicin, use the ideal body weight.
  - For amphotericin, in an obese patient, use the adjusted body weight.

- Pregnancy:
  - FDA category C (toxic in animals): Fluoroquinolones, colistin, linezolid, clarithromycin, vancomycin, trimethoprim/sulfamethoxazole and chloramphenicol
  - FDA category D (possible human risk): Aminoglycosides, tetracyclines and tigecycline

How to dose colistin: ESCMID and IDSA 2019 recommendations

- We recommend initiating IV therapy with a CMS loading dose of 300 mg CBA (~9 million IU) infused over 0.5–1 hours and to administer the first maintenance dose 12–24 hours later.

- We recommend that for a patient with normal renal function, administer a daily dose of 300–360 mg CBA (~9–10.9 million IU), divided into two and infused over 0.5–1 hour at 12-hour intervals.

- Adjust based on renal clearance (or else use polymyxin B)

Factor 6: Assess the side effects of the antibiotic

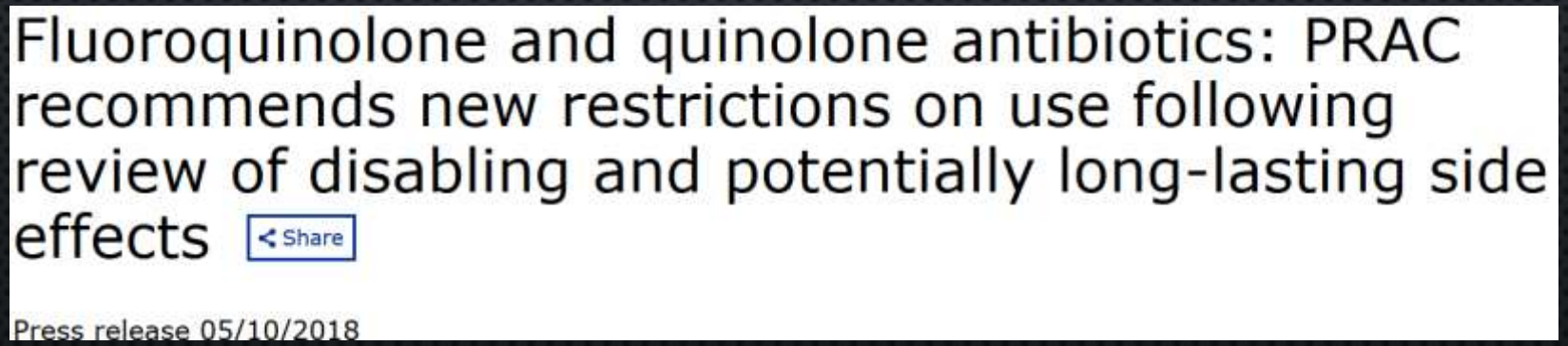
- Example: In a patient with acute kidney injury who is infected with a *Pseudomonas aeruginosa* that is susceptible to both meropenem and colistin, meropenem is a better choice
- Note interactions with warfarin and oral contraceptive pills
- Allergies

Susceptible patients[26, 27]

- Cardiac patient:
  - Fluoroquinolones and macrolides prolong the QTc
- Epileptic patient:
  - High dose penicillins in renal failure patients, imipenem/cilastatin, fluoroquinolones and 4th generation cephalosporins (cefepime)
  - Cefepime can cause nonconvulsive status epilepticus i.e. diagnosis is mainly by in-patient EEG
  - Beware of interactions between anti-epileptics and antibiotics!

SAFETY WARNINGS REGARDING FLUOROQUINOLONES[28]

- SIDE EFFECTS INCLUDE ACHILLES TENDON RUPTURE, RETINAL DETACHMENT, AORTIC DISSECTION, AORTIC ANEURYSM, HYPOGLYCEMIA, PERIPHERAL NEUROPATHY AND ACUTE DELIRIUM / PSYCHOSIS


Fluoroquinolone and quinolone antibiotics: PRAC recommends new restrictions on use following review of disabling and potentially long-lasting side effects

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Press release 05/10/2018

TRIMETHOPRIM/SULFAMETHOXAZOLE LINKED TO ARDS

Severe Acute Respiratory Failure in Healthy Adolescents Exposed to Trimethoprim-Sulfamethoxazole.

