Syllabus

Antibiotic Therapy in Practice

Course Madrid November 26th to 28th, 2015

UMC Utrecht

Maastricht UMC+

azM en UM werken samen onder de naam Maastricht UMC+

Contents

Dear participant,

Welcome to first international edition of the three-day course “Antibiotic therapy in practice”, organised by the University Medical Center Utrecht, in collaboration with the Ramón y Cajal Hospital Madrid, the Hospital Clínic Barcelona and the Maastricht University Medical Center.

Although antibiotics belong to the most generally prescribed drugs, medical curricula often provide quite a limited background into the rationale behind the choices made in the treatment of infectious diseases. Moreover, these choices appear to become more difficult by the day as antimicrobial resistance spreads and worsens.

The course will deal with the antibiotics most often prescribed in European hospitals. The most relevant infections will be covered together with their main pathogens and (empirical) therapies. A significant part of the program will also be dedicated to repetition and practice of the matter. In general, we strive for a maximum of interaction.

We wish you three education and pleasant days, and hope to incite your enthusiasm for our fascinating specialties.

In general
The course is provided by staff members of the University Medical Center Utrecht, Maastricht University Medical Center, Ramón y Cajal University Hospital, Hospital Clínic de Barcelona and the University of Cologne. A total of [34] participants will attend the course [in 1/2 groups]. [The division in groups can be found on page ... of the syllabus].

Voting system
During the course, questions will be posed, which are mostly multiple choice, and to which the participants will answer through a voting system. The keypads used are very user-friendly. Once the question appears on the screen you can vote; you can change your answer as long as the question screen in the presentation is open. The last answer you give before the screen is closed will be registered. When the LED lights up green, this indicates that your answer has been received by the system.

Participants will receive a numbered response keypad during the course, which has to be returned at the end of the course.

Presentation of clinical case
Participants are asked to prepare a case from their (or a colleagues) practice with an "antibiotic question or dillemma". Please use no more than 6 slides and insert a question for discussion. Additional (multiple choice) questions may be added by the faculty. Please send your case as early as possible, but on November 1st at the latest to sec-bonten@umcutrecht.nl.

Syllabus and slides
The main teaching points of the course can be retrieved in this syllabus, which you will receive both on paper and electronically. The complete slide-sets will not be diffused, but on request specific slides may be made available.

Names of the antibiotics
In the course generic names of antibiotics are used, with one exception: augmentin for the combination of amoxicillin + clavulanic acid.

Evaluation
As a requirement for accreditation of the course and to improve possible future editions you are requested to fill out the evaluation form. This form can be found in the back of this syllabus.

Accreditation
The course is internationally accredited by the UEMS with 16 points. Furthermore the course is accredited by the Dutch Association of Paediatrics (NVK), the Dutch Association of Internists (NIV), the Dutch Association of Medical Microbiology (NVMM) and for intensive care (internal medicine, cardiology, pulmonary medicine, anaesthesiology, surgery and neurology) with 18 points. Dutch

accreditation takes place via GAIA, for this we need your BIG registration number (please take upon registration).

Mobile phones
Participants (and teachers) are kindly but quite urgently requested to turn their mobile phones to silent mode and to not keep them on their tables.

Location of the course
The course will be given at the
NH Puerta de Alcalá
Alcalá, 66, 28009 Madrid, Spain
T. + 34 91 435 10 60
www.nh-hotels.com

Transport from the airport
-Taxi: flat rate of €30 applies for transport from Barajas / Adolfo Suarez airport to the hotel.
-Metro "Principe de Vergara" lines 2 and 9: approximately €5 for a one-way ticket incl. supplement.
-Airport express bus: €5, O'Donnell stop and Cibeles stop are both 800-1000m from the hotel.

Rooms
Lodging is in a two-person bedroom for single or for double use (in case you have indicated your roommate and he/she agrees). Breakfast buffet is included.

Meals
Lunch (November 26, 27 and 28) and dinner (November 26 and 27) are included. Please let us know if you require any dietary precautions.

Contact / questions
For questions and answers please contact Ms Els den Tex and Ms Bregje van Stipdonk.
UMC Utrecht, Department of Medical Microbiology G04.614, 3584 CX Utrecht, The Netherlands
T: 088-7557676; e-mail: sec-bonten@umcutrecht.nl

PARTICIPANTS

Group 1	Group 2
Becude	Bulatovic Calasan
de Graan	Flinsenberg
Geurts	Goto
Van der Heijden	Honing
De Kort	Van Keimpema
Kusters	Van Kruijsdijk
Lieveld	Lamberts
Mlejnek	Nijhuis
Oostwoud	Opdam
Oswald	Ramos Diaz
Van Ruitenbeek	Sahir Mattar
Shaib	Segers
Van der Spek	Van der Spek - Haverkort
De Stoppelaar	Stam
Telgt	Torres Resta
Tinholt	van Meer
van der Leeuw	Vareil
Vanderstraeten	Victor Olayeni
Vinclair	De Vrankrijker

Program

	Group 1	Group 2
	Thursday November 26	**Thursday November 26**
8:45-9:00	*Registration*	
9:00-9:15	**Welcome**	
9:15-10:15	**Introduction microbiology and antibiotics**	
10:30-11:00	**PK/PD**	
11:00-11:30	*BREAK*	
11:30-13:30	**Beta-lactam antibiotics and resistance**	
13:30-14:45	*LUNCH*	
14:45-15:30	**Tetracyclines, glycylcyclines, macrolides, clindamycin, rifampicin**	**Fluoroquinolones, Cotrimoxazole, Nitrofurantoin, Fosfomycin**
15:30-16:30	**Respiratory infections**	**Urinary tract infections**
16:30-17:00	*BREAK*	
17:00-17:45	**Fluoroquinolones, Cotrimoxazole, Nitrofurantoin, Fosfomycin**	**Tetracyclines, glycylcyclines, macrolides, clindamycin, rifampicin**
17:45-18:45	**Urinary tract infections**	**Respiratory infections**
18:45-20:00	*BREAK*	
20:00-21:00	*DINNER*	
21:00-22:00	**Interactive questions**	

	Friday November 27	**Friday November 27**
9:00-9:45	**Microbiological diagnostics**	
9:45-10:30	**Aminoglycosides and polymyxins**	
10:30-11:15	**Vancomycin, linezolid and daptomycin**	
11:15-11:45	*BREAK*	
11:45-12:30	**Intra-abdominal infections, Clostridium, Metronidazole and Fidaxomycin**	**Endocarditis**
12:30-13:30	**Fever in neutropenic patients**	**Sepsis and catheter-associated bacteremia**
13:30-14:45	*LUNCH*	
14:45-15:30	**Endocarditis**	**Intra-abdominal infections, Clostridium, Metronidazole and Fidaxomycin**

15:30-16:30	**Sepsis and catheter-associated bacteremia**		**Fever in neutropenic patients**
16:30-17:00		*BREAK*	
17:00-18:00	**Case-discussions**		**Case discussions**
18:00-19:00	**Interactive questions**		**Interactive questions**
21:00	*DINNER IN MADRID*		

	Saturday November 28		**Saturday November 28**
9:00-9:45	**Yeast and molds, antifungal agents**		**Skin and soft tissue infections**
9:45-10:45	**Treatment of systemic fungal infections**		**Infections with MDR organisms**
10:45-11:15		*BREAK*	
11:15-12:00	**Skin and soft tissue infections**		**Yeast and molds, antifungal agents**
12:00-13:00	**Infections with MDR organisms**		**Treatment of systemic fungal infections**
13:15-13:30	*BREAK*		
13:30-14:15	**Interactive questions**		
14:15-14:30	**Closing remarks**		
14:30	*LUNCH*		

Faculty

Dr Edwin Boel, clinical microbiologist UMC Utrecht

Dr Tjomme van der Bruggen, clinical microbiologist UMC Utrecht

Prof Rafael Cantón, clinical microbiologist Hospital Ramón y Cajal

Dr Miquel Ekkelenkamp, clinical microbiologist UMC Utrecht

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Prof Harald Seifert, clinical microbiologist, University of Cologne

Drs Jan Sinnige, clinical microbiologist, UMC Utrecht

Prof Alex Soriano, infectious diseases specialist Hospital Clínic Barcelona

Prof Jordi Vila, clinical microbiologist Hospital Clínic Barcelona

Organisation

Ms Els den Tex

Ms Bregje van Stipdonk

Dr Miquel Ekkelenkamp

Relevant disclosures / possible conflicts of interest

Dr Edwin Boel: none

Drs Jan Sinnige: none

Dr Tjomme van der Bruggen: invited speaker for Abbvie

Dr Miquel Ekkelenkamp: advisory board Nordic Pharma, participation in studies Shionogi, Cempra, Basilea

Dr Rafael Cantón: participation in educational programs AstraZeneca, MSD-Cubist and Novartis, participation in research studies AstraZeneca, Ferrer International, MSD-Cubist and Pfizer, consultancies Basilea and Bayer.

Prof. Alex Soriano: speaker for Novartis and Pfizer

Prof. Harald Seifert: grant or research support, paid consultant, speakers' fees or advisory board member: Astellas, AstraZeneca, Basilea, Cubist, Durata, FAB Pharma, Gilead, InfectoPharm, MSD, Novartis, Pfizer, Roche Pharma, Tetraphase, The Medicines Company, Theravance, ThermoFisher.

Prof Jordi Vila: grant or research support, paid consultant, speakers' fees or advisory board member: AstraZeneca, MSD-Cubist, Ferrer Internacional, Cepheid, Becton-Dickinson

Dr Astrid Oude Lashof: none

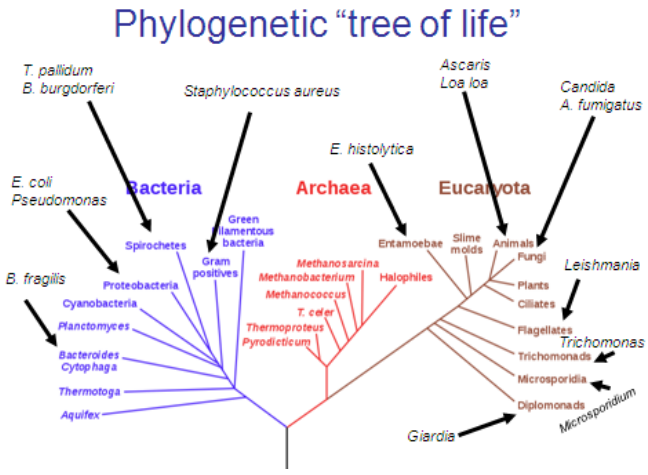
Abbreviations

AMP-C: Enzyme that hydrolyzes penicillins and cephalosporins (in Enterobacters, Citrobacters, Serratia's en Morganella's)
ARE: Amoxicillin-Resistant Enterococcus
ASE: Amoxicillin-Susceptible Enterococcus
BSI: Bloodstream Infection
CA: Community-Acquired
CAP: Community-Acquired Pneumonia
CF: Cystic Fibrosis
CFU: Colony-Forming Unit
CLSI: American guideline-commission for resistance testing
CoNS: Coagulase-negative staphylococus (e.g. *S. epidermidis*)
CR-BSI: Catheter-Related Bloodstream Infection
CPE: Carbapenemase-Producing Enterobacteriaceae (or:)
CRE: Carbapenem-Resistant Enterobacteriaceae
CURB 65 score: Score to determine severity of CAP
ESBL: Extended-Spectrum Beta-Lactamase
EUCAST: European Committee on Antibiotic Susceptibility Testing
GAS: Group A streptococcus / *Streptococcus pyogenenes*
GBS: Group B streptococcus / *Streptococcus agalactiae*
HA: Hospital-Acquired or Healthcare-Associated
HACEK: Haemophilus (Now: Aggregatibacter) aphrophilus / Aggregatibacter actinomycetemcomitans / Cardiobacterium hominis / Eikenella corrodens / Kingella kingae – Causative agents of endocarditis.
HAP: Hospital-Acquired Pneumonia / Healthcare-Associated Pneumonia
IDSA: Infectious Diseases Society of America
IFI: Invasive Fungal Infection
MBC: Minimal Bactericidal Concentration
MDR: Multi-Drug Resistant
MIC: Minimal Inhibitory Concentration
MO: Micro-organism
MRSA: Methicillin-Resistant *Staphylococcus aureus*
MSSA: Methicillin-Susceptible *Staphylococcus aureus*
PBP: Penicillin-binding protein
PMO: Pathogenic micro-organism
PK/PD: Pharmacokinetics / Pharmacodynamics
PSI-score: Pneumonia Severity Index score (for CAP)
SAB: *Staphylococcus aureus* Bacteremia
SIRS: Systemic Inflammatory Response Syndrome
STD: Sexually Transmitted Disease
SWAB: Stichting Werkgroep Antibiotica Gebruik (Dutch Antibiotic Guideline Working Group)
UTI: Urinary Tract Infction
VAP: Ventilator-Associated Pneumonia
VRE: Vancomycine-Resistente Enterococcus

Introduction:
Micro-organisms, antibiotics, resistance and PK/PD

Infections

Of all the micro-organisms which surround us, only a minimal percentage is capable of causing infections in humans. These micro-organisms, however, are found amongst many different branches of the phylogenetic "tree of life"



Whether an infection develops after contact with a micro-organism depends on its virulence (capacity to cause disease), the burden of exposition (e.g. number of bacteria), the contact route (airways, skin, etc) and the immune status of the host. The host's immunity includes many different factors, in particular: genetic factors (such as HLA), immunesuppression, co-morbidities, breach of the natural barriers / defenses, co-infections, nutritional status, prior exposure / vaccination and developed specific immunity and the presence of foreign bodies.

Classifications of bacteria

A rough classification of bacteria can be made based on the following characteristics:

Thickness of the cell wall: Gram-positive bacteria have a thick cell wall, outside of their cell membrane, Gram-negative bacteria have a thin cell wall between two cell membranes.

Form: round / cocci vs rods / bacilli

Use of oxygen: anaerobic bacteria grow badly or even die in the presence of oxygen; non-fermenters need oxygen for their growth

These rough properties of bacteria may inform us about their genetic relatedness and their likely susceptibility to different antibiotics.

Important bacteria within these groups are:

Gram-positive cocci:

-Staphylococci: coagulase-negatieve staphylococci (CoNS) and *S. aureus*

-Streptococci: viridans ("greening") streptococci, hemolytic streptococci, pneumococci

-Enterococci: amoxicillin-susceptible enterococci (ASE), amoxicillin-resistant enterococ (ARE), and vancomycin-resistant enterococci (VRE)

Gram-positive rods (usually quite specific infections):

-Mycobacteria, *Nocardia*, *Actinomyces* (=anaerobic), *Listeria*, *Corynebacterium*

Gram-negatieve cocci:

-Meningococ (Neisseria meningitidis), gonococ (Neisseria gonorrhoeae)

Gram-negative rods:

-*Haemophilus influenzae*

-Enterobacteriaceae:

-*E.coli*-group (includes *Klebsiella* and *Proteus*)

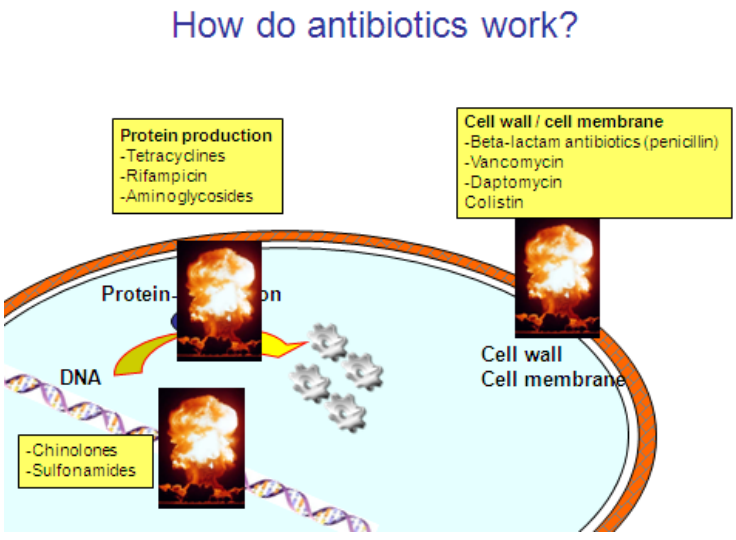
-*Enterobacter*-group (AMP-C positive), includes *Serratia*, *Morganella*, *Citrobacter*

-Non-fermenters: *Pseudomonas aeruginosa*, *Stenotrophomonas*, *Acinetobacter*

Anaerobes:

-Gram-negatives: e.g. *Bacteroides spp.*

-Gram-positives



Antibiotics

In principle "the antibiotics" include only the antibacterial substances which are produced by micro-organisms, whether or not they are subsequently chemically modified. When an antibacterial substance is produced completely synthetically it is officially an antimicrobial chemotherapeutic agent

(e.g. the fluoroquinolones, the sulfonamides). In practice, and in this course, often all antibacterial substances which are not disinfectants are called “antibiotics”.

Since the discovery of the sulfonamides and the penicillins in the thirties of the last century, a large number of antibiotics have been discovered and developed. Over the last twenty years, however, the development has almost halted. At the moment, less than one new antibiotic is registered per year, which only very rarely belongs to a new antibiotic class.

The main targets of antibiotics are the cell wall and cell membrane (i.e.: the cell integrity), the protein synthesis and the bacterial DNA.

Resistance and susceptibility tests

Resistance against antibiotics existed already long before we started using them in medicine. Antibiotics are part of the chemical warfare between micro-organisms which has been raging for millions of years. Not surpisingly, micro-organisms have developed defense mechanisms against them.

The original definitions of “susceptible” and “resistant” parted from the expected chance of clinical emprovement when using an antibiotic. If the chance of cure was >90%, the micro-organism was deemed susceptible; if this chance was < 60%, the micro-organism was resistant. In laboratory practice, susceptibility is determined by establishing the concentration of antibiotic needed to impede bacterial growth (the Minimal Inhibitory Concentration or MIC). Whether a micro-organism is susceptible is then determined by comparing this MIC with the expected concentration at a site of infection. Additional information on the micro-organism and clinical data are also taken into regard. For instance, bacteria with a low MIC for a certain antibiotic may be classified as resistance if they are known to develop resistance under treatment, or if patients are known to fail on therapy.