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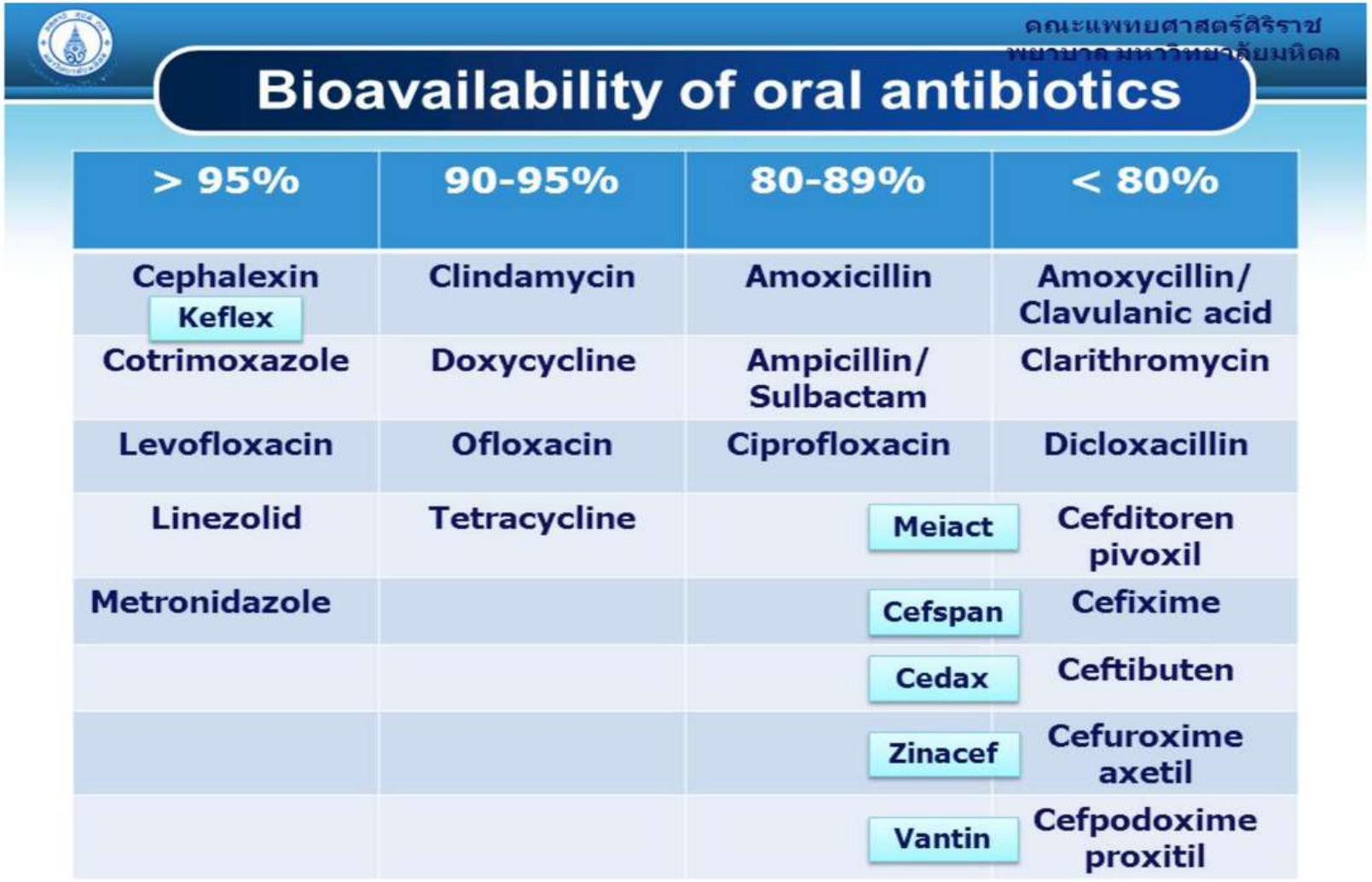
Abstract

Pulmonary toxicity induced by trimethoprim-sulfamethoxazole (TMP-SMX) has been described, although the disease process is poorly understood. We report 5 previously healthy adolescent patients who developed acute respiratory failure while taking TMP-SMX. Four of the 5 adolescents required extracorporeal membrane oxygenation support, and 2 of the teenagers died. All children required a tracheostomy, and all cases were complicated by pneumothoraces and pneumomediastinum. The majority of children were prescribed TMP-SMX for the treatment of acne vulgaris.

Piperacillin-tazobactam with vancomycin is associated with nephrotoxicity[58]

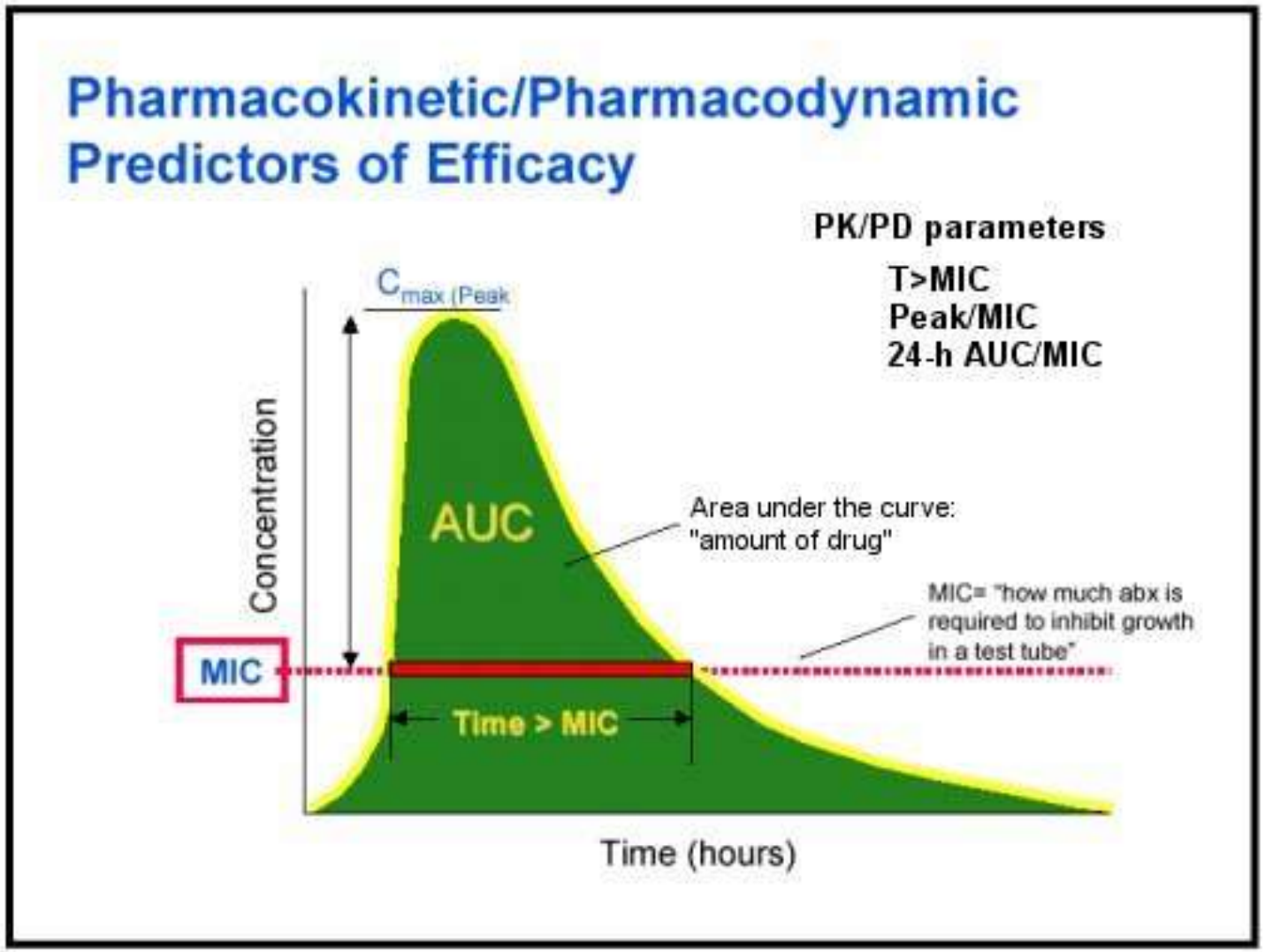
- University of Kentucky in 2018: 10,236 patients.
- Piperacillin-tazobactam + vancomycin vs meropenem + vancomycin
- The combination of piperacillin-tazobactam + vancomycin was associated with 2x increased odds of acute kidney injury