The main laboratory methods to determine antibiotic susceptibility of bacteria are:

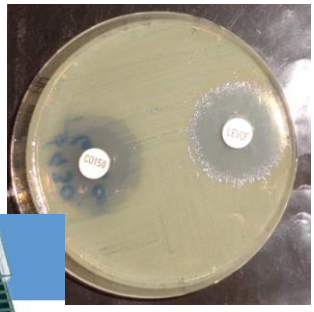
Disk-diffusion: an agar plate is inoculated with a bacterial suspension. On top antibiotic disks are placed. The size of the inhibition zone predicts whether a bacterium is susceptible.

E-test: an agar plate is inoculated with a bacterial suspension. A strip with rising concentrations of the antibiotic is placed on the agar plate. The point where the inhibition zone intersects with the strip is the MIC.

Automated microdilution: cups with freeze-dried antibiotics are filled with a bacterial suspension. The lowest concentration at which no growth occurs is the MIC.

E-test

Microdilutie



Disc-diffusie

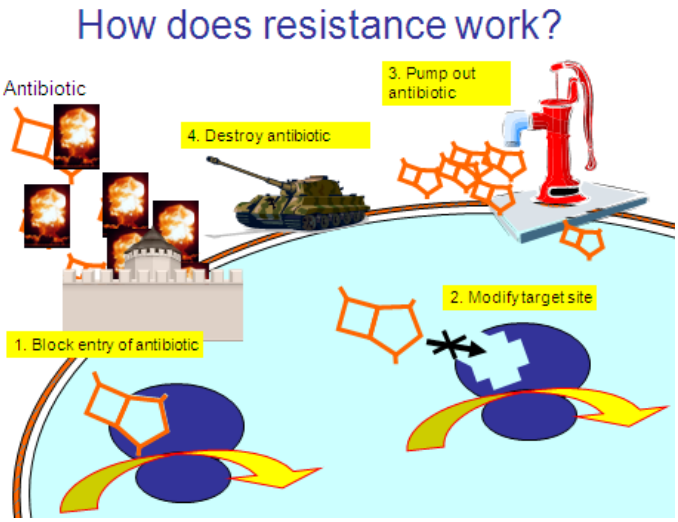
The main mechanisms of resistance are:

-Blocking absorption of the antibiotic

-Modification of the target site

-Pumping out the antibiotics

-Hydrolyzing the antibiotics

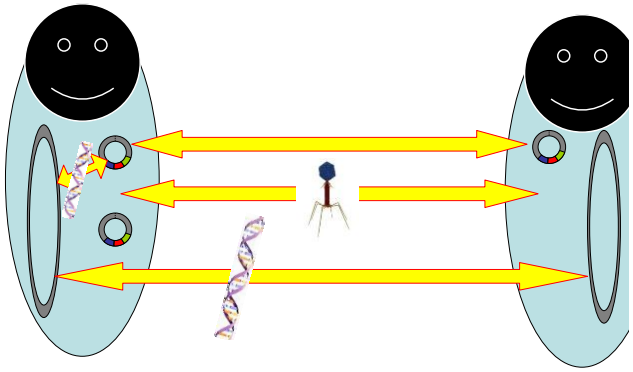


The resistance of a micro-organism is genetically encoded. This genetic information may be exchanged between different micro-organisms; sometimes even between micro-organisms which are only very distantly related (such as enterococci and staphylococci). Transfer of resistance genes may occur through:

-Transfer of plasmids (plasmid DNA and chromosomal DNA may be exchanged)

-Bacteriophages = bacterial viruses, which may integrate genes into the chromosome

-Direct uptake of DNA from the environment



Pharmaco-kinetics and pharmacodynamics (PK/PD)

Preferably, the choice of antibiotic treatment is determined by clinical data, often however it is based on pharmacological properties. The main PK/PD-parameters of antibiotics are:

Minimal inhibitory concentration (MIC): the minimal concentration required to halt bacterial growth.

Minimal bactericidal concentration (MBC): the minimal concentration required to kill bacteria (a decrease in bacterial numbers by a factor of 100 or more within 12-24 hours).

Peek concentration (C_{max}): the maximal concen tration reached at a site (usually the bloodstream)

Trough concentration (C_{min}): the minimal concentration reached at a site (usually the bloodstream), / the concentration just prior to the next dosing.

Area under the curve (AUC): the exposition to an antibiotic, measured per 24 hours

Oral resorption

Distribution / penetration in body compartments

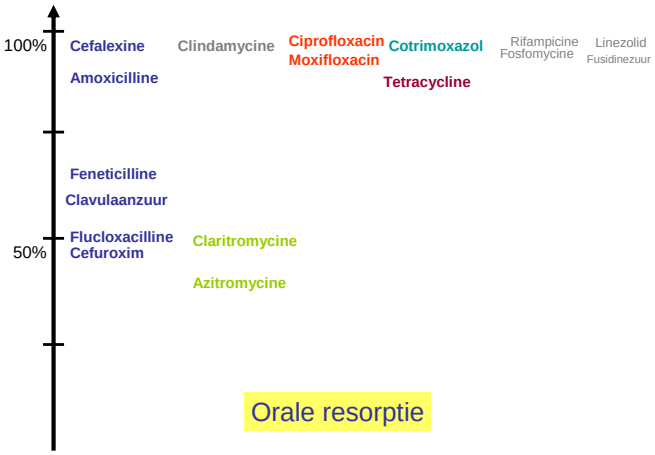
Post-antibiotic effect (PAE): the period that an antibiotic keeps inhibiting bacterial growth after its concentration has dropped below the MIC

Synergy: the combination of two antibiotics has a stronger antibacterial effect than either separately

Antagonism: the combination of two antibiotics has a weaker antibacterial effect than the most active of the two.

Some antibiotics exert **concentration-dependent killing,** the higher the concentration, the faster bacteria are killed. Examples are the fluoroquinolones and the aminoglycosides. The activity of the antibiotic depends on the ratio between the peak concentration and the MIC (C_{max}/MIC) or between the area under the curve and the MIC (AUC/MIC).

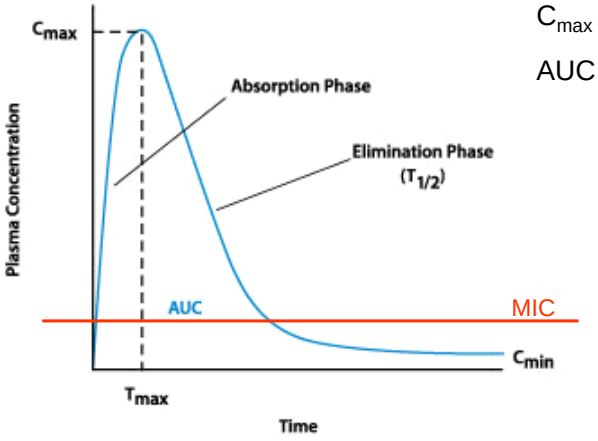
Some antibiotics mainly exert **concentration-independent killing**, also designated time-dependent killing; a higher concentration hardly leads to an increase in the speed at which bacteria are killed. Examples are the beta-lactam antibiotica, clindamycin and the macrolides. The activity is primarily dependent on the percentage of the time the concentration remains above the MIC (%T > MIC).



%T > MIC

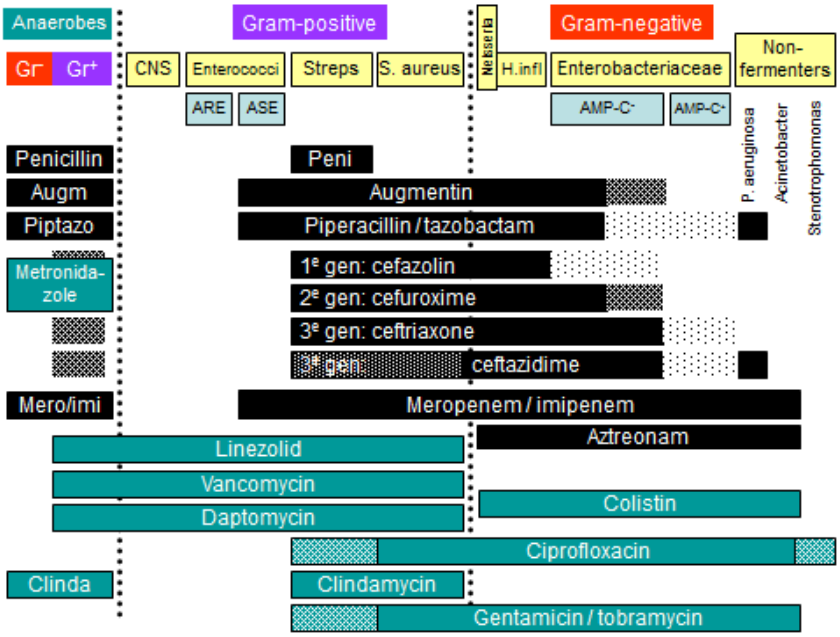
C_{max} / MIC

AUC / MIC



Antibiotic spectrum

The micro-organisms against which an antibiotic is active, are also labeled its "antimicrobial spectrum". "Broad-spectrum antibiotics" are active against both Gram-positive and Gram-negative bacteria. When multiple antibiotics are combined for a treatment, it is attempted to minimize the overlap in antimicrobial spectra of the different drugs.

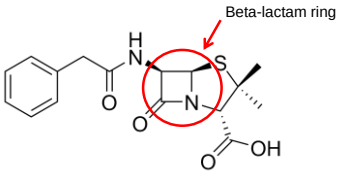


N.B.: This schematic representation is mainly intended to provide a global overview of the spectrum of activity of the different antibiotics. It does not grasp all the nuances and exceptions, and additional antibiotic resistances need to be considered.

Beta-lactam antibiotics

The beta-lactam antibiotics all contain the so called beta-lactam-group (see below). They exert their activity through binding to the penicillin-binding proteins (PBPs); PBPs are enzymes which cross-link the peptidoglycans in the cell wall, a process needed to secure bacterial stability and homeostasis. When this is inhibited, the integrity of the cell wall is compromised. The bacteria can no longer maintain their homeostasis and burst open. Cross-linking by PBPs is only required in cells that are multiplying; therefore, the main activity of beta-lactam antibiotics is against growing bacteria.

Penicilline



Different classes of beta-lactam antibiotics are available. In clinical practice we use:

<u>Penicillins</u>

-Narrow-spectrum: penicillin, penicillin G, feneticillin

-Broad-spectrum penicillins: amoxicillin

-Antipseudomonal penicillins: piperacillin

-Penicillinase-stable penicillins: cloxacillin, flucloxacillin

-Combinations w/ beta-lactamase-inhibitors: amoxicillin/clavulanic acid, piperacillin/tazobactam

<u>Cefalosporins</u>

-1th generation: cefazolin, cefalexin

-2th generation: cefuroxime

-3th generation: ceftriaxone, cefotaxime, ceftazidime

-4th generation: cefepime (not used in The Netherlands)

-5th generation: ceftarolin, ceftobiprole (activity against MRSA)

<u>Carbapenems ("last resort-antibiotics" for infections with MDR Gram-negative rods)</u>

-Ertapenem (no activity against *P. aeruginosa*)

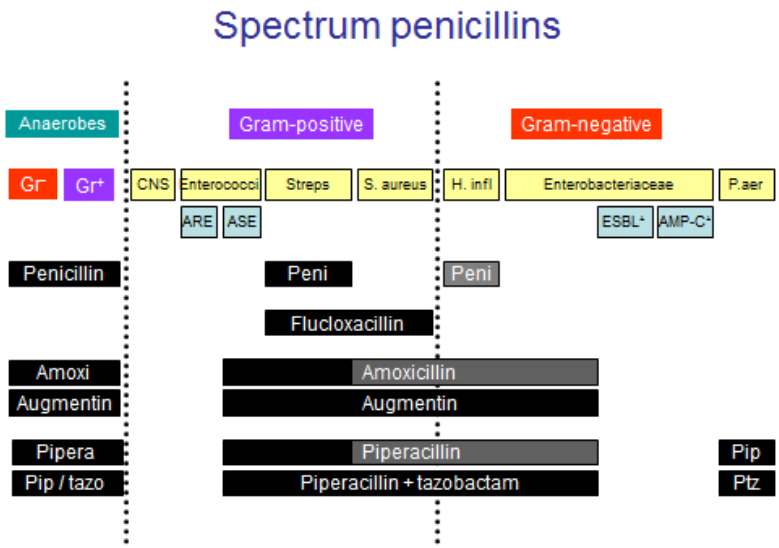
-Imipenem / cilastin (cilastin increases imipenem half life)

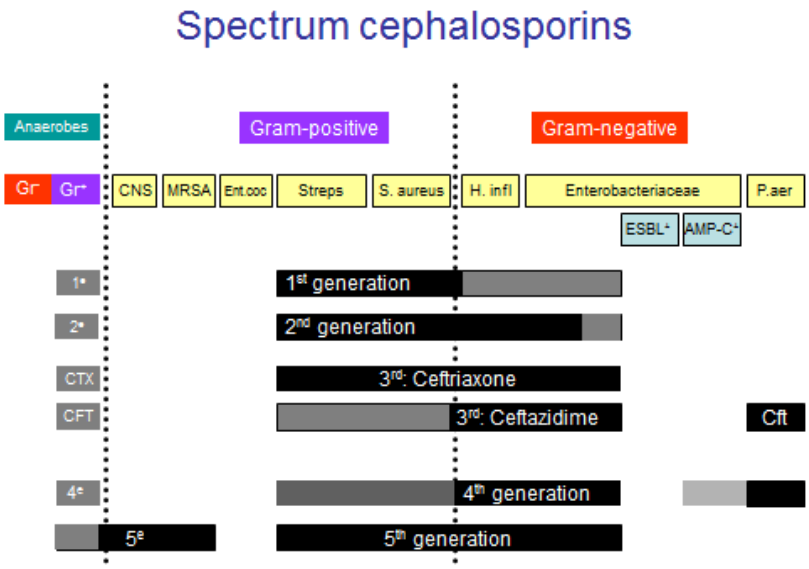
-Meropenem

Monobactams

-Aztreonam

Beta-lactam antibiotics exert a concentration-independent bactericidal effect. The main parameter for their activity is the percentage of the time the concentration remains above the MIC (%T>MIC).



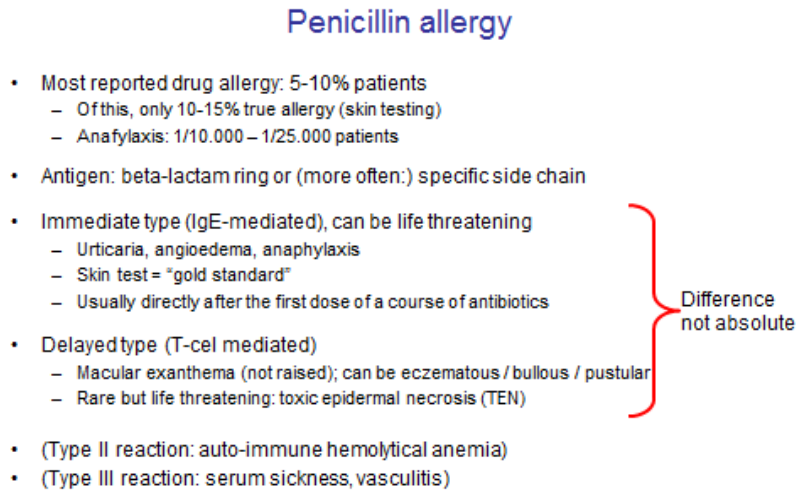


Adverse reactions to beta-lactam antibiotics

Common: gastro-intestinal side effects, hypersensitivity / allergy, rashes

Sporadic: increase in hepatic enzyme levels, cholestasis, EBV-related hypersensitivity, interstitial nephritis

Uncommon: hematological disorders, coagulation disorders. Imipenem is associated with an increased risk of seizures in patients suffering neurological diseases / infections.



IgE-mediated reactions are almost universally encountered after the first dose of an antibiotic course. Previously the patient will have been sensitized for the drug; during the sensibilisation patients usually do not suffer from any symptoms, as B-cells still need to develop and the IgE-level needs to be built up. Skin tests are quite senstive for IgE-mediated allergies (the gold standard is monitored exposition to the drug). However, the antigenic determinant (=the metabolite to which the immune system reacts) has been established for only a limited number of antibiotics. For penicillin the antigenic determinant is known.

Cross-reactivity between beta-lactam antibiotics

The cross-allergenicity between penicillins and cephalosporins has in the past been grossly overestimated: (1) in old studies penicillin-preparations were often contaminated with cephalosporins and vice versa, and (2) "allergy" was often poorly defined, not clearly differentiating from "hypersensitivity". Furthermore, patients with penicillin-allergy / penicillin-hypersensitivity have a higher a priori chance of allergy/hypersensitivity to (any) other antibiotics. The often quoted 10% is in practice much lower.

An estimate based on a large meta-analysis from 2007 (PMID: 17321857) found an 8% chance of hypersensitivity to 1st generation cephalosporins in patients with reported hypersensitivity to penicillins (not confirmed with skin tests) and an odds ratio of 4.8 for hypersensitivity for other antibiotic classes; patients without reported hypersensitivity had a chance of 1.5% of developing a skin reaction to 1st generation cephalosporins. Patients with hypersensitivity to penicillines did not have an increased risk of an allergic reaction to 2nd and 3rd generation cephalosporins; in fact, the odds ratio of a reaction was 0.45 compared to other antibiotic classes. Cross-allergy with carbapenems is believed

to be more frequent than to 2nd and 3rd generation cephalosporins, at about 1%. Cross-allergy between penicillins and aztreonam has not yet been reported (although aztreonam and ceftazidime may cross-react due to having identical side-chains).

Although these insights have not yet been fully implemented in clinical practice, it appears that 3rd generation cephalosporins can be safely administered to patients with (suspicion of) penicillin-allergy, preferably with the first administration under medical supervision. Most 2nd generation cephalosporins (including cefuroxime) are probably also safe, but due to a higher structural resemblance to penicillins it may be more prudent to use 3rd generation cephalosporins. In patients with a positive skin test, the chance of cross-allergy is estimated at a maximum of 1%. Care should still be taken with 1st generation cephalosporins and carbapenems in these patients. Also, for patients with severe allergic reactions (such as angioedema, anaphylaxis and toxic epidermal necrolysis), advise should be sought from a allergologist before any beta-lactam may be administered.