FACTOR 7: PHARMACOKINETICS AND PHARMACODYNAMICS (PK/PD): BIOAVAILABILITY



Vancomycin is not absorbed orally

PK/PD PARAMETERS



ACTIVITY TYPE

Pattern of Activity	Antibiotics
Type I Concentration-dependent killing and Prolonged persistent effects	Aminoglycosides Daptomycin Fluoroquinolones Ketolides
Type II Time-dependent killing and Minimal persistent effects	Carbapenems Cephalosporins Erythromycin Linezolid Penicillins
Type III Time-dependent killing and Moderate to prolonged persistent effects.	Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin

WHAT THIS MEANS IN PRACTICE

- Aminoglycosides and fluoroquinolones:
  - Higher peak to MIC is better
  - Use single large doses – several meta-analyses were done in the 1990s which demonstrated reduced side effects and similar efficacy of single dose aminoglycosides[32, 33]
- Beta-lactams and carbapenems:
  - Longer time above MIC is better
  - Use small doses at high frequency
- Vancomycin and tetracyclines:
  - Higher 24h area under curve to MIC is better
  - Increase the dose given multiple times during the day

Recent paradigm shifts

Paradigm shift 1: Early oral switch[36]

Traditionally, you should 'always' give IV antibiotics for the following conditions

- ☐ Complex bone/joint infections,
- ☐ Deep abscesses
- ☐ Cystic fibrosis
- ☐ Endocarditis or intravascular infection,
- ☐ Central nervous system infection,
- ☐ Bacterial meningitis,
- ☐ Central venous device infection,
- ☐ Immunocompromised infection
- ☐ *S. aureus* bacteraemia,
- ☐ Gram negative blood stream infections
- ☐ Necrotising enterocolitis
- ☐ Malabsorption, severe diarrhoea and/or uncontrolled nausea and vomiting
- ☐ Neonate (discuss with Paediatric SMO)

Early switch for gram negative bacteremia[37]

- Mayo Clinic in 2019: 346 patients
- Gram negative bacteremia from urinary tract infections
- IV group and oral transition cohort had no difference in treatment failures

- More IV-line related complications with the IV group and those patients stayed longer in the hospital

Early switch for MRSA bacteremia[38]

- Currently, 2 weeks of IV treatment is "mandatory" for *Staphylococcus aureus* bacteremia
- Study by Detroit Medical Center in 2019: 492 patients included with MRSA bacteremia
- Vancomycin / daptomycin vs linezolid / trimethoprim-sulfamethoxazole
- No difference in outcome

Oral antibiotics for infective endocarditis?

- Traditionally 6 weeks of IV antibiotics must be given to treat infective endocarditis
- Copenhagen University Hospital in 2019: 400 patients with left sided infective endocarditis
- About 2 weeks of IV therapy followed by PO (with dual active antibiotic)
- No difference in patient outcomes

PARADIGM SHIFT 2: SHORTER IS BETTER

- Article by a Professor of infectious diseases at Brighton and Sussex Medical School in 2017[42]
- The antibiotic course has had its day
- The idea that stopping antibiotic treatment early encourages antibiotic resistance is not supported by evidence
- Drop the "complete the course" mantra

VENTILATOR ASSOCIATED PNEUMONIA: MOVING FROM 15 DAYS OF TREATMENT TO 8 DAYS

- Hôpital Saint-Louis at Paris in 2003: Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs.[43]

- Comparable effectiveness between 8d and 15d of antibiotics

ULTRA-SHORT-COURSE ANTIBIOTICS IN VENTILATOR ASSOCIATED PNEUMONIA?[44]

- Brigham and Women's Hospital in 2017: 1290 patients eligible
- Daily minimum positive end-expiratory pressure of ≤5 cm H2O and fraction of inspired oxygen ≤40% for at least 3 days
- No difference between 3d of antibiotics vs > 3d

3 DAYS OF ANTIBIOTICS FOR COMMUNITY-ACQUIRED PNEUMONIA[45, 46]

- Study in Netherlands in 2006:
  - Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia
  - More than 100 patients enrolled (on amoxicillin)
  - No difference between the 3d vs 8d of treatment

- French study in 2018:
  - 310 patients randomized
  - Stable patients
  - 3d of beta-lactam same as 8d

PARADIGM SHIFT 3: PATHOGEN-DIRECTED THERAPY AND DE-ESCALATION

- Guidelines used to emphasize empiric broad-spectrum therapy since the 1980s-1990s

- With increasing multi-drug resistance, cultures and other techniques for microbe identification are needed to direct therapy

- Using regional data to create antibiograms, effective narrow-spectrum antibiotics may be recommended for certain infections:
  - Otherwise, re-assess the need for broad-spectrum antibiotics within 48-72h and de-escalate based on culture results

NARROW-SPECTRUM TREATMENT IN COMMUNITY-ACQUIRED PNEUMONIA[47]

- Study in Netherlands in 2005: 303 patients. Prospective randomized study.

- Narrow spectrum group was given mostly penicillin G while broad-spectrum received amoxicillin/clavulanate + macrolide.
  - Most pneumonias are caused by penicillin susceptible *Streptococcus pneumoniae* there

- Clinical outcome same in both groups

SHOULD WE COVER FOR RESISTANT ORGANISMS EMPIRICALLY IN HEALTHCARE ASSOCIATED PNEUMONIA?[48]

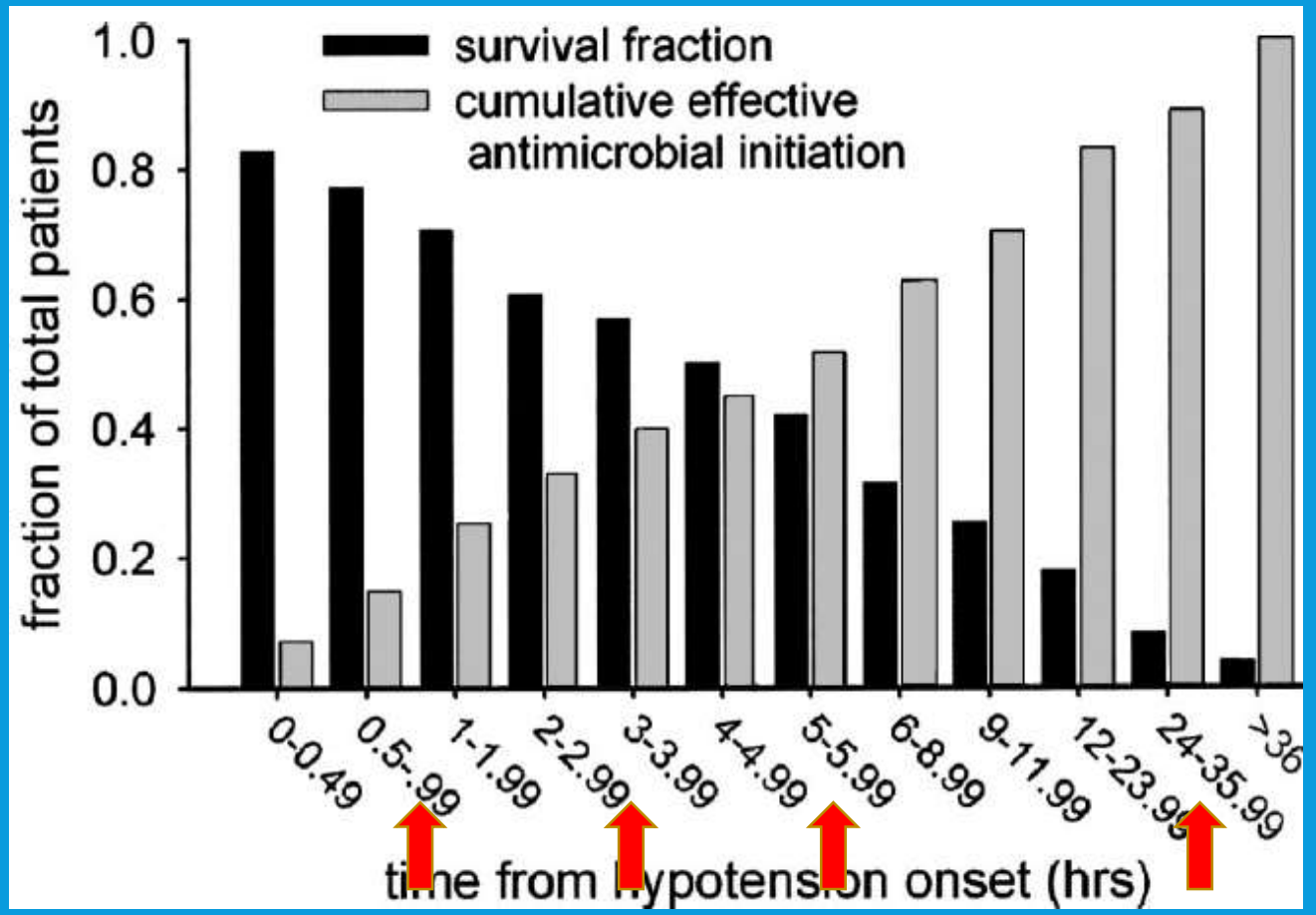
- IDSA and ATS guidelines of 2019 on pneumonia