A possible protocol for use of beta-lactam antibiotics in case of (reported) penicillin-hypersensitivity is the following:

- Angioedema, anaphylaxis, Stevens-Johnson, exfoliative dermatitis
  - No beta-lactam antibiotics, unless explicit permission allergologist
- Delayed-type reaction, unclear reaction (no indication angioedema or anaphylaxis) or negative skin test
  - No penicillins or (relative contra-indication:) carbapenems
  - Cephalosporins permitted
- Immediate type reaction, positive skin test or no skin test
  - No penicillins or 1st generation cephalosporins
  - 1% chance of reaction to 2nd / 3rd generation cephalosporins (with positive skin test), administration with monitoring, "graded challenge" if needed
- Reaction >10 years ago (including positive skin test)
  - Beta-lactams with monitoring (first administration)
- Exposure to beta-lactams without reaction (often accidental)
  - Allowed to receive this type of beta-lactam antibiotic

Beta-lactam resistance

Beta-lactams antibiotics make up 50-70% of all antibiotics prescribed in European hospitals, and they are part of almost all first line regimes in patients with acute sepsis. Therefore, resistance to beta-lactams can have a huge impact on the antibiotic policies in an hospital. The main outbreaks with resistant bacteria, concern bacteria resistant (amongst others) against beta-lactams, such as MRSA,

ESBL-producing enterobacteriacaea and carbapenemase-producing enterobacteriaceae. The four main mechanisms by which bacteria become resistant to beta-lactam antibiotics are:

1- Blocking influx of antibiotics into the cell
- -In particular non-fermenters (*Pseudomonas*, *Acinetobacter*)
- -Porin mutations enterobacteriaceae (resistance when combined with beta-lactamases)

2- Alteration of the target site (=penicillin-binding protein / PBP)
- -MRSA, Penicillin-resistant pneumococci, amoxicillin-resistant enterococci
- -Augmentin-resistant *Haemophilus influenzae*

3- Efflux pumps
- -In particular non-fermenters (*Pseudomonas*, *Acinetobacter*)

4- Enzymatic degradation of antibiotics / beta-lactamases
- -In particular by Gram-negative bacteria
  - -Enterobacteriaceae ("normal" beta-lactamases, ESBL, AMP-C, carbapenemases)
  - -Amoxicillin-resistant *Haemophilus influenzae* (augmentin susceptible)
  - -Non-fermenters
- -Penicillin-resistant *S. aureus* (still susceptible to augmentin)

Gram-positive bacteria mostly acquire resistance against beta-lactam antibiotics by alterations in the target site (the PBP). Since the cell wall of Gram-positives does not lie in a periplasmic space, beta-lactamases are excreted completely extracellularly, making the of their production relatively high. The only relevant exception to this rule is *Staphylococcus aureus*, which often produces a beta-lactamase to degrade penicillin and amoxicillin.

Main beta-lactam resistances in Gram-positive bacteria

***S. aureus*, penicillin-resistant, (flu)(cl)oxacillin/methicillin-susceptible (MSSA)**
- -Resistant to penicillin/amoxicillin by production of penicillinase: augmentin still active
- -80-90% of all *S. aureus* strains are penicillin/amoxicillin-resistant

Methicillin-resistant *S. aureus* (MRSA)
- -Resistant through alteration of penicillin-binding protein (PBP2A or PBP2'), augmentin is therefore not active
- -Resistant against all beta-lactams and all combinations with betalactamase-inhibitors, except 5th generation cephalosporins

Amoxicillin-resistant enterococci (ARE) / *Enterococcus faecium*

-Hospital clones of *Enterococcus faecium* are almost unequivocally amoxicillin-resistant (*E. faecalis* is nearly always amoxicillin-susceptible)

-Resistance through alteration of PBP: augmentin is therefore not active

Penicillin-resistant pneumococci

-Decreased susceptibility through modification of PBP: no added value augmentin

-Clinically still responsive to penicillin (but with advise to administer higher dosages)

Main beta-lactam resistances in Gram-negative bacteria

Enterobacteriaceae with Extended spectrum beta-lactamase (ESBL)

-Betalactamase-enzym, (usually) coded on plasmid

-Resistant against all penicillins and most cephalosporins; susceptible to carbapenems

-Unclear whether cephalosporins tested active (such as cefoxitin) may be used

-Unclear whether beta-lactam/beta-lactamase inhibitor combinations may be used if tested active.

-Prevalence has been rapidly increasing since approximately the year 2000. In some countries up to 50% of clinically isolated enterobacteriaceae positive.

Enterobacteriaceae with AMP-C beta-lactamase

-Beta-lactamase, (usually) coded on chromosome; sometimes on plasmid

-Resistant against all penicillins and most cephalosporins; susceptible to carbapenems

-Unclear whether cephalosporins tested active (such as cefepime) may be used

-Intrinsically present in all Enterobacters, Serratia's and Morganella's, and in most Citrobacter spp.

Enterobacteriaceae with carbapenemase

-Beta-lactamase, coded on plasmid

-Codes for resistance against all beta-lactams

-Often only low-level resistance. To become clinically relevant may need to be combined with a second mechanism of resistance (such as ESBL)

***Haemophilus influenzae*, amoxicillin-resistant**

The Netherlands: 12% of the strains; higher in lung patients.

-Resistance as result of beta-lactamase, augmentin is active.

***Haemophilus influenzae*, amoxicillin- and augmentin-resistant**

The Netherlands: 2-3% of the strains; in lung patients >10%.

-Resistance by PBP-alteration, no added value of augmentin over amoxicillin.

Pseudomonas aeruginosa

-Many mechanisms of resistance, including antibiotic influx, upregulation of efflux pumps, and beta-lactamases.

-Betalactamase-inhibitors (e.g. tazobactam with piperacillin) usually do not increase activity.

Metronidazole

Metronidazole is a nitroimidazole drug. The first nitroimidazole drug was azomycine, isolated from a streptomycete; metronidazole, however, is synthesized completely chemically. The antibiotic is active against anaerobic bacteria (both Gram-positive and Gram-negative) and against certain protozoa (e.g. *Giardia*, *Trichomonas* and amoebae). The bacteria or protozoa metabolize metronidazole to a radical, which inflicts damage to the DNA leading to cell death.

Pharmacology

Metronidazole is almost fully resorbed when taken orally. It achieves high tissue levels, also in brain tissue. De drug is metabolized hepatically for 90% and does not need to be adjusted for renal function. In case of severe hepatic disfunction the dose needs to be lowered. Plasma half life of metronidazole is approximately 9 to 10 hrs and the antibiotic could be therefore dosed once daily; in practice, however, administration is 3 or 4 times daily. Metronidazole has a high salt burden when administered intravenously. 500 mg iv metronidazole contains approximately 1 gram NaCl.

Indications

-Intra-abdominal infections, in combination with a cephalosporin (or sometimes ciprofloxacin). Prophylaxis for intra-abdominal surgery.

-*Clostridium difficile* disease

-Treatment of abscesses, including brain abscesses (combined with cephalosporin)

-Pelvic inflammatory disease (combined with fluoroquinolone)

-Bacterial vaginosis

-Specific infections in upper respiratory airways (in combination therapy)

-Several parasitic diseases: *Giardia*, amoebae, *Trichomonas*

Toxicity

The main side effect of metronidazole is peripheral neuropathy with long term usage. Furthermore, it may produce gastro-intestinal side effects, hypersensitivity reactions and allergies. Rare side effects include stomatitis with sometimes a metallic taste in the mouth, pancreatitis, hepatitis and reversible neutropenia. Metronidazole may interact with alcohol, leading to flushing, nausea, headaches and palpitations. The etiology of these symptoms is not clear, possibly they are due to inhibition of aldehyde-dehydrogenase.

The drug has theoretical mutagenic effects, but clinical evidence for this effect in humans is completely lacking. However, it is recommended to avoid metronidazole in the first trimester of the pregnancy (B2).

Fluoroquinolones

Fluoroquinolones are synthesized completely chemically and therefore belong to the antimicrobial chemotherapeutic drugs. They inhibit the DNA-gyrase (also topoisomerase II) and the topoisomerase IV, enzymes needed to eliminate the DNA-supercoils which appear when DNA-strands are separated for replication (cutting the DNA strands and then reattaching the ends). The most commonly used fluoroquinolones are ciprofloxacin, norfloxacin, ofloxacin, levofloxacin en moxifloxacin.

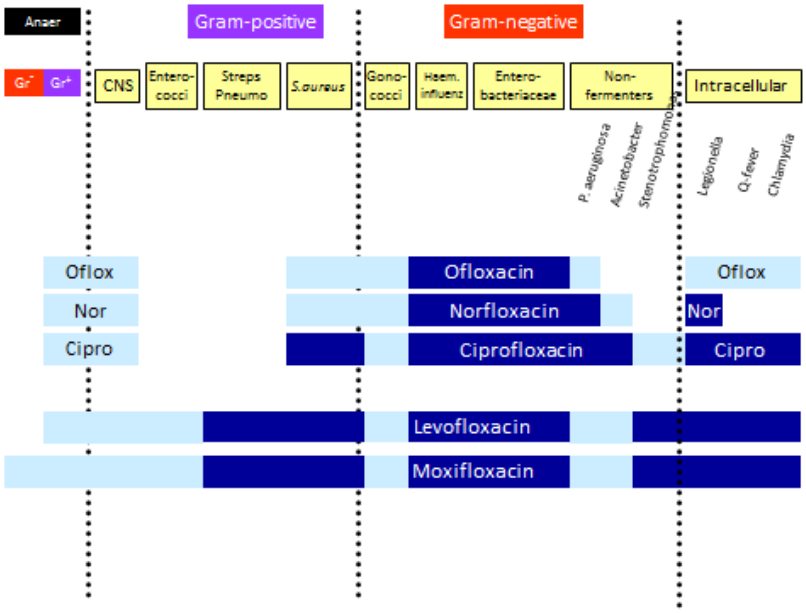
Pharmacology

Fluoroquinolones are absorbed almost completely when taken orally. However, simultaneous use of antacids containing Mg, Al, or Ca will hinder absorption, as will preparations containing Fe or Zn. Fluoroquinolones have a high volume of distribution and a high penetration into tissues (less for norfloxacin). Dosages are adapted in case of severly impaired renal function, except that of moxifloxacin.

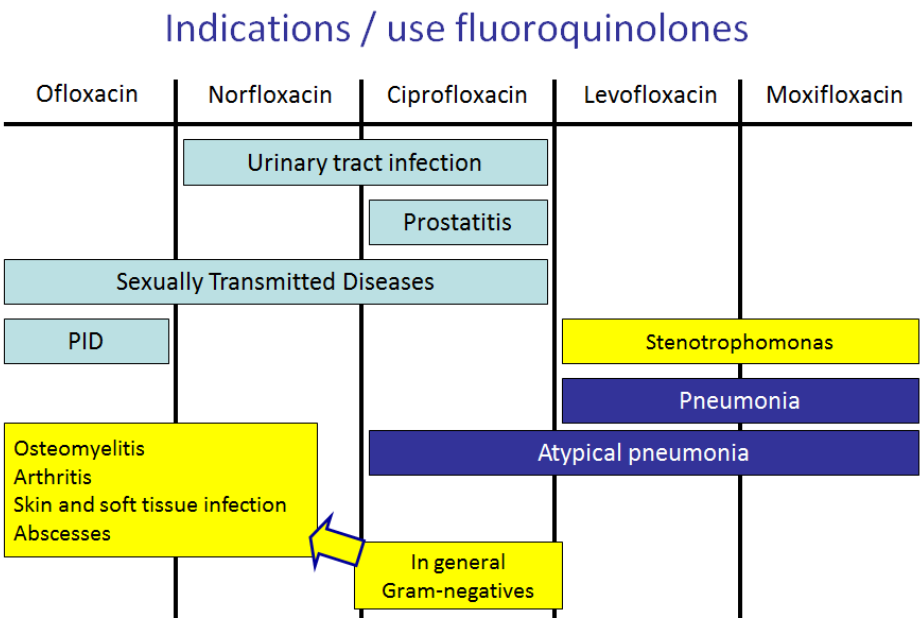
Toxicity

Fluorquinolones may produce gastro-intestinal side effect and rashes. Neurological symptoms are sometimes reported (headache, dizziness, insomnia, seizures). Uncommon but typical complications are those related to connective tissue: in parcticular tendinitis and rupture of the achilles tendon are notorious; an association with retinal detachment has been reported.

Spectrum



Ofloxacin, norfloxacin and ciprofloxacin are in particular active against aerobic Gram-negatives. Ciprofloxacin has a reasonable activity against *S. aureus*, but activity against streptococci (including pneumococci) is low. Levofloxacin and moxifloxacin do have strong activity against streptococci; these two antibiotics are, however, less active than ciprofloxacin against non-fermenters. Moxifloxacin is the only fluoroquinolone with reasonable activity against anaerobes. Fluoroquinolones used to be very active against gonococci, but resistance has become very common in these bacteria (in some countries up to 50%). Resistance against fluoroquinolones can develop under long term monotherapy, especially in *S. aureus* and *P.aeruginosa*.



Co-trimoxazole

Co-trimoxazole consists of the combination of two antibacterial chemotherapeutic drugs: sulfamethoxazole and trimethoprim in a ratio of 5:1. Both components inhibitit the synthesis of folic acid and in that way the production of DNA (folic acid is needed to construct the "A"s and the "G"s). The drug has a high oral resorption and achieves high levels in kidney, lungs, bile, saliva, breast milk and prostate; the trimethoprim concentration in cerebrospinal fluid is 40% of the concentration in serum, that of sulfamethoxazole reaches about 80% of the concentration in serum. Elimination is renal (with 60-80% inactive metabolites) and partially biliary.

Co-trimoxazole is active against both Gram-positives and Gram-negatives (including *Burkholderia* species), and also against some parasites and fungi (e.g. Toxoplasma en Pneumocystis). It is not active against enterococci, *P. aeruginosa* or anaerobes. Which of the two components is the most active differs per micro-organism. The combination may be synergistic (lowering MICs by a factor 4 to 8). However, most common bacterial pathogens susceptible to co-trimoxazole are also susceptible to trimethoprim monotherapy.

The most common side effects of co-trimoxazole are gastro-intestinal and skin reactions (from common rash to Stevens Johnson syndrome). More rare are bone marrow depression (most common in HIV-patients, patients with immunosuppressive therapy and the elderly) and nephrotoxicity (in particular reversible worsening of pre-existing impairments in renal function). Trimethoprim may increase serum creatinine without decrease in GFR, probably due to competitive inhibition of tubular secretion. Co-trimoxazole may It is considered safe in the 2nd and 3rd trimester of pregnancy, but is not to be taken after the 35 week of gestation due to a higher risk of kernicterus in the neonate.

Nitrofurantoin

Nitrofurantoin is an antibacterial chemotherapeutic drug. It probably has various modes of action, including binding to ribosomes, inhibition of enzymes and damaging of the DNA. The drug is almost fully resorbed with oral administration. Half is metabolized and half is excreted in active form into the urine, where it reaches very high concentrations. Tissue concentrations are negligeable. Because of accumulation of metabolites, it is advised to avoid nitrofurantoin in patients with a GFR < 30 ml/min.

The only indication for nitrofurantoin is cystitis, including long term prophylaxis. It is active against *E. coli*, *Klebsiella*, *Citrobacter*, stafylococci, streptococci and enterococci. *P. aeruginosa*, *Proteus*, *Serratia*, *Enterobacter* and *Acinetobacter* spp are generally resistant.

It is dosed 4 dd 50 mg or 2dd 100 mg (slow-release). The main side effects are gastro-intestinal complaints and hypersensitivity. Interstitial lung fibrosis is a rare complication of long term

usage. In pregnancy it is contraindicated in the week prior to childbirth (or when the mother is experiencing contractions), due to the risk of hemolytic anemia in the neonate.

Fosfomycin

Fosfomycin is a bactericidal antibiotic that inhibits formation of the cell wall. It is active against Gram-positive cocci and enterobacteriaceae. Anaerobes and *P. aeruginosa* are usually resistant. In principle, (uncomplicated) urinary tract infections are the only indication for its use. For cystitis it is taken as a single dose of 3 grams. Although it is not registered for pyelonephritis, it is sometimes used if no other oral options are available, in a dosage of 3 grams/48 hrs for the duration of the treatment.

Fosfomycin is sometimes used intravenously as a rescue antibiotic for MDR pathogens, generally as part of a combination therapy. Different dosages have been reported, usually 2 to 3 times daily 5 to 8 grams (the maximum dose of 3 x 8 grams for meningitis). Availability of the intravenous preparation may however be difficult in some countries.

The oral bioavailability of fosfomycin is approximately 40%. The drug is excreted unchanged in urine (30-60%) and faeces. It attains high tissue concentrations, but penetrates badly into the cerebrospinal fluid. After a single dose it remains active in the urinary tract for more than 40 hours.

Toxicity of fosfomycin is low. The main reported side effects include gastro-intestinal symptoms, vaginitis and headaches.

Tetracyclines (and glycylcyclines)

Oxytetracycline was isolated in the 1950s from a streptomycete. Often used modifications are tetracycline, doxycycline, minocycline and tigecycline. The tetracyclines inhibit the bacterial protein synthesis through binding to the 30S ribosomal subunit.

The oral resorption of doxycycline and minocycline is 90-100%, that of tetracycline 60-70%. Tigecycline can only be administered intraveneously. These drugs achieve high concentrations in lungs, liver, kidney, brain, sputum, mucosa, bile and placenta. Tetracycline is primarily excreted renally. Doxycycline, minocycline and tigecycline are mainly excreted in faeces. In case of severe renal impairment, doxycycline is the tetracycline of first choice.

The tetracyclines are active against Gram-positive cocci (stafylococci, streptococci, pneumococci) and certain Gram-negatives (gonococci, *H. influenzae*). The tetracyclines active against the causative agents of atypical pneumonia, including Coxiella (Q-fever), and against a large group of "special" bacteria (*H. pylori*, *Borrelia*, *Nocardia*, *Rickettsia*, *Bordetella*, *Treponema*, *Brucella).*

Furthermore, they can be used for treatment of certain protozoa (malaria, entamoeba). Minocycline is active against *Stenotrophomonas*. The activity of tetracycline, doxycycline and minocycline against enterobacteriaceae is limited, activity against anaerobes is variable.

Indications for tetracyclines are respiratory infections, skin infections and STDs. Furthermore, they are first choice for a large group of diverse infections, such as rickettsiosis, brucellosis and M. Lyme.

Tetracyclines may cause erosions to the esophagus ("pill esophagitis"). Through depositions in calcifying bone and teeth they may lead to irreversible tooth decoloration and even temporary growth impairment in children. Tetracyclines should therefore be avoided in children under the age of 14 years. Another relevant is side effect may be photosensitivity (redness / rash when skin is exposed to sunlight).

Tigecycline, the only currently available glycylcycline, has a glycylamido-moiety added to the tetracycline structure which enhances its activity against Gram-positive and Gram-negative aerobic bacteria. It is also active against most anaerobic bacteria. Tigecycline is used in some centers as (empirical) treatment of MRSA-infections, or for enterobacteriaceae resistant to beta-lactam antibiotics. For the latter indication it is not considered an agent of first choice. Successful treatment of *C. difficile* with tigecycline has been reported anecdotically.

Macrolides

Erythromycin, the first macrolide antibiotic was isolated in 1952 from a *Saccharopolyspora erythraea* isolate cultured from a Fillipino soil sample. Azithromycin and clarithromycin were developed by chemical modification of erytromycin. These antibiotics bind the 50S subunit of the bacterial ribosome, inhibiting bacterial protein synthesis. The oral resorption of macrolides is 30 to 60%, and the drugs reach high intracellular concentrations, in particular in leukocytes. The half life of erythromycin is 1.5 hrs, that of clarithromycin 5 hrs, and that of azithromycin 72 hrs. Azithromycin can therefore be dosed as a three-day course in the treatment of respiratory infections, maintaining active levels for a week. Dosages of erythromycin and azithromycin are not corrected for kidney function; clarithromycin dosing is only adapted in case of severe renal failure. Erythromycin and azithromycin are available as IV-formulations.

Macrolides are broad-spectrum antibiotics with good activity against Gram-positive cocci (*S. aureus*, hemolytic streptococci / pneumococci), against bacteria causing atypical pneumonia (*Chlamydophila*, *Mycoplasma*, *Legionella*) and against several specific Gram-negative bacteria (Helicobacter, *Campylobacter*, *Haemophilus*, *Neisseria*, *Moraxella*, *Pasteurella*, *Bordetella*, *Vibrio*). Also, they are active against several bacteria which are not cultured in routine diagnostics, such as

Bartonella (cat scratch disease), *Borrelia* (Lyme disease) and *Leptospira*. Furthermore, azithromycin and clarithromycin are active against (atypical) mycobacteria and are, amongst others, used in the treatment of leprosy, Mycobacterium avium complex infections and *Mycobacterium abscessus*. The main indications for macrolides are skin and soft tissue infections, pneumonia and sexually transmitted diseases.

The main adverse effects of macrolides are gastro-intestinal, and QT-elongation (with risk of torsade de pointes and ventricular arrhythmia); for both the risk is highest with erythromycin. Hypersensitivity reactions to macrolides may occur. Intravenous erythromycin may induce phlebitis.

Telithromycin is the only available ketolide, a chemically modified macrolide. It has grossly the same spectrum of activity as macrolides, but is designed to overcome macrolide-resistance. The main indication is mild to moderate CAP. The FDA recommends against telithromycin use, for its risk of potentially fatal hepatic toxicity.

Clindamycin

Clindamycin is the only available antibiotic of the group of the lincomycins, which were originally isolated in 1962 from a streptomycete. Like the macrolides it binds the 50S subunit of the bacterial ribosome, inhibiting the protein synthesis. Oral resorption of clindamycin is virtually 100% and the antibiotic reaches high levels in tissues and abscesses. The elimination is primarily through bile and faeces ($T_{1/2}$ 2.5 hrs) and the dose is not adjusted for renal function. Clindamycin is active against aerobic Gram-positive bacteria, in particular against staphylococci and streptococci; it also inhibits anaerobes (both Gram-positive and Gram-negative anaerobes).

Because of its high penetration in tissues, its high oral resorption and its activity against Gram-positive cocci, clindamycin is often used in the treatment of skin and soft tissue infections, including osteomyelitis and arthritis, and for treatment of abscesses and empyema. When combined with antibiotics that cover Gram-negative aerobes (enterobacteriaceae in particular) it can be used to treat mixed infections such as intra-abdominal infections or Fournier's disease. Clindamycin inhibits the production of toxins by susceptible Gram-positive cocci and is therefore used in the (combination-)treatment of necrotizing fasciitis by group A streptococci and toxic shock syndromes caused by *S. aureus.*

The main side effects of clindamycin are gastro-intestinal, including *Clostridium difficile* infection. Rashes and mild elevation of liver enzymes may also occur.

Vancomycin

Vancomycin, together with teicoplanin, belongs to the glycopeptide antibiotics. It is active against Gram-positive bacteria, including MRSA, coagulase-negative stafylococci, enterococci and *Clostridium difficile*. It is unactive against Gram-negatives, as the molecule is too large to diffuse through the porins of the outer cell membrane. Vancomycin is less active against *S. aureus* than the beta-lactam antibiotics are.

Vancomycin-resistance is uncommon. MSSA is almost never resistant to vancomycin, MRSA may have a decreased susceptibility. Coagulase-negative staphylococci sometimes have a decreased susceptibility, but spread of such strains has not been reported. However, resistant enterococci (VRE) are commonly associated with outbreaks – although their pathogenicity is often questionable.

Main indications for vancomycin:

- Infections with coagulase-negative staphylococci (infections of prostheses, line-infections, endocarditis, meningitis in patients with neurological drains or shunts).
- MRSA-infections
- Alternative to beta-lactam antibiotics for infections with *S. aureus* or streptococci
- Infections with enterococci (infections of prostheses, line-infections, endocarditis)
- Infections with *Clostridium difficile* (oral administration)
- Ocular infections (general coverage Gram-positive micro-organisms)

Main adverse effects of vancomycin:

- "Red man"-syndrome when the antibiotic is infused to rapidly (<60 min): rapidly developing rash of head / neck / trunk, sometimes with hypotension. Usually disappears within 20 minutes after the infusion is terminated. This does not constitute an allergic reaction and vanomycin may still be administered (be it more slowly).
- Phlebitis
- Hypersensitivity / rash
- Rare: hepatotoxicity, neutropenia
- Short courses of vancomycin have very limited (if any) nephrotoxicity, although it may enhance aminoglycoside nephrotoxicity in combination therapy. However, long term treatments (e.g. endocarditis, infected prostheses) do carry a significant risk of loss of kidney function.

Administration / dosage:

- As a bolus infusion: in principle gram q12h; a loading dose (1.5-2 grams) may be desireable in case of severe infections.
- As a continuous infusion: in principe 2 grams/24 hrs with a 1 gram loading dose
    - Vancomycin is stable for 24 hrs at room temperature.
- The exact dosage for longer term administrations is based on therapeutic drug monitoring, aiming for the following serum levels:
    - Trough level: 10-15 mg/l
    - Trough level in necrotizing pneumonia, osteomyelitis, endocarditis, meningitis: 15-20 mg/l
    - In case of continuous infusion: 20-25 mg/l (continuus serum level)
- Blood levels are drawn to guarantee the effectiveness of the treatment, not to prevent toxicity. A high serum level may however indicate developing renal pathology.
- Alternative: teicoplanin 400 mg q 24 hrs. The first day, as a loading scheme, the drug is administered q 12 hrs. (No control of blood levels)

Linezolid

The oxazolidinones, linezolid (2000) and tedizolid (2015), are completely synthetic drugs which exert their action through binding to the 50S ribosomal subunit and inhibition of the protein synthesis. The oxazolidinones are active only against Gram-positive bacteria, including some Mycobacteria, and retain activity against many resistant micro-organisms, such as MRSA, VRE and most CoNS. At normally achieved concentrations it is bacteriostatic. Linezolid is almost fully absorbed from the intestinal tract. It reaches high tissue concentrations in bone, lungs, skin and muscles and reasonable levels in the cerebrospinal fluid.

Linezolid is mainly used in the treatment of infections (presumed to be) caused by Gram-positive cocci, in particular in settings where resistance against beta-lactam antibiotics (MRSA) is high. This includes skin and soft tissue infections, pulmonary infections and sepsis.

Of concern with linezolid use are its side effects. Linezolid can be neurotoxic: it can lead to peripheral neuropathy, which is often painful, and to optic neuropathy with loss of color perception and vision. Peripheral neuropathy is less often reversible than optic neuropathy. These side effects have been reported to occur in approximately 1% of the cases, in particular with long-term treatment (4-10 months). The second main side effect is myelosuppression, mainly thrombocytopenia, which is reported in <1% to as high as 15% of patients. Myelosuppression is generally reversible, and is

associated with end-stage renal disease. Since both side effects are associated with duration of therapy, it is recommended not to treat for periods longer than 28 days, and to regularly check hematological parameters if the duration of treatment exceeds 10 days.

Daptomycin

Daptomycin was isolated from *Streptomyces roseosporus* and is the only lipopeptide antibiotic currently available. It is solely active against Gram-positive bacteria, including anaerobic Gram-positives, and has a bactericidal, concentration-dependent activity. The antibiotic inserts intself into the cell membrane, where it forms aggregates that disrupt the cell membrane, leading to ion leakage and depolarization.

Daptomycin is not resorbed intestinally and only available as an infusion, dosed once daily at 4 to 6 mg/kg depending on the indication. It has a low volume of distribution (remains mostly extracellular) with poor penetration in the lungs, CSF and infected bone (levels of 5-10% of the serum concentrations). Daptomycin is inactivated by lung surfactant and can therefore not be used to treat pulmonary infections.

The main side effect of daptomycin is skeletal muscle toxicity: myopathy with muscle pains, elevation of creatine phosphokinase (CPK). This effect is usually reversible. It may possibly be aggravated by concomitant use of statins. Other, less common side effects include gastro-intestinal complaints, liver function test disturbances, hypersensitivity and nephrotoxicity (<1%).

Daptomycin is generally used to (empirically) treat resistant staphylocci (MRSA and VRSA), as an alternative to vancomycin. It is registered for skin and soft tissue infections and for staphylococcal bacteremia.

Rifampicin

Rifampicin is a bactericidal antibiotic from the rifamycin-group. It exerts its function by inhibition of the DNA-RNA polymerase (blocking transcription to mRNA). The antibiotic is active against Gram-positive bacteria, Mycobacteria, intracellular bacteria (*Bartonella*, *Rickettsia*, *Coxiella*) and some Gram-negatives (*Neisseria*, *Haemophilus*, *Legionella*). Enterobacteriaceae and non-fermenters are almost unequivocally resistant.

Rifampicin kills bacteria in biofilms and is therefore often used in the treatment of infected prostheses (valves, joints, neurological shunts). Other indications are the treatment of mycobacterial infections (tuberculosis, *M. avium*, leprosy), MRSA-eradication and eradications of meningococci.

Rifampicin is dosed 600 mg q 24 hrs or 300-450 mg q 12 hrs. Concurrent ingestion of food decreases the oral resorption.

Resistance against rifampicin develops through spontaneous mutations in the rpoB-gene, which encodes a subunit of the DNA-RNA polymerase. One mutation in this gene may suffice. If rifampicin is administered as monotherapy, the chance is relatively high that a single bacterium may develop such a mutation and be selected – leading to resistance and therapeutic failure. Therefore, rifampicin is preferably only given as part of a combination treatment.

Rifampicin has many interactions through induction of the cytochrome P450. The main adverse effects are rashes and gastro-intestinal side effects. Far less frequent are hepatotoxicity, hematological disturbances, renal toxicity and lupus-like syndromes with high drug levels. Use of rifampicin leads to an orange discoloration of tears and urine.

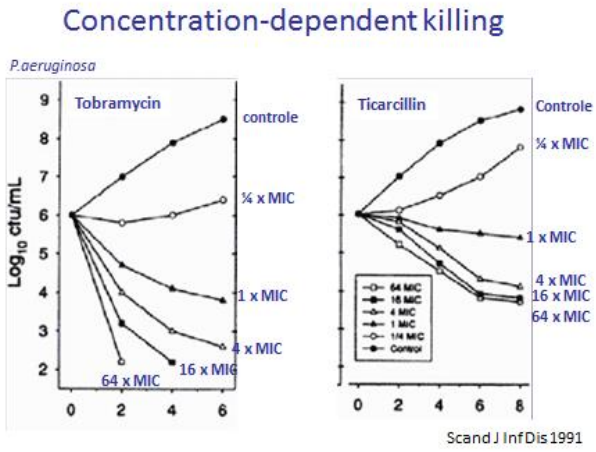
Fidaxomicin

Fidaxomicin is the first (and only) available macrocyclic antibiotic. The mechanism of action is inhibition of the RNA-polymerase. Fidaxomycin is a narrow-spectrum antibiotic, with activity against Gram-positive bacteria and in particular against *Clostridium difficile*. The drug is not resorbed orally, leading to high intestinal concentrations.

The only indication for fidaxomicin is recurring *C. difficile* infections. In studies it is as effective as vancomycin in achieving remission of the infection and may be more effective in preventing further recurrences. The main adverse effects are gastro-intestinal.

Aminoglycosides

The bactericidal effect of aminoglycosides is believed to be mainly due to binding of the drugs to the 30S ribosomal subunit of bacteria. This binding causes the bacteria to misread the messenger-RNA and to produce toxic proteins. Additionally, aminoglycosides appear to have a disruptive effect on the cell membranes of Gram-negative bacteria. The most commonly used antibiotics of this class are gentamicin, tobramycin and amikacin. For certain indications streptomycin (tuberculosis), paromomycin (parasitic infections) and neomycin (ear drops) are still used.
The bacterial killing by aminoglycosides is concentration-dependent: the higher the concentration, the more rapid the antibacterial activity.

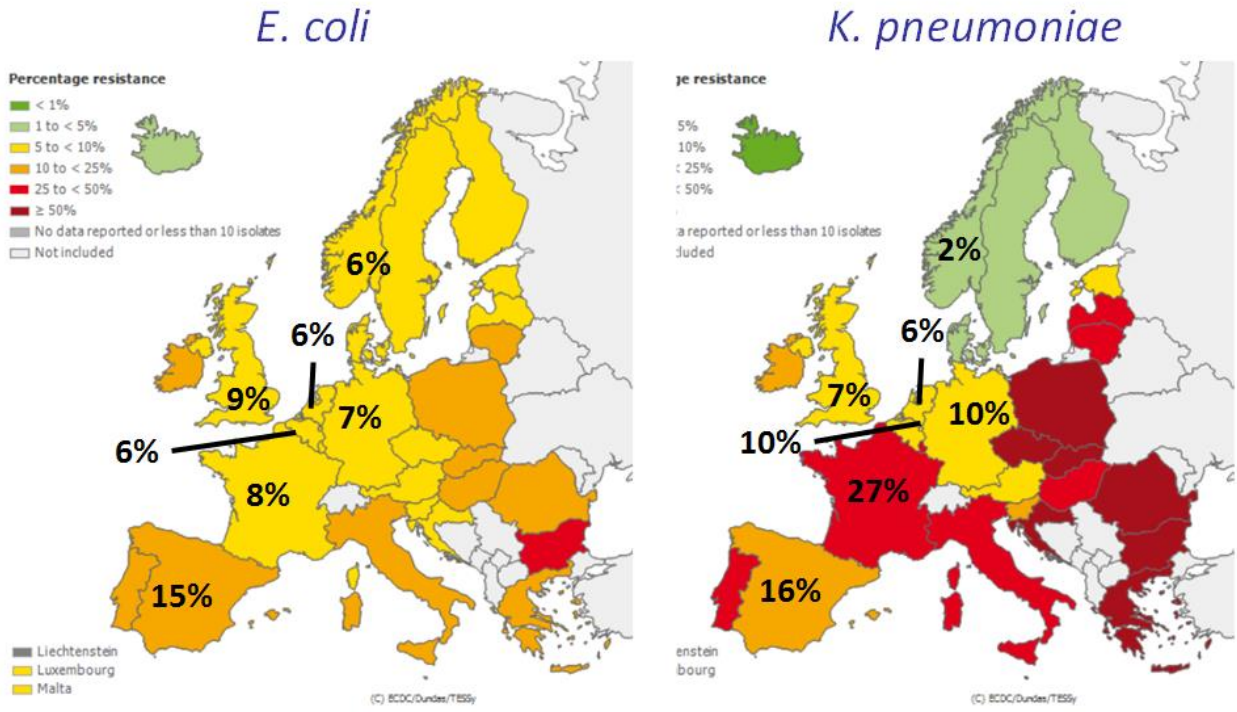


The bacterial killing by aminoglycosides (here tobramycin) is concentration-dependent: the higher the concentration, the more rapidly bacteria are killed. Beta-lactam antibiotics (here ticarcillin) have a time-dependent killing. Increasing concentrations above the MIC hardly speed up the killing rate.

Spectrum and resistance

Aminoglycosides are active against most Gram-negative bacteria. Against Gram-positive cocci their (staphylococci, streptococci, enterococci) activity is mainly synergistic with other antibiotics. Anaerobes are intrinsically resistant against aminoglycosides, as is *Stenotrophomonas maltophilia*.

Percentage aminoglycoside-resistant strains Europe (blood cultures EARS-Net 2013):



Farmacokinetics

Oral resorption of aminoglycosides is minimal; for systemic treatment they need to be administered intraveneously or intramuscularly. Clearance is almost fully renal, with a half life of 2-3 hrs (shorter in children but longer in neonates). Aminoglycosides reach relatively low tissue levels; the penetration in cerebrospinal fluid is low.

Adverse effects

The toxicities of aminoglycosides are nephrotoxicity, through accumulation in the tubular cells of the kidney, and ototoxicity / vestibular toxicity, due to accumulation in the hair cells. The risk of renal toxicity is especially high in patients with pre-existing impairment of renal function. It is not fully clear to what degree aminoglycoside toxicity is reversible. It appears that after discontinuation of therapy vestibular toxicity is almost universally reversible, and nephrotoxicity usually is. However, hearing loss is often largely irreversible; patients do not usually report it until it has progressed to an advanced stage. Rare side effects (<1%) include hypersensitivity, agranulocytosis, neurotoxicity and gastro-intestinal complaints.

We assume (at the UMCU) that a single administration of aminoglycosides does not produce any relevant toxicity. In patients with severe sepsis or septic shock we attribute the decrease in renal function to acute tubular necrosis due to hypotension.

Local / topical use

- Selective decontamination of the digestive tract (SDD, often tobramycin + colistin + amfotericin B)
- Nebulization or dry powder inhalation with tobramycin and amikacin is used in CF-patients to suppress or eradicate *P. aeruginosa* colonisation. Infected parts of the lung are hardly reached; therefore inhalation therapy is not suitable to treat pneumonia.
-Eye drops, ear drops and unguents with aminoglycosides are available.
-Aminoglycosides may be used to impregnate foreign body materials (spacers, beads, etc).