- The term healthcare associated pneumonia has been dropped:
  - It has led to excess use of broad-spectrum antibiotics
  - Note that HCAP ≠ HAP

- There is NO NEED to empirically cover for MRSA or *Pseudomonas spp.* (unless there exist other risk factors)
  - The risk of multi-drug resistant organisms with HCAP is not much higher when compared to patients with community-acquired pneumonia

- Respiratory fluoroquinolones are no longer preferred agents

PARADIGM SHIFT 4: START ANTIBIOTICS EARLY ON IN SERIOUSLY ILL PATIENTS[59]



2016 2010 2005 1990s

Study in Canada in 2006

Looked at > 2,000 patients with septic shock

Starting appropriate antibiotics earlier reduces mortality

Solutions to prevent the abuse of antibiotics

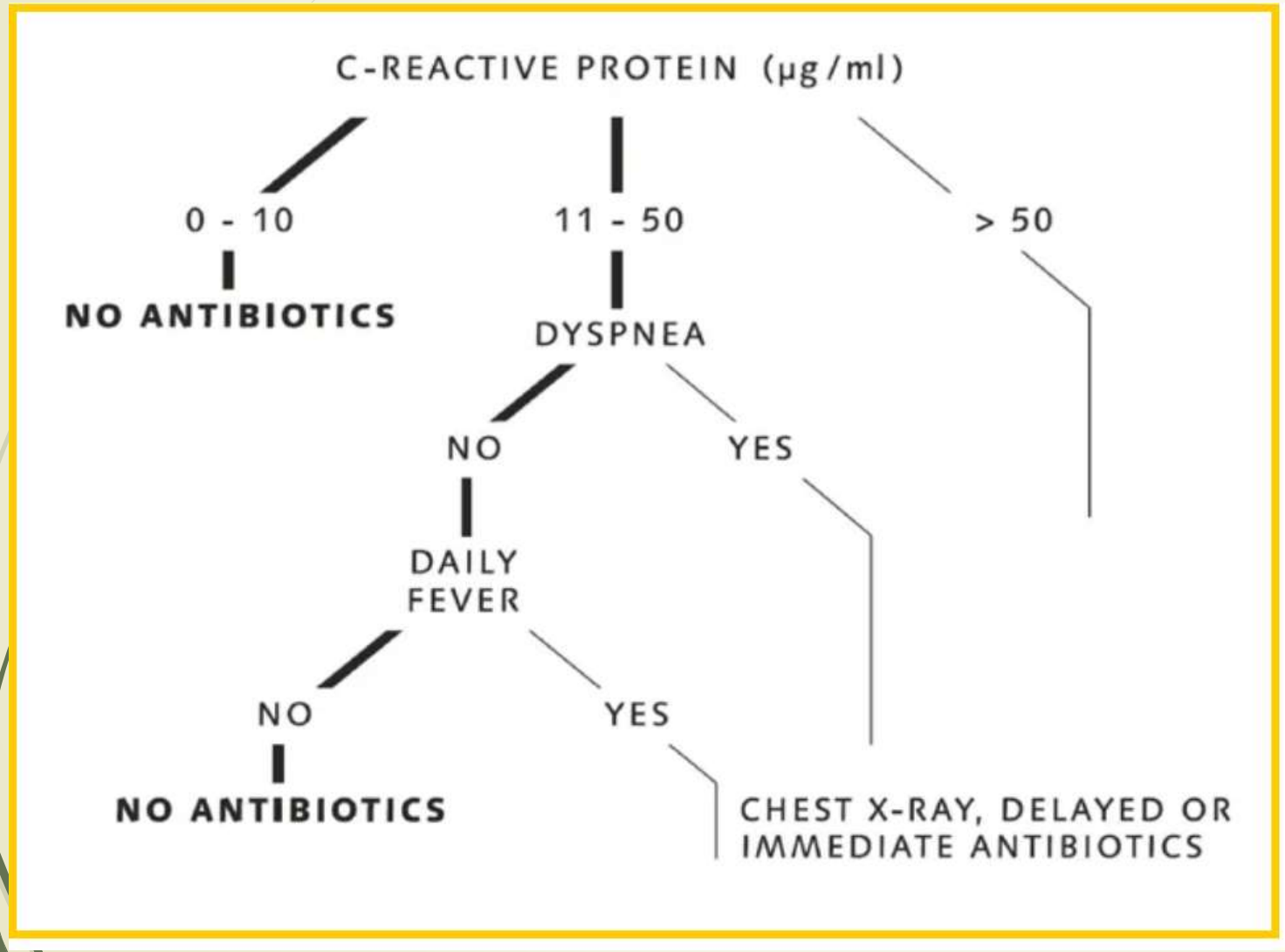
Better communication

- Guidelines – regional, national and hospital-level:
  - Based on evidence and antibiograms
  - Simplifies the task of healthcare providers
  - Helps medico-legally, especially when patients die after de-escalation of treatment
- Take time with your patient:
  - Discuss the pros and cons of antibiotic treatment
  - Campaigns on social media, TV, etc.
- Talk with your colleagues:
  - Get a second opinion when unsure
  - Clinical pharmacists help e.g. in adjusting the doses of antibiotics
- Make sure you write down in your notes why the antibiotic/s were started and the duration – so that other doctors know what is happening and don't start unnecessary antibiotics