Dosage intravenous / systemic

It is believed that aminoglycosides have a “maximum toxicity”: above a certain serum level, the tubular cells and hair cells do not take up more of the antibiotics and are therefore not damaged worse. Since the bacterial killing is concentration-dependent aminoglycosides are nowadays administered once daily for all indications (assuming a normal kidney function): this provides maximal effect shortly after infusion, followed by an “aminoglycoside-free interval” in which the damaged cells can recover.

Suggested IV dosing regimens gentamicin/tobramycin, administration once daily:

-Empiric combination-therapy in sepsis: 5-7 mg/kg

-Monotherapy in urosepsis: 7 mg/kg

-Combination therapy in endocarditis: 3 mg/kg

-Combination therapy for *P. aeruginosa* infectionss: 5-7 mg/kg (CF-patients 10 mg/kg)

Therapeutic drug monitoring

Aminoglycoside serum levels are determined to prevent or timely detect nephrotoxicity. In treatments with aminoglycosides an "aminoglycoside-free interval" is pursued, in which the tubular cells and the hair cells can recover. In patients who will be treated for more than two or three days, and patients with pre-existing impairment of renal function, drug levels need to be monitored (first sample after 1st or 2nd dose).

In patients with a normal renal function, gentamicin and tobramycin are under 0.5 mg/l after 14 hours. In clinical practice, maximum trough levels of 0.5 mg/l are accepted in once daily dosing (taking into account that 0.5 is already quite high). With the above suggested dosing regiments, sufficiently high peak levels are attained and these do not need to be monitored. However, a more extensive monitoring including peak levels may be in order for certain patient categories with strongly deviant pharmacokinetics and patients who will be treated frequently with aminoglycosides (for instance ICU-patients and CF-patients).

Polymyxins (colistin)

The polymyxins are polypeptide antibiotics which were isolated as far back as 1947 from the Gram-positive soil bacterium *Bacillus polymyxa*. Of the different polymyxins only polymyxin B and colistin (=polymyxin E) are used as antibiotics. Both polymyxins are mixtures of several major components. The polymyxins became near to obsolete in clinical practice in the eighties and ninetees, due to toxicity issues, but have regained favor in the twentieth century, due to the emerging antibiotic resistance in Gram-negative bacteria. All Gram-positive bacteria are resistant, as are most Gram-negative anaerobes. Aerobic Gram-negatives are mostly susceptible, with some notable exceptions: Proteus, Serratia, Morganella, and Burkholderia species are usually resistant, as are pathogenic Neisseria species (gonococci and meningococci).

The polymyxins are hardly absorbed after oral administration. Intravenous and inhaled colistin are administered as the inactive prodrug colistin methanesulfonate (CMS), also known as colistimethate, which is degraded in vivo to colistin through loss of the methanesulfonate groups. The

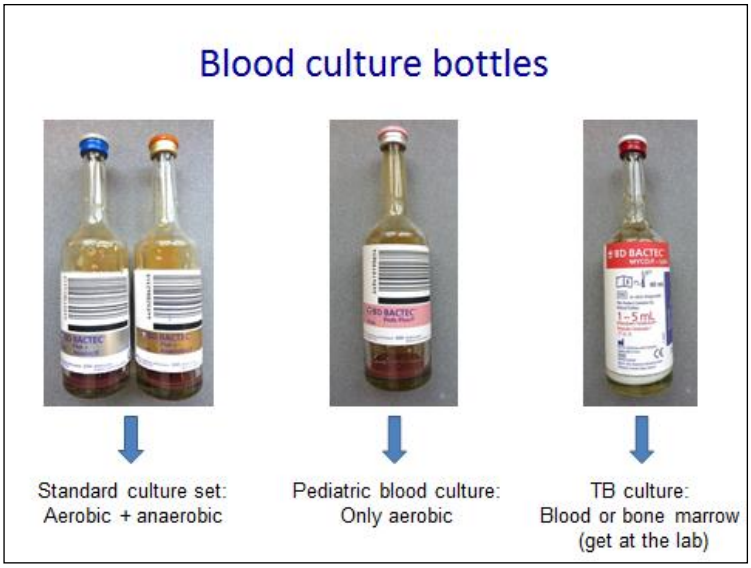
positively charged colistin molecule binds to the negatively charged lipopolysaccharides on the outer cell membrane of Gram-negative bacteria. It disrupts the cell membrane integrity, making it more permeable, ultimately leading to cell death.

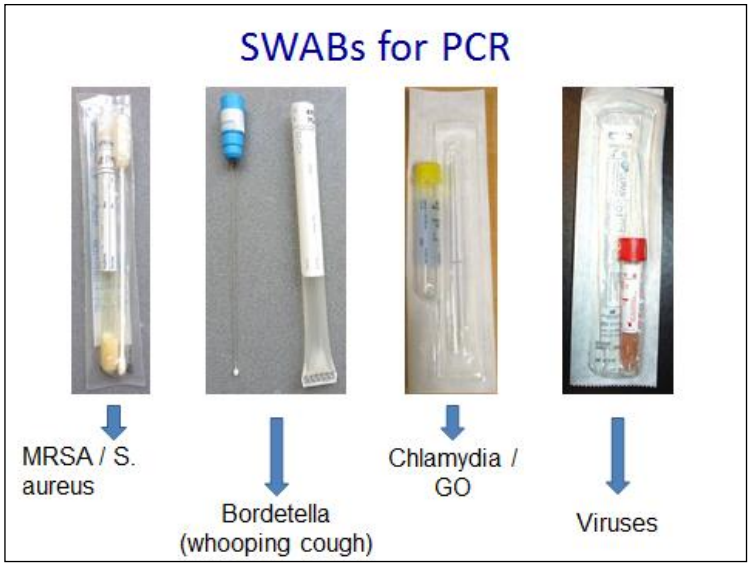
Systemic CMS is mainly used for the treatment of infections with multiresistant enterobacteriaceae (such as carbapenemase-resistant *E. coli* and *Klebsiella*) and non-fermenters (Acinetobacters and *P. aeruginosa*). If at all possible, colistin should be used only as a part of an antibiotic combination therapy. It is generally considered a less active antibiotic than the beta-lactams and reaches limited tissue levels. The only approved indication for monotherapy is urosepsis. Oral colistin is used for selective decontamination of the GI-tract in ICUs, inhaled colistin is used for respiratory infections / colonization with *Pseudomonas aeruginosa* in CF-patients. As with the aminoglycosides: inhalation therapy is not indicated for acute infection.

Different calculations of colistin quantity are used: **80 mg CMS = 33 mg colistin base activity = 1 Million international units.** Dosage recommendations have been going up over the last years, as peak plasma levels achieved with old dosages (1 M IU q8h) barely appeared to reach the susceptibility breakpoints. Currently the recommendation by the European Medicines Agency (EMA) for use in systemic infection is a loading dose of 9 M IU, followed by 4,5 M IU q12h or 3 M IU 18h (i.e.: 720 mg CMS loading dose, followed by 360 mg q12h or 240 mg q8h).

The main, infrequent, side effects of colistin are nephrotoxicity and neurotoxicity. Nephrotoxicity has been reported to be as high as 26% in older studies; new insight places this at a much lower level. Nephrotoxicity of CMS is less than that of the aminoglycosides. Also neurologic symptoms have been reported particularly in older literature, ranging from dizziness and paresthesias to visual disturbances, seizures and even neuromuscular blockade.

Materials for microbiological diagnostics





Advantages of swabs

-Often easier in use

-For some diagnostic procedures: part of a standardized process

Advantages of patient samples

-Possibility to make a direct stain

-More sensitive

-Possibility to test for a wide array of micro-organisms (such as mycobacteria, anaerobes)

-Materials are often stored during a certain period

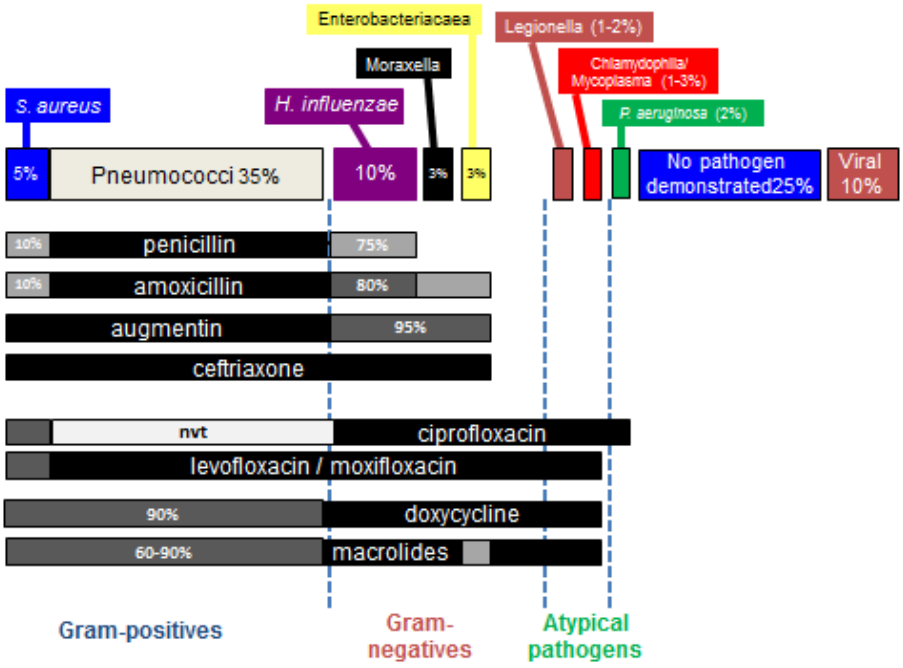
-Quantification easier

Community-acquired pneumonia (CAP)

Community-acquired pneumonia or CAP is an acute symptomatic infection of the lower respiratory tract. Gold standard is the finding of a new pulmonary infiltrate on imaging (chest CT or chest X-ray). To be classified as CAP (and not HAP) it has to be acquired outside the hospital or within 48 hours of admission. The incidence has been reported at 5-11 per 1000 per year in adults.

Overall mortality of CAP is estimated at 4-5 %. Using the PSI-score and the CURB-65 score, a more accurate estimation of mortality may be obtained for different patient groups. Depending on the geographic region, lower respiratory infections cause 4% to 8% of all deaths.

Pathogens CAP, with percentage susceptibility for commonly used antibiotics (The Netherlands)

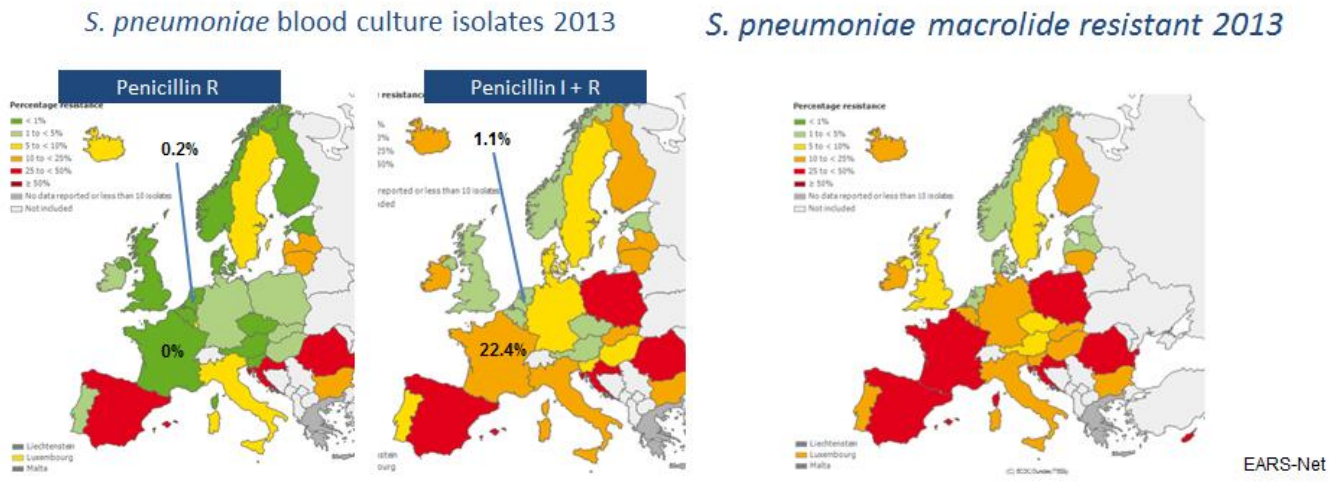


Resistance to CAP-pathogens

Pneumococci

MICs of pneumococci have been going up over the last decades. The breakpoints for resistance have gone up with them (from 0,06 mg/l to 2,0 mg/l). In many European countries, intermediately resistant and resistant pneumococci make up a large part of the isolates. Penicillin / beta-lactams are still considered first choice therapy, even for resistant isolates, but higher dosages are used of up to 4 million units 6 times/day. Thus far, penicillin-resistance has not been associated with therapeutic failure (but this may start to occur if MICs continue to rise). There is no true difference in susceptibility between penicillin, amoxicillin and ceftriaxone. Differences in choice and activity are

attributed to the dosages, resorption and distribution of the antibiotics. Since the mechanism of resistance resides in changes to the PBP and not in the production of beta-lactamases, the addition of clavulanic acid does not overcome resistance in pneumococci.



Resistance of pneumococci to macrolides is high troughout Europe. Data on tetracycline-resistance is scarce. It is believed to be stable at about 10%. Resistance to respiratory fluoroquinolones (levofloxacin, moxifloxacin) is still low, at approximately 1%, but may rapidly go up with increased use of these antibiotics.

H. influenzae

Resistance of H. influenzae to amoxicillin varies, mostly it is reported at around 20%. Resistance to augmentin is usually below 10%, but its significance is unclear (augmentin is probably still active).

Resistance to ceftriaxone and fluoroquinolones is practically non-existant, to tetracyclines usually lower than 3%. Resistance to macrolides is about 5-10%, but since correlation between activity and MIC is low, most strains are classified “intermediately resistant” (you can use it, but you cannot trust it too much).

Atypical CAP-pathogens

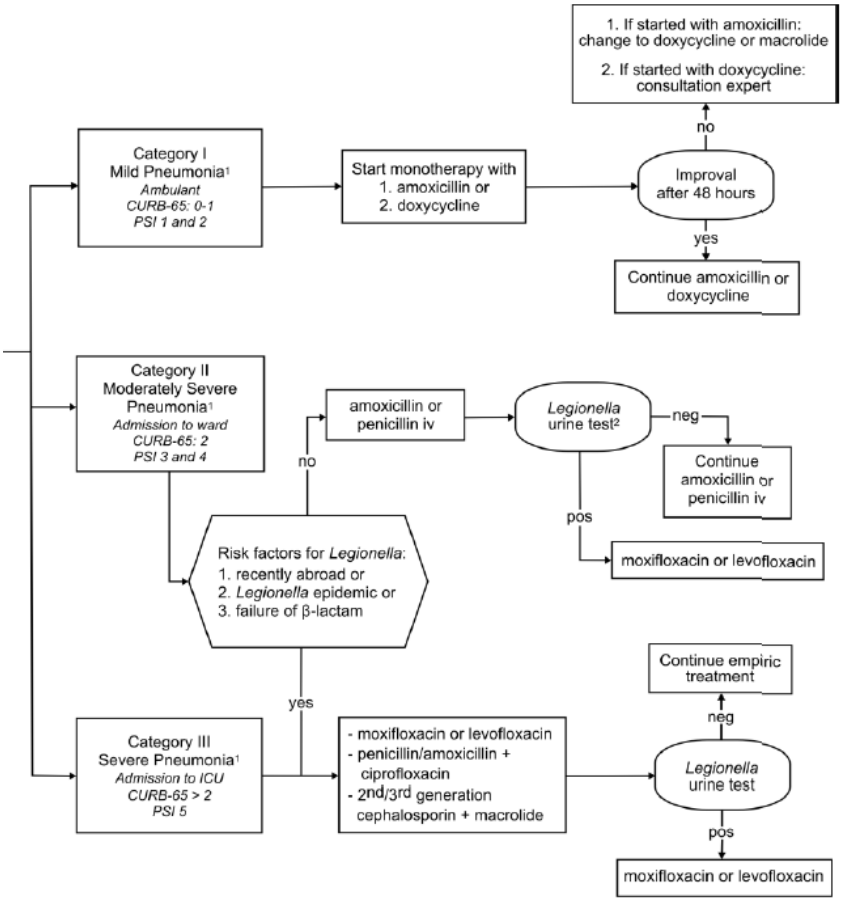
At this moment acquired resistance does not appear to be a problem in these pathogens (Legionella, Mycoplasma, Chlamydophila, Coxiella)

Empiric treatment of CAP, according to SWAB-guideline

The SWAB-guideline recommends to classify patient into three categories: mild pneumonia, moderately severe pneumonia and severe pneumonia. One of three classifications may be used. It is recommended to choose one for your hospital and adhere to it.

- Pragmatic: (1) Treatment as outpatient, (2) Admitted to ward, (3) Admitted to ICU

- CURB-65, acronym for: **C**onfusion of new onset; **U**rea > 7 mmol/l ; **R**espiratory rate > 30 breaths per minute or greater ; **B**lood pressure < 90 mmHg systolic or < 60 mmHg diastolic; age **65** or older. One point per element, added score determines classification
- PSI (pneumonia severity index) score or Fine score, see: www.longdoc.nl/formPSI.htm



Hospital-acquired pneumonia (HAP)

Pneumonia which presents itself 48 hours or more after admission to a hospital is designated hospital-acquired pneumonia, or HAP. When a patient is also on mechanical ventilation we talk about VAP (ventilator-associated pneumonia). A pneumonia acquired in a longterm care facility, by outpatients receiving intravenous antibiotic therapy or on dialysis, or by patients who have been admitted to a hospital in the preceding 90 days, is called a healthcare-associated pneumonia (HCAP). The causative pathogens of HAP, VAP and HCAP are grossly comparable, as is the therapy.

HAP is presumably caused by aspiration of bacteria from the oropharynx. Healthy people also aspirate – in particular during their sleep – but usually are capable of clearing these bacteria by coughing and through the action of the ciliated airway epithelial cells. Use of antibiotics and antacids,

and decreased ciliary function may change the bacterial flora of the oropharynx, which becomes more like the flora of the gut (more enterobacteriaceae, and more non-fermenters). These micro-organisms are possibly more pathogenic in the lungs than the flora of the upper airways.

When a patient aspirates massively (stomach contents or gastric tube feeding), he may develop what we call an "aspiration pneumonia", although in fact every HAP is an aspiration pneumonia. Stomach acid is sterile and usually causes a chemical pneumonitis; when antacids are used the chances of an infectious HAP increase.

Diagnosis of HAP

The distinction between a HAP and other causes of acute respiratory symptoms, such as atelectasis and sputum plugs, may be very hard. The gold standard for the diagnosis of HAP is a positive culture of a broncho-alvealar lavage (BAL) combined with a novel infiltrate on a chest X-ray. Een negative culture of BAL practically excludes a HAP.

However, especially in patients who are not intubated, diagnostics are often limited to a culture of sputum or of the oropharynx; these cultures may also be positive when a patient suffers from tracheobronchitis or merely represent colonization.

Antibiotic therapy for HAP / VAP / HCAP

Antibiotic therapy for HAP should be tailored to local epidemiology in hospitals and advice on empiric therapy differs significantly between countries and between centers.

The 2005 IDSA-guideline devides HAP in early (within 5 days) HAP and late (>5 days) HAP. In the first five days patients are not expected to have extensively resistant bacterial colonization of the oropharynx: MSSA, susceptible *E. coli*, *H. influenzae*, pneumococci. As empiric therapy a third-generation cefalosporin, a penicillin / betalactamase-inhibitor combination or even ertapenem is suggested. Selected studies have found a high proportion of more resistant micro-organisms in patients admitted more than five days, such as *P. aeruginosa*, MRSA and *Acinetobacter baumannii*. This epidemiology is, however, highly variable. In The Netherlands, for instance, MRSA and *Acinetobacter* are hardly encountered as nosocomial pathogens. Blindly following the IDSA-recommendations for empiric therapy, i.e. a combination of three drugs, would lead to gross, unnecessary overuse of antibiotics in many countries / centers. Most Dutch hospitals do not differentiate between early and late HAP for their choice of therapy.

Empiric therapy differs widely between hospitals. Usually a broad-spectrum penicillin or a 2nd or 3rd generation cephalosporin chosen, sometimes in combination with an aminoglycoside (in particular if the patient is unstable). Local epidemiology and culture results have to be taken into account, to decide whether ESBL and MRSA need to be covered. For MRSA-coverage a glycopeptide (vancomycin) or linezolid may be added. For ESBL-coverage either a carbapenem is used or an

aminoglycoside is added to the therapy. In general 7 days therapy suffices, for HAP by *P. aeruginosa* in general 14 days therapy is recommended.

Empiric choice HAP UMC Utrecht: ceftriaxone (ceftazidime if *P. aeruginosa*)
Empiric choice HAP Maastricht UMC: piperacillin/tazobactam

When massive aspiration occurs, and infection is suspected, many centers choose to include antibiotic coverage of anaerobic bacteria. Possibilities are using a penicillin (amoxicillin/clavulanic acid or piperacillin + tazobactam), or by adding metronidazole to the therapy.

Clostridium difficile infections

C. difficile is a Gram-positive, anaerobic rod that forms spores. These spores are highly resistant and are not killed by alcohol handrubs. (Hand desinfection is therefore not effective to counter hospital spread.) The bacteria are relatively resistant against antibiotics and outbreak-strains usually have MICs which are even higher. There is, however, currently no indication that relevant resistance to metronidazole or vancomycin has developed. Asymptomatic carriage of *C. difficile* occurs in 3% of adults and up to 50% of neonates. It is suggested that neonates do not suffer from this colonization because they lack the toxin-receptor in the gut.

The pathogenicity of *C. difficile* is determined by the production of two toxins: toxin A (or enterotoxin) and toxin B (or cytotoxin). Toxin B is 10x as potent as toxin A. Some strains are more pathogenic than others and more likely to produce outbreaks; this is probably due to the production of higher levels of toxins. The main example of such an epidemic strain is the 027 clone.

C. difficile causes diarrhea and colitis, in exceptional cases colitis without diarrhea. It is a nosocomial pathogen, generally associated with use of broad-spectrum antibiotic therapy. In severe cases it may cause pseudomembraneous colitis or even fulminant colitis and toxic megacolon. The typical white plaques or "pseudomembranes" are composed of proteins, leukocytes and mucus leaking from the intestinal wall; this leakage is caused by the toxins. In The Netherlands *C. difficile* causes 1,5% of community-acquired diarrhea.

Diagnostics for *C. difficile*

Clostridium difficile infections can be diagnosed by tests that detect the toxins (rapid tests or tests against cell lines) or by PCR-tests (directed at the genes for the toxins) and by culture. Culture of *C.difficile* is also possible, but is in general only used for typing of isolates during outbreaks.

Therapy van *C. difficile*

If a patient with a *C. difficile* infection is using antibiotics, these need to be stopped (if possible). Often this will suffice as treatment. First-line antibiotic treatment is oral metronidazole 500 mg q8h, 10 days. Second choice is oral vancomycin 125 mg or 250 mg q6h, 10 days. 250 mg is available as a capsule, 125 mg is available as orally taken iv-fluid. For severe infections vancomycin is advised. Fidaxomicin may be an alternative.

In case of critical situations, in which oral administration is not possible, intravenous metronidazole may be administered (500 mg q8h), if needed combined with vancomycin through nasogastric tube or by enema. Surgical interventions may in exceptional cases be indicated.

Approximately one fourth of the patients suffers a relapse or reinfection after antibiotic therapy. Definitive clearance of the infection may prove difficult, in particular in patients with

extensive co-morbidities. For a first relaps either the original therapy with metronidazole is repeated or the patient is treated with vancomycin. If the infection continues to relaps, several different treatments can be attempted (Dutch SWAB-guideline):

-Fidaxomicin 500 mg q12h, 10 days

-Vancomycin tapering scheme (see for instance the SWAB-guideline for possibilities)

-Longer treatment with metronidazole or vancomycin: 10-14 days

-Faecal transplant: the patients receives intestinal flora of a healthy “donor”.

For other treatments clinical evidence is insufficient or non-existent. Succesfull treatment with tigecycline (intravenous) has been described in a few case reports. Effect of probiotics has never been demonstrated.

Intra-abdominal infections / peritonitis

Intra-abdominal infections are subdivided into primary and secondary infections.

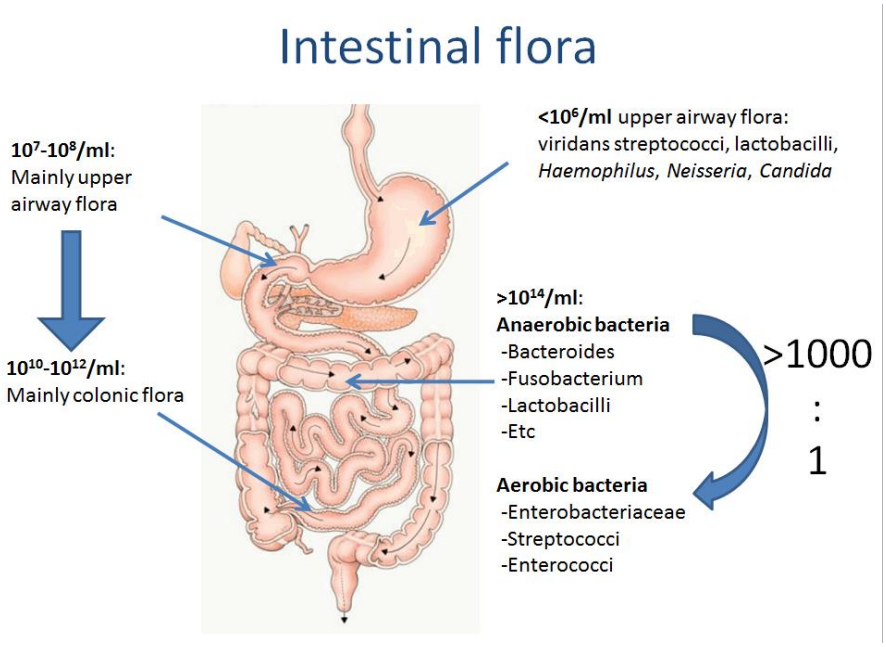
Primary intra-abdominal infections / spontaneous bacterial peritonitis (SBP)

In spontaneous bacterial peritonitis micro-organisms reach the peritoneal cavity via the blood flow or lymphatic flow. The intestines are intact. This occurs almost exclusively in patients with pre-existing ascites. The main pathogens are enterobacteriaceae, pneumococci and sporadically Candida spp. The diagnosis is made based on the granulocyte count in the ascites. (Cut-off >0,5 10^9/liter, or >0,25 10^9/liter.) The bacterial load is often very low; therefore microbiological diagnostics are usually performed by directly inoculating the perioneal fluid into blood culture bottles.

Empirical antibiotic therapy usually consists of ceftriaxone (1 dd 2 grams), 10-14 days.

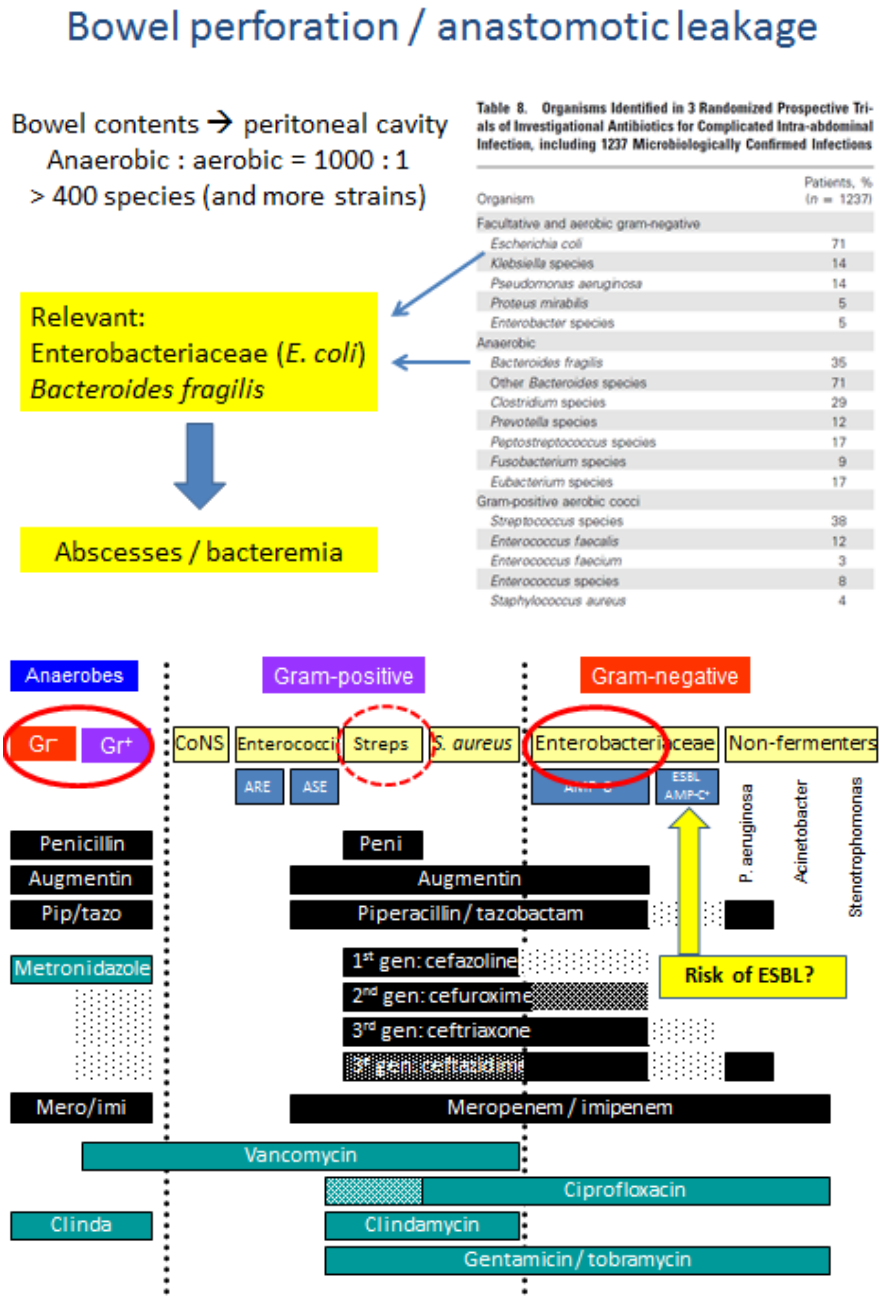
Secondary intra-abdominal infections

Secondary peritonitis develops if intestinal flora reaches the peritoneal cavity through perforations (sometimes micro-perforations). This flora varies throughout the intestinal tract. In the proximal tract it contains a limited load of upper airway flora, more distally in the gut the bacterial load increases and anaerobes, enterobacteriaceae, and enterococci start to predominate (next to the streptococci which can also be found in the more proximal parts). The colonic flora is composed of 99.9% anaerobes.



Use of antacids and/or mechanical ventilation elicits changes in the flora of stomach and duodenum: the bacterial load increases and the patient may become colonized with enterobacteriaceae, Pseudomonas and Candida.

Although an average person will have more than 400 different bacterial species coolonizing his gut (and many more different bacterial strains), only a minor part of these are responsible for the infectious complications in secondary peritonitis. These are mainly enterobacteriaceae and *Bacteroides fragilis*. Enterobacteriaceae often cause bacteremia, Bacteroides spp are mainly responsible for abscess formation.



Multiple options are available for antibiotic therapy in abdominal infections. Mainstay of therapy consists of coverage of Gram-negative anaerobes and enterobactericeae. The role of enterococci and Candida species in peritonitis is unclear, but in any case quite limited.

Enterococci are not capable of causing abscesses by themselves and are very rare causes of bacteremia from an abdominal focus; in community-acquired secondary peritonitis and in animal models no added value has been found in their antibiotic coverage. Isolation of enterococci from the abdominal cavity is, however, an unfavorable prognostic sign. Specific enterococcal therapy is only added if the bacteria are demonstrated and not drained. It may be considered empirically in very severe infections not reacting to primary therapy.

Also Candida spp are regularly isolated from abdominal cultures without causing complication. As with enterococci, coverage for Candida should be restricted to cases where the yeast has actually been isolated, and only considered empirically in severe infections not responding to primary therapy.

Common antibiotic policies for (prevention of) secondary peritonitis

Profylaxis for abdominal surgery:

- Cefazolin + metronidazole

Community-acquired infection / perforation:

- Ceftriaxone + metronidazole OR augmentin + gentamicin
- Consider the need to cover ESBL
- Adapt therapy to culture results if needed

Hospital-acquired infection / perforation:

- Ceftriaxone + metronidazole (+/- gentamicin)
- Consider the need to cover ESBL
- Adapt therapy to culture results if needed
- Consider coverage of enterococci and/or Candida if isolated and empirically in severe infections not responding to primary therapy

Duration of antibiotic treatment (IDSA-guideline)

Profylaxis / no spill in abdominal cavity

- Maximum 24 hrs

Perforation of stomach / duodenum / proximal jejunum

- If surgery within 24 uur, no use of antacids and no malignancy: maximum 24 hrs

Adequate source control

- Standard 4 days[1], maximum of 7 days

Persisting perforation

- Depending on clinical picture

Pyogenic abscesses (including liver): if possible perform drainage

- Drained: 2-4 weeks
- Not drainabel: 4-6 weeks

[1]Based on a study by Sawyer e.a. (NEJM 2015 PMID 25992746) we would recommend 4 days as a standard. In this study no difference in outcome was found between a standardized duration of 4 days and a duration based on symptoms (fever, leukocytosis, ileus) with a median of 8 days. Both groups had 20% complications (surgical site infection, recurrent intra-abdominal infection or death).

Cholangitis / cholecystitis

Cholangitis: obstruction of bile ducts with secondary infection

Cholecystitis: inflammation / infection of the gall bladder without acute obstruction

In principle only coverage of enterobacteriaceae is required: anaerobes are rare as cause and enterococci are considered to be of low virulence. In practice, however, the antibiotics of choice often also cover these micro-organisms.

Antibiotic policy UMCU:

- Cholecystitis, resection of gall bladder: no antibiotics (besides operative prophylaxis).
- Cholecystitis, no resection of gall bladder: augmentin 10-14 days.
- Cholangitis: augmentin + gentamicin. If adequate drainage has been secured and fever has subsided: stop after 24 hrs.
- Cholangitis with bacteremia: augmentin + gentamicin. If adequate drainage has been secured and fever has subsided: stop after 3 days.

Pancreatitis

Usually sterile process → inflammation due to the action of pancreatic enzymes

Can necrotize and become secondarily infected.

- Usually monobacterial infection
- Mainly enterobacteriaceae; sporadically *Pseudomonas*, Gram-positives or *Candida*

RCTs: no advantage of antibiotic therapy in acute pancreatitis → antibiotics only in severe pancreatitis with > 30% necrosis.