Limit access to antibiotics

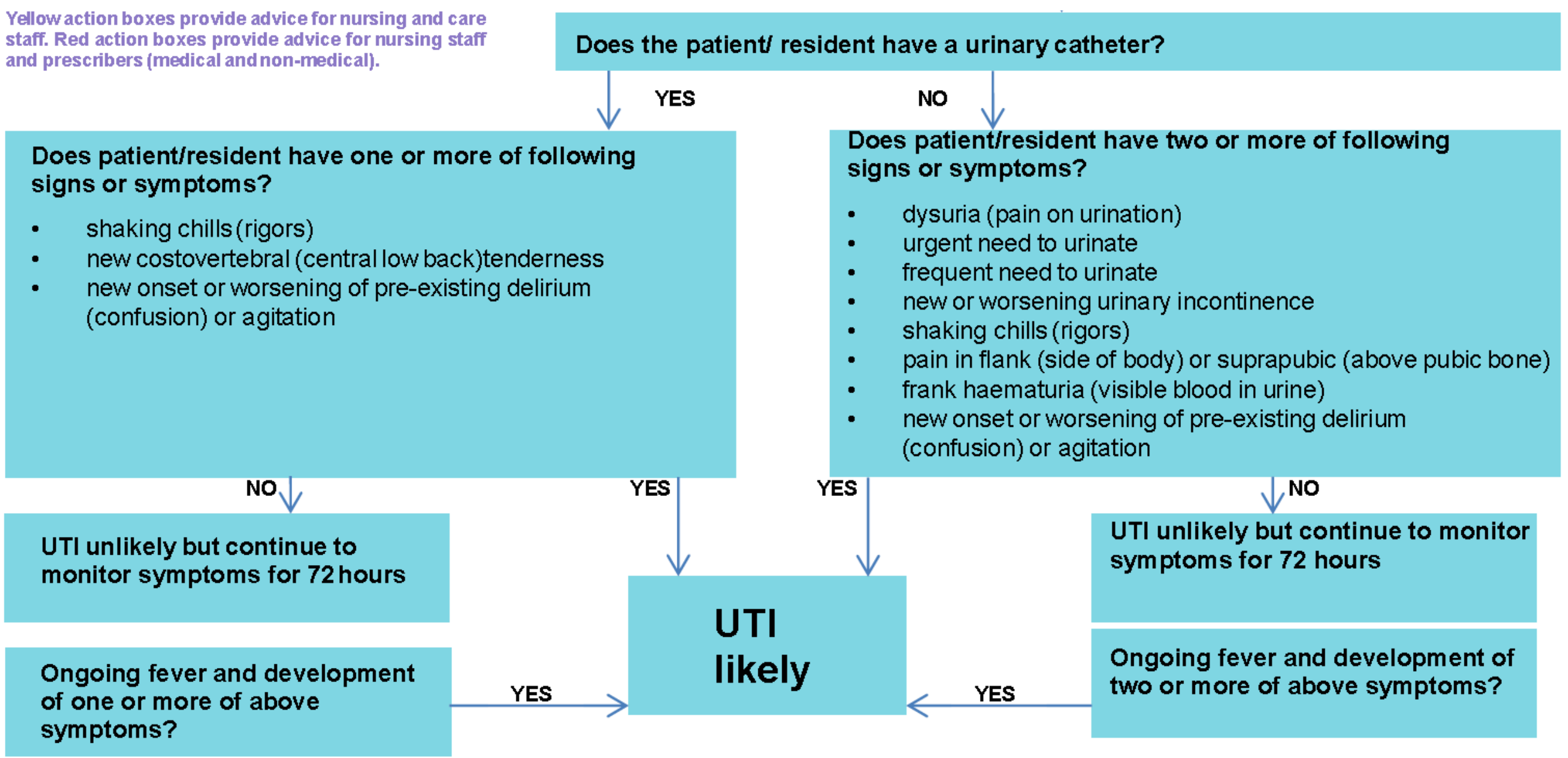
- Pre-authorization or prospective audit and feedback or formulary restriction or post-prescription review:
  - Can be done by a pharmacist or an antimicrobial stewardship team
- No over the counter medications
- Re-authorization of antibiotics every 3 days
- Only certain trained staff with prescribing rights can prescribe antibiotics
- Make antibiotics a controlled drug?

Clinical Decision Support Tools[52]



For identification of pneumonia:

From the University of Zurich in Switzerland. Published in 2011. Helped to reduce antibiotic prescription by 9%.



From the Public Health Agency. HSC. Northern Ireland. Published In 2018.

Does the benefit outweigh the risk?

- Lower your threshold for prescribing antibiotics if the risk of death is high
- How to know risk of death?
  - Pneumonia: CURB-65 or PSI scores
  - ICU: APACHE score
  - Septic: qSOFA and SOFA scores

Not everyone with high chance of dying needs antibiotics

- Example: 60y F with stage IV colon cancer invading into the bladder and uterus, presents with multiple pelvic abscesses that cannot be drained. She has bacteremia from an ESBL *Escherichia coli* – should she be treated with meropenem?

- Example: 65y M with lymphoma refractory to chemotherapy presents with metastases to the brain. His GCS drops, is intubated and develops a ventilator associated pneumonia. Should he be treated?

Infection prevention and control matters

- Patients often get recurrent ventilator associated pneumonia or persistent decubitus ulcers in the hospital
- Treating with antibiotics alleviate the current symptoms but lead to relapse after the antibiotics are stopped
- Should antibiotics be continued under these circumstances?
- Prevention is better than cure – use bundles to avoid the infection in the first place!

TAKE HOME MESSAGE: ANTIBIOTIC PRESCRIPTION CAN BE COMPLICATED!

- Do not under-utilize antibiotics
- Do not prolong the use of antibiotics when there is no clear infection
- Do not treat a positive culture in the absence of disease
- Do narrow antimicrobial therapy when a causative organism is identified:
  - 50% of cultures will remain negative – de-escalate or stop antibiotics when clinically stable for 24-48 hours
- Do not give prolonged prophylactic antibiotics
- Avoid the use of fluoroquinolones when possible

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Questions?