- Broad Gram-negative, Gram-positive and anaerobic coverage
- Adapt therapy to culture results
- If needed: drainage of necrosis

Skin and soft tissue infections

Many classifications of skin and soft tissue infections can be made. Here we use:

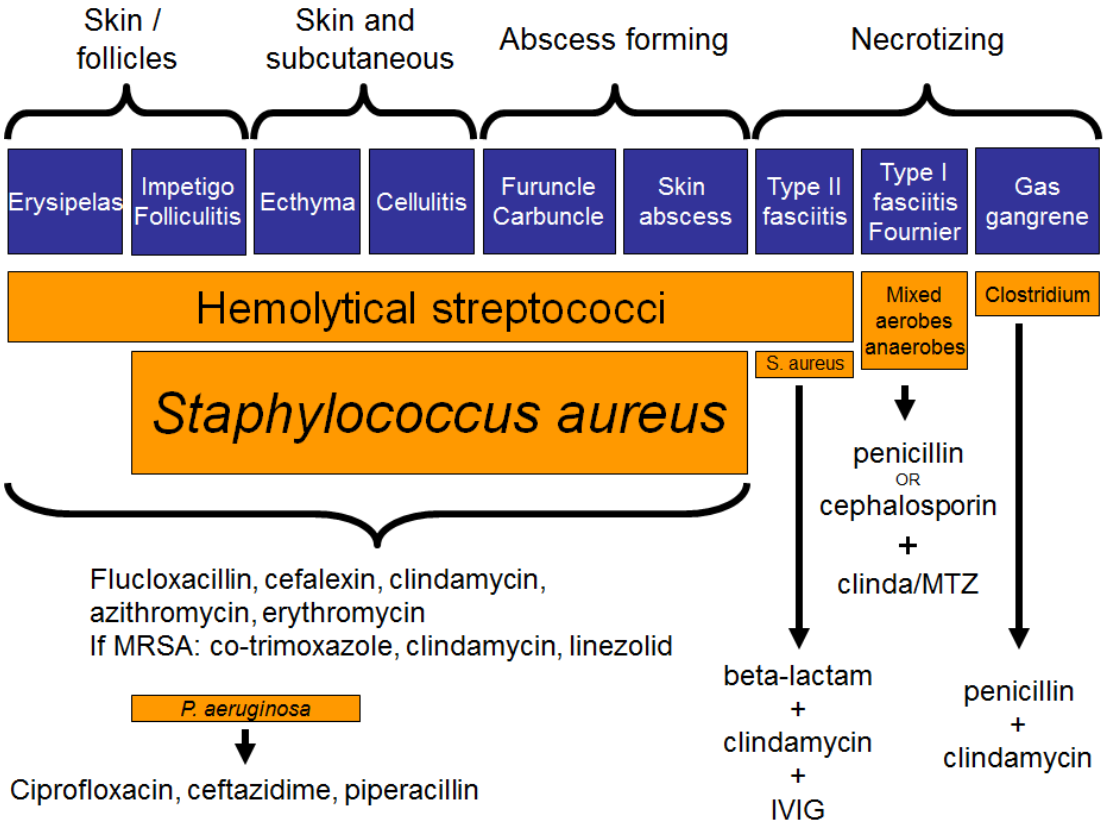
(1) Superficial infections of skin and follicles

(2) Infections in which subcutaneous tissue is involved

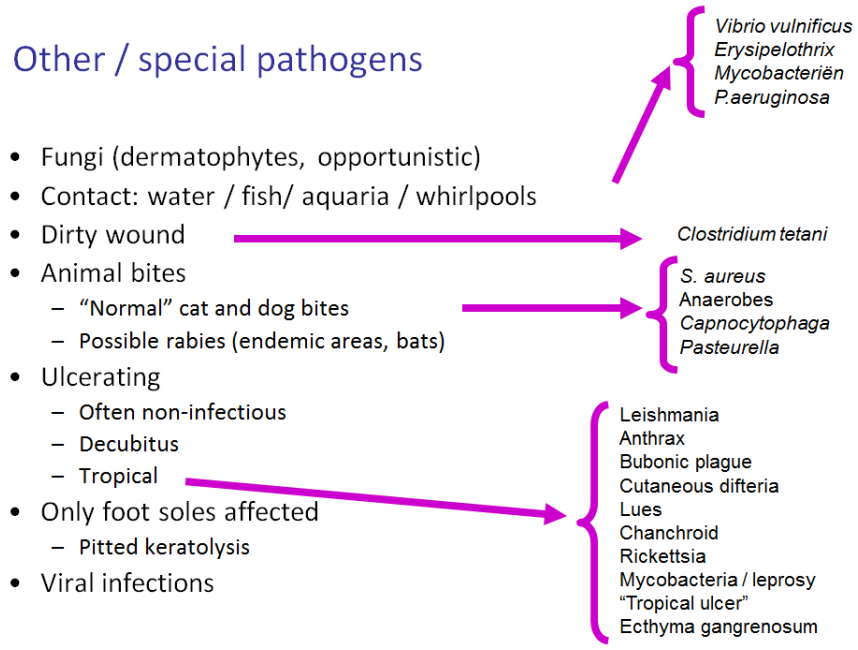
(3) Infections with abscess formation

(4) Ulcerating infections

(5) Necrotizing (expanding) infections



Most infections of skin and soft tissue are caused by Gram-positive cocci: *Staphylococcus aureus* and hemolytic streptococci (Group A / *S. pyogenes*, sometimes group C or G / *S. dysgalactiae*). However, if the infection does not respond to therapy, in case of specific clinical presentations or in case of certain anamnestic clues (contact with animals, contact with water, travel abroad) other pathogens should also be considered.



Ulcerating infections ("ecthyma") may also be caused by *S. aureus* and hemolytic streptococci. In immunocompromized patients this may, however, be caused by ecthyma gangrenosum, a disease in which septic emboli cause skin ulcerations. Usually the pathogen is *P. aeruginosa*, and antibiotic therapy should be adapted accordingly.

Therapy for skin infections

Therapy for most skin infections can be treated with an oral beta-lactam antibiotic such as (flu)cloxacillin or cefalexin, with alternatives being clindamycin or a macrolide. Resistance of Gram-positive cocci against beta-lactam antibiotics is very rare in The Netherlands (<1%); resistance against macrolides and clindamycin is somewhat more frequent (+/-10%). Strains resistant to clindamycin are also resistant to macrolides. In regions where community-acquired MRSA is frequent, other antibiotics may be used. Often co-trimoxazole or clindamyin are then first choice, although CA-MRSA may be resistant to these pathogens. An alternative oral agent is linezolid to which resistance of MRSA almost does not occur. For some superficial infections (impetigo, erysipelas) topical therapy may be an option.

Necrotizing fasciitis

Necrotizing fasciitis is subdivided into type I and type II infections. Type I infections are caused by mixed flora, usually including anaerobes; generally these occur around the perineum or in the head and neck area. Type II infections are monobacterial and are caused by Group A streptococci, sometimes in combination with *S. aureus* or even by *S. aureus* alone; these infections usually affect the extremities.

Characteristics of necrotizing fasciitis are inflammation of the skin with rapid extension, severe pain (more severe than the affliction of the skin appear to justify), high inflammatory parameters, and an elevated creatine kinase (CK). Echography may give indications to whether or not the patient suffers fasciitis, but the diagnosis is finally made by surgical exploration.

The primary therapy is surgical. Type I infections are treated with broad spectrum therapy against Gram-positive cocci, Gram-negative rods and anaerobes. For instance ceftriaxone + metronidazole, ceftriaxone + clindamycin, piperacillin/tazobactam, or augmentin + gentamicin.

Type II infections are treated with a beta-lactam antibiotic (for instance penicillin) + clindamycin (to inhibit toxine production by Group A streptococci) + intravenous immunoglobulins (IVIG, to neutralize toxins). The evidence for treatment with clindamycin and with IVIG is from retrospective studies and from one underpowered clinical trial, and some centers may find this insufficient for a drug as expensive as IVIG. At the UMC Utrecht, however, the choice has been made to use it.

Urinary Tract Infections

Urinary tract infections (UTIs) usually cause complaints of a painful, frequent voiding. The main causative pathogens are *E. coli*, *Klebsiella*, enterococci and *Proteus mirabilis*, together responsible for 90% of the community-acquired infections and for 85% of the nosocomial infections. Recently, it has come into doubt whether cultures with enterococci (de facto: *E. faecalis*) truly represent UTIs or should be generally regarded as contamination. If the infection is limited to the bladder, we talk about cystitis. When the infection ascends to reach the pyelum and the kidney tissue, it may cause a pyelonephritis (or pyelitis), which is characterized by fever and / or flank pain and costovertebral angle tenderness. When the infection causes severe systemic symptoms, it becomes a urosepsis.

Diagnosis of urinary tract infections

Little research has been done into sensitivity, specificity and predictive value of diagnostics in urinary tract infection, and a gold standard is lacking. Generally, the diagnosis is made based on the combination of bacteriuria and leukocyturia/pyuria. The differential diagnosis consists mainly of vaginatis and urethritis.

Bacteriuria

A clear cut-off point for the number of bacteria per ml of urine (cfu's/ml) to establish UTI does not exist. Cut-offs between 10^2 and 10^5 per ml have been suggested and used, the former probably too aspecific, the latter probably too little sensitive. Interpretation based on a combination of the bacterial load with the presence or absence of leukocyturia may improve the diagnostic accuracy. At the UMC Utrecht, usually $\geq 10^4$ cfu's/ml is applied. If symptomatology is suspect or the patients suffers pyuria the cut-off is lowered to $\geq 10^3$ cfu's/ml; at the infectious diseases outpatient clinic UTI is considered already when a patient has $\geq 10^2$ enterobacteriaceae or enterococci in his/her culture.

Erroneously high cfu-counts may occur as a result of faecal contamination of the sample, or due to too long transportation times (bacteria keep growing). Erroneosly low cfu-counts may occur as a result of frequent voiding, the use of antibiotic therapy, slow-growing micro-organisms (such as yeasts), single-sided pyelonephritis and due to obstruction of a urether.

Leukocyturia

Leukocyturia may be determined by:

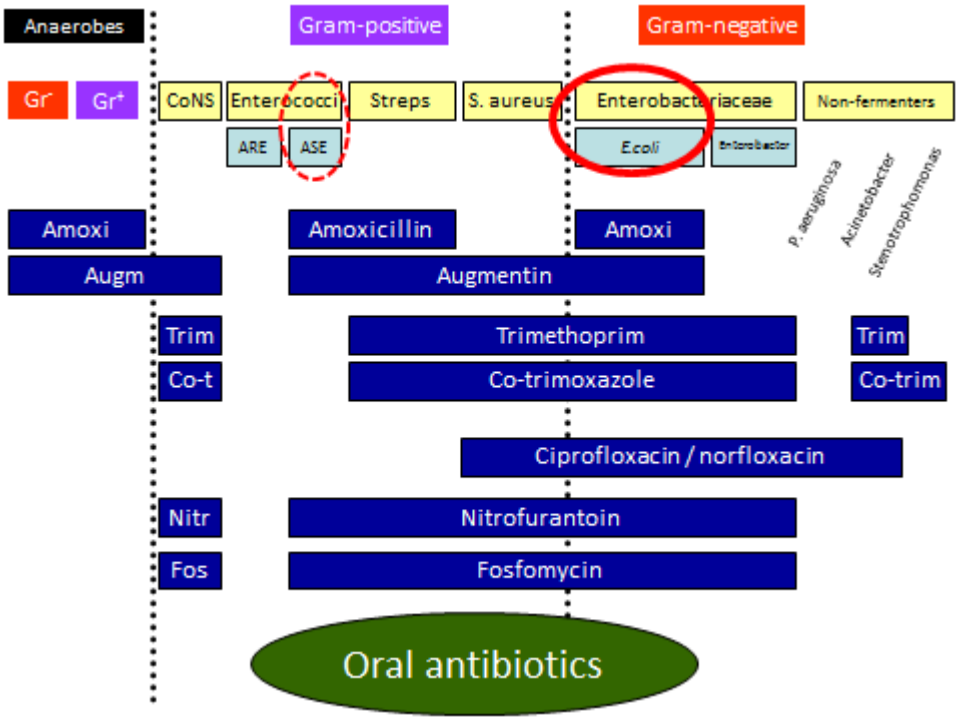
-Microscopy (stained or unstained): the numbers of leukocytes are reported per high-power field (hpf). The cut-off applied is usually 5 or 10 leukocytes/hpf

-(Flow)cytometrometry. The number of leukocytes are reported per µl. Usually 25 leukocytes/µl is considered the cut-off.

-Measurement of leukocyte esterase by dipsticks. A color reaction occurs on the stick as a result of enzymatic action by the leukocytes. Often this is translated to a corresponding number of leukocytes / µl.

Therapy of UTIs

The empiric therapy for UTIs should target enterobacteriaceae. In some cases it is considered necessary to also cover enterococci, although it is questionable whether these can truly cause UTIs in the absence of obstruction. In the choice of antibiotic therapy, previous culture results and local epidemiology should be considered. Antibiotics that achieve high urinary concentrations are chosen. In case of pyelonephritis or urosepsis, the antibiotic should also achieve adequate tissue levels. For treatment cystitis specific UTI-antibiotics such as nitrofurantoin and fosfomycin can be used which do not have a place in the treatment of other diseases and are not expected to cause cross-resistance.



Therapy for asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as 2 separate cultures demonstrating bacteriuria ≥ 10^5 cfu's/ml without symptoms. In principle no treatment is indicated (IDSA-guideline), unless the patient will undergo a procedure in the urinary tract. Evidence from doubleblind randomized studies suggest that treatment of asymptomatic bacteriuria may in fact increase the risk of UTI.

Previously it was thought that pregnant women should be screened for asymptomatic bacteriuria and treated to avoid pyelonephritis and premature births. However, a recent Dutch study found no effect on the occurence of premature birth and a number needed to treat of 40 to prevent one case of (treatable) pyelonephritis (Kazemier e.a., Lancet ID, online aug 2015).

Therapy for cystitis

Dutch NHG / SWAB-guideline

1st: nitrofurantoin 100 mg q12h, 5 days

2nd: fosfomycin 3 grams once

3rd: trimethoprim 300 mg once daily, 3 days

Men, girls < 12 years, diabetic patients

1st: nitrofurantoin 100 mg q12h, 7 days

2nd: trimethoprim 300 mg once daily, 7 days

Pregnant women

1st: nitrofurantoin 100 mg q12h, 7 days (not around delivery)

2nd: augmentin 625 mg q8h, 7 days

Other guidelines / recommendations

The Sanford Guide recommends co-trimoxazole (if resistance <20%) as first choice, with nitrofurantoin and fosfomycin as alternatives.

The IDSA-guideline and UpToDate suggest a choice of nitrofurantoin, co-trimoxazole, trimethoprim, fosfomycin or pivmecillinam (the latter is used in selected countries).

Therapy in pyelonephritis

Adequate renal tissue levels required, therefore nitrofurantoin and norfloxacin are not considered good choices. Experience with fosfomycin is too scarce (also, if used, higher dosages would probably be needed than in cystitis).

Dutch NHG / SWAB-guidelines

1st: augmentin 625 mg q8h, 10 days

2nd: co-trimoxazole 960 mg q12h, 10 days

3e: ciprofloxacin 500 mg q12h, 10 days

Sanford Guide: fluoroquinolones (5-7 days). Alternatives: augmentin, co-trimoxazole, ceftibuten (all 14 days)

IDSA-guideline: 1st fluoroquinolones, 2nd co-trimoxazole, 3rd beta-lactam antibiotics

Therapy for cystitis / pyelonephritis with urinary catheter in place

One month after catheterisation almost 100% of patients has bacteriuria. In 1-4% of the cases this will lead to fever and/or bacteremia. The risk of ascending infection is particularly high when obstruction of the catheter occurs. Pyuria has a low positive predictive value for UTI, but absence of pyuria makes UTI highly improbable. The diagnosis is therefore mainly based on the urine culture and clinical symptoms. The symptoms —fever, rigors and chills, malaise, cognitive changes, flank pain, acute hematuria— may sometimes be non-specific.

Before antibiotic treatment is initiated, urine cultures should always be performed. If possible, results should be awaited for tailored therapy. In principle the choice of antibiotics is the same as for UTIs without a catheter. In case of systemic symptoms treatment should be prolonged to 10 days, else 5 days will suffice. The catheter should be exchanged as part of the treatment.

There is no evidence for the use of prophylactic antibiotics for catheter removal or exchange.

Therapy in severe pyelonephritis and urosepsis

Severe pyelonephritis and urosepsis are the main cause of Gram-negative sepsis / bacteremia. Therapy is principally directed at enterobacteriaceae. Enterococci are only very rarely the cause of urosepsis (mostly due to acute obstruction). The initial treatment is intravenous, and the in the choice of antibiotics, previous culture results, prior antibiotic therapy and general epidemiological data should be considered.

Choice of therapy is in general a beta-lactam antibiotic: a 2nd or 3rd generation cephalosporin or a penicillin/beta-lactamase inhibitor combination. Often the beta-lactam is combined with an aminoglycoside, to broaden the spectrum and to achieve more rapid sterilization of the blood (although it not determined whether this improves the outcome).

If the risk is high that the infection is caused by a strain resistant to 2nd / 3rd generation cephalosporins and penicillin/beta-lactamase inhibitor combinations —because of specific patient risk factors, patient cultures or based on local epidemiology— the empiric therapy needs to be adapted. Such resistant strains are usually ESBL-producing enterobacteriaceae. Therapy may be adapted by the addition of a second antibiotic (usually an aminoglycoside), or by treating with a carbapenem.

Dutch SWAB-guidelines:

No culture results / no ESBL-positive cultures, options:

-Ceftriaxone (+/- gentamicin)

-Cefuroxime (+/- gentamicin)

-Amoxicillin + gentamicin

-Augmentin

Risk factor for ESBL (=recent use of cephalosporin or fluoroquinolone)

-Add gentamicin to therapy

<u>Proven ESBL-carrier in previous 12 months</u>:

-Carbapenem (meropenem or imipenem)

Sanford guide:

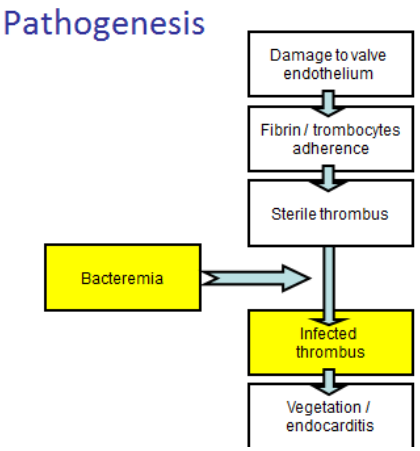
- Fluoroquinolone (iv), ampicillin + gentamicin, ceftriaxone, piperacillin/tazobact
- Alternative: ertapenem, doripenem

IDSA: no guideline urosepsis

Endocarditis

Endocarditis is an infection of the intracardial epithelium, in which usually the cardiac valves are affected. The infection may be limited to formation of a vegetation, but may also progress to valve destruction, formation of cardial abscesses and even fistula formation. Endocarditis is classified according to the affected valves (left sided vs right sided), based on the type of valve (native, with congenital malformation, prosthetic valve), based on the circumstances of infection (community-acquired, hospital-acquired, in iv-drugs use), and based on the clinical picture: acute vs subacute. The clinical difference between acute and subacute endocarditis (in the pre-antibiotic era these terms indicated the expected time until death of the patient) distinguishes between likely pathogens of the disease and is relevant for its prognosis. Acute endocarditis has a higher mortality –20%, vs 10% in subacute endocarditis – and patients are more likely to experience embolic complications.

- Acute endocarditis
    - Fulminant progression, high fever, severe sepsis
    - Destruction of the affected valve
    - Likely pathogens: *S. aureus*, CoNS, pneumococci, hemolytic streptococci
- Subacute endocarditis
    - More indolent progression, often patients have fever / subfebrile temperatures for longer periods of time
    - Likely pathogens: Viridans streptococci, *S. gallolyticus*, enterococci, HACEK-groep, Coxiella



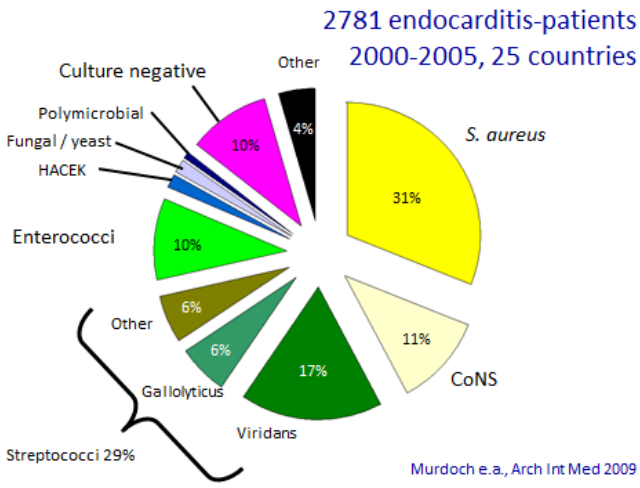
Endocarditis probably develops by infection of damaged valve endothelium. In animal models it has proven nearly impossible to induce endocarditis without prior mechanical damaging of the animal's valve.

Symptoms of endocarditis

- Fever, malaise, fatigue
- Complications of emboli
  - Splinter hemorrhages, petechiaea → peripheral abscesses, CVA's
- Hemodynamic symptoms
  - Murmurs (85%), dyspnea, shock
- Anemia
- Immunological symptoms / circulating immuuncomplexes: glomerulonefritis, Osler nodes

Causative pathogens in endocarditis

The main causative pathogens in endocarditis are staphylococci (*S. aureus* and CoNS), streptococci and enterococci. The relative frequency is dependent on the underlying co-morbidities. In nosocomial infections *S. aureus* is mostly encountered; in case of prosthetic heart valves CoNS are relatively more frequent. Infections with *Streptococcus gallolyticus* and *Streptococcus infantarius* (previously called "*Streptococcus bovis*") are strongly associated with colonic malignancies and are an indication for coloscopy.



Pathogens in non-reference centers

(Selton-Suty e.a., CID 2012)

Microorganisms	No. (%) of Patients (n = 497)	
Streptococcaceae	240	(48.3)
Streptococci	180	(36.2)
Oral streptococci[a]	93	(18.7)
Group D streptococci[b]	62	(12.5)
Pyogenic streptococci	25	(5.0)
Enterococci	52	(10.5)
Other Streptococcaceae[c]	8	(1.6)
Staphylococcaceae	180	(36.2)
Staphylococcus aureus	132	(26.6)
Coagulase-negative staphylococci	48	(9.7)
Other microorganisms[d]	42	(8.5)
HACEK group	6	…
Enterobacteriaceae	4	…
Propionibacterium acnes	4	…
Pseudomonas aeruginosa	3	…
Lactobacillus species	2	…
Corynebacterium species	2	…
Coxiella burnetii	2	…
Bartonella quintana	1	…
Tropheryma whipplei	1	…
Candida species	6	…
Miscellaneous[e]	11	…
≥2 Microorganisms[f]	9	(1.8)
No microorganism identified	26	(5.2)

In case of suspected endocarditis three sets of blood cultures should be drawn with an interval of at least 15 minutes. The first set (and preferably also the second and third) should be drawn before antibiotic therapy is initiated. If positive, the blood cultures should be repeated until they remain negative to monitor whether the treatment is effective (for instance every 48 hours). Persistingly positive blood cultures indicate inadequate therapy: either the antibiotics should be revised or surgical intervention may be required.

Some pathogens in endocarditis are slow growers, in particular the Gram-negative bacteria in the HACEK-group. Blood cultures in suspected endocarditis are therefore incubated two weeks instead of the usual 5-7 days. (Although in general, due to improvements in culture media, also the HACEK-organisms now usually grow within a maximum of 4 days.) Test forms that accompany these blood cultures should clearly state the suspicion of endocarditis.

Negative blood cultures in endocarditis patients are usually caused by the administration of antibiotics before blood cultures were drawn. However, in some cases endocarditis is caused by micro-organisms which are not cultered in routine diagnostics, namely:

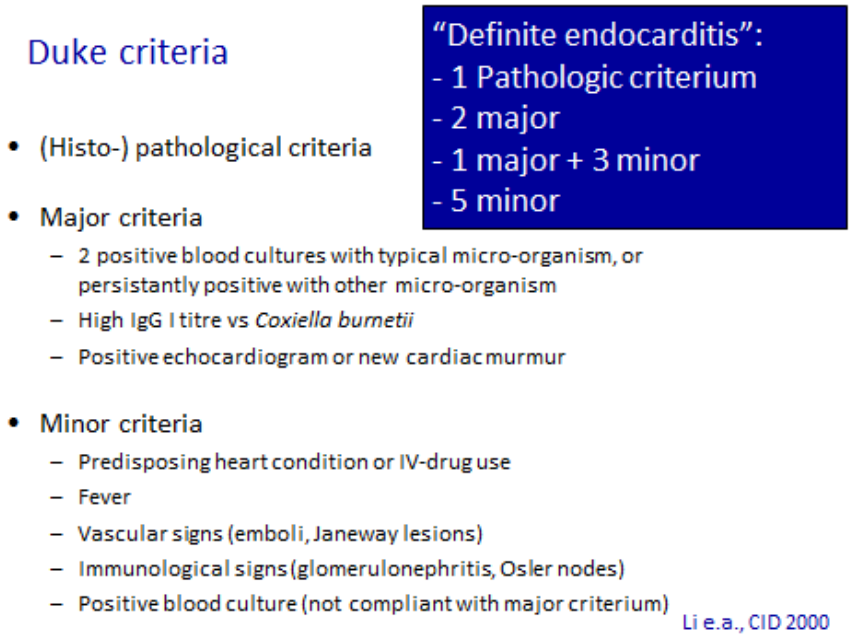
- *Coxiella* / Q-fever: demonstrate by serology or PCR
- *Brucella*: may be cultured (blood culture), but is more rapidly detected by serology. Always mention a suspecion of Brucellosis on the test form, because of the risk of lab-contagion.
- *Bartonella* (cat scratch disease): serology
- *Tropheryma whipplei* (M. Whipple): PCR
- *Chlamydia* / *Mycoplasma*: serology or PCR

For diagnostics into these diseases it is generally recommended to consult a microbiologist or ID-specialist.

Diagnosis of endocarditis / imaging

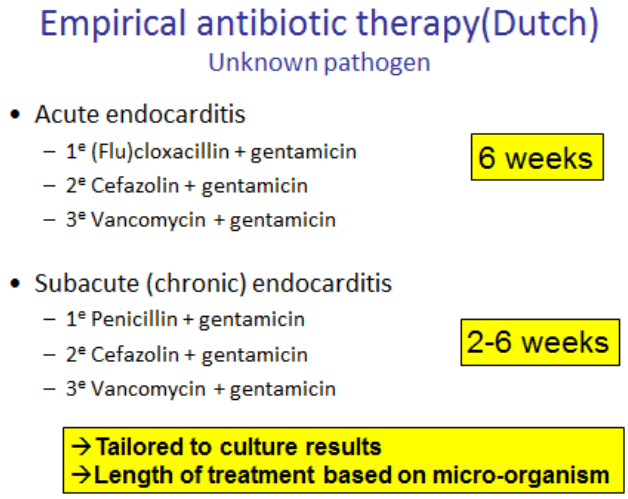
The diagnosis of endocarditis resides in the combination of microbiological criteria (demonstrating a likely pathogen) and anatomical criteria (suspect imaging / pathology). The Duke criteria were developed for scientific purposes and classify cases as “possible”, “probable” or “definite” endocarditis.

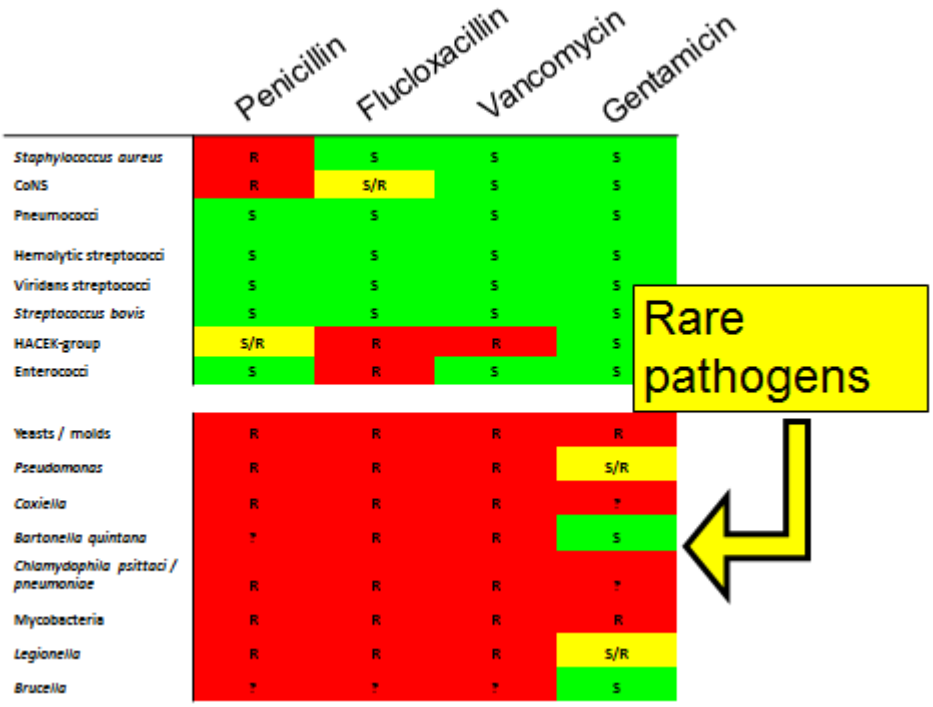
Imaging usually consists of echocardiograpy. Transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography (TTE), in particular in patients with prosthetic valves, valvular abscesses and small vegetations. However, to detect abscesses within the myocardium (e.g. septum) TTE also relatively unsensitive. Other, more recent imaging modalities, such as PET-CT or CAT-scans of the heart may be better suited to detect such lesions.



Treatment of endocarditis

Endocarditis is always treated with antibiotics; sometimes the disease requires also surgical intervention. Bacteria accumulate in high densities in the vegetations, are protected by biofilms and difficult to reach for leukocytes. Therefore, antibiotics are dosed higher than for other infections and preferably bactericidal antibiotics are used. In principle, the full treatment is administered intravenously. The empirical choice is based on the clinical presentation (acute versus subacute), the definitive choice of agents and the length of treatment are determined based on the isolated pathogens.





Surgical intervention is indicated in case of:

- Heart failure
- Valve destruction / severe insufficiency mitral or aortic valve
- Fungal endocarditis or endocarditis with extensively resistant micro-organism
- Abscesses or fistula
- Vegetations >10 mm (risk of embolic complications)
- Emboli, unless already a cerebrovascular accident has occured (relative contra-indication due to intracerebral bleeding with anticoagulative therapy)

In a randomized study with endocarditis patients who suffered severe valve dysfunction, patients who underwent surgery promptly had the same overall survival but fewer embolic complications than patients for whom the surgery was postponed (http://www.ncbi.nlm.nih.gov/pubmed/22738096).

Endocarditis prophylaxis

Indications for endocarditis prophylaxis were previously very non-specific and included patients with very limited risk of the disease, with a number needed to treat to avoid one case of endocarditis of roughly 20.000. The indications have therefore been severely reduced to three catogories of patients:

- Patients who have suffered endocarditis previously
- Patients with prosthetic valves (including bioprostheses)
- Certain congenital heart diseases

For the exact indications see: http://www.webshop.hartstichting.nl/producten/producten.aspx?CatID=71&pID=3765 or: http://circ.ahajournals.org/content/116/15/1736.long or: http://jac.oxfordjournals.org/content/57/6/1035.long

Choice of prophylaxis Dutch guideline:

- Dental procedures / upper airways (coverage of streptococci)
    - Amoxicillin 3 gram po / 2 gram iv
    - 2nd: clindamycin 600 mg po
- Tractus digestivus / urogenitalis (*if* antibiotics are indicated: cover also enterococci)
    - Amoxicillin 3 gram po / 2 gram iv
    - 2nd: vancomycin 1 gram iv
- Surgery in infected area, such as skin abscess / furuncle (cover *S. aureus*)
    - (Flu)cloxacillin 2 gram po
    - 2nd clindamycin 600 mg po

Choice of prophylaxis British Society of Antimicrobial Chemotherapy guideline:

- Dental procedures / upper airways (coverage of streptococci)
    - Amoxicillin 3 gram po / 2 gram iv
    - 2nd: clindamycin 600 mg po
- Other procedures (coverage streptococci, enterococci and staphylococci; staphylococci covered by gentamicin)
    - Amoxicillin 1 gram iv + gentamicin 1,5 mg/kg iv
    - 2nd: teicoplanin 500 mg iv + gentamicin 1,5 mg/kg iv

Staphylococcus aureus bacteremia and endocarditis

S. aureus bacteremia is strongly associated with endocarditis (a priori chance of endocarditis 12%). In cases of persistingly positive blood cultures with *S. aureus* or persisting fever despite adequate antibiotic therapy and no alternative focus, endocarditis should be excluded.

Intravascular catheter-related infections / “line-infections”

Line infections are the most common causes of nosocomial bacteremia. They develop when bacteria or fungi colonize an iv-catheter, form a biofilm and disperse through the circulation. Colonization of a catheter can be on the outside or on the inside; the latter being more difficult to demonstrate by laboratory culture. Micro-organisms reach the catheter through (1) the skin, (2) hubs in the infusion system, (3) the circulation, or (4) contaminated infusion fluids.

The incidence is dependent on the type of iv-catheter. A review of 200 studies (Maki e.a., Mayo Clinic Proceedings 2006) found the following incidences:

- Port-a-cath: 0.1 / 1000 line days
- Tunneled catheter: 1.6 / 1000 line days
- Arterial line: 1.7 / 1000 line days
- Standard central line: 2.7 / 1000 line days

The main pathogens differ per country and per hospital, but generally the top 5 is the following:

- 1: CoNS
- 2: *Staphylococcus aureus*
- 3-5: Enterobacteriaceae, enterococci, and *Candida* spp.

Symptoms of a line infection may be systemic (SIRS) and / or localized at the line exit site (purulence, redness, swelling and tenderness). A line infection may be complicated by severe sepsis and septic shock, metastatic abscesses and endocarditis, and by the development of an infected thrombus. Most complications are seen in line infections due to *S. aureus*: with this pathogen the a priori chance a patients has metastatic abscesses or endocarditis is 10-15% and one in ten bacteremias relapses after treatment. Also *Candida* line infections are often complicated: in particular *Candida* endophtalmitis is a feared complication. Therefore, fundoscopy is indicated in any case of line infection or demonstrated colonization of a catheter tip with *Candida* spp (sensitivity of blood cultures for candidemia is limited). Patients with cultures positive catheter tips for *S. aureus* or *Candida* spp always need to be treated with systemic antimicrobial therapy, even in the absence of (systemic or localized) symptoms.

Diagnosis

The gold standard for the diagnosis of line infections is obtaining two positive blood cultures (from the infected catheter and a peripheral blood culture) and a positive culture of the catheter tip with the same micro-organism. Sometimes the diagnosis is made solely based on a positive catheter tip or blood

culture, combined with clinical improvement after removal of the line and in absence of an alternative focus of infection.

Treatment

Treatment consists first of all of removal of the catheter. In case of infection with CoNS or enterococci this usually suffices. On the contrary, *S. aureus* and *Candida* spp require treatment even when the blood cultures remain negative. Empirical therapy is usually aimed at the causative agents of sepsis (*S. aureus* and enterobacteriaceae, if necessary also non-fermenters), which can be tailored once the pathogen has been isolated. Follow-up blood cultures need to be drawn to confirm that the bacteremia has been resolved, at least in infections with *S. aureus*, *Candida* spp or *P. aeruginosa*. Persistently positive blood cultures despite therapy (and removal of the catheter) may indicate complications and requires further diagnostics / search of a secondary focus. The duration of antimicrobial therapy depends on the micro-organisms, the symptoms and the complications. In principle:

CoNS or enterococci: removal of the catheter usually suffices

Enterobacteriaceae: 1 week

P. aeruginosa / *S. aureus*: 2 weeks

Candida spp: until 2 weeks after the last positive blood culture (repeat until negative)

S. aureus with hematogenic complications / *Candida* with endophtalmitis: 6 weeks

Infected thrombus (regardless of pathogen): 6-8 weeks

"Salvage" of an infected catheter

When a tunneled line is essential to the patient and replacement is very complicated, it is sometimes attempted to "save" the catheter with an "antibiotic lock", a high concentration of antibiotics which are left in the system. Pre-conditions are that the infection is caused by a pathogen with low virulence (CoNS or enterococci), that the patient is not septic and that blood cultures under therapy remain negative. In practice, this treatment consists of infusion of vancomycin + heparin, for 7 to 14 days (combined with systemic therapy).

Sepsis

Sepsis is defined as a "life-threatening condition, in which the reaction of the host to infection damages the own tissues and organs".
SIRS (Systemic Inflammatory Response Syndrome) is defined by the presence of two or more of the following symptoms:

-Fever >38,3˚ C or hypothermia < 35,6˚ C

-Leukocytosis > 12 10^9/l or leukopenia <4 10^9/l

-Tachycardia > 90/min

-Tachypnea > 20/min

When a patients has SIRS + a focus of infection this is usually considered "sepsis". Sepsis may be accompanied by bacteriemia, but this is often not the case. Vice versa: bacteriëmia does not always indicate or cause sepsis (brushing your teeth already produces bacterima in most people).

Pathogens causing sepsis

Reliable epidemiological data on the causative agents and foci of sepsis are not available. However, data on pathogens isolated from blood *are* available. These vary according to setting (nosocomial vs hospital-acquired), patient category and co-morbidity, and geographical location (for instance: in Asia infections with *Klebsiella spp* and with *Burkholderia pseudomallei* are quite common).

The most commonly isolated pathogens in community-acquired bacteremia are: **1. *E. coli,* 2. pneumococci, and 3. *S. aureus*.** Empirical antibiotic therapy will therefore need to cover at least these three bacteria.

In hospital-acquired bacteremia the order is usually: 1**. coagulase-negative staphylococci (CoNS), 2. *S. aureus*, 3. *E. coli*, 4. enterococci and 5. *Klebsiella species***. CoNS and enterococci seldom cause severe infections. The three other pathogens will however need to be adequately covered by the empirical antibiotic regimen.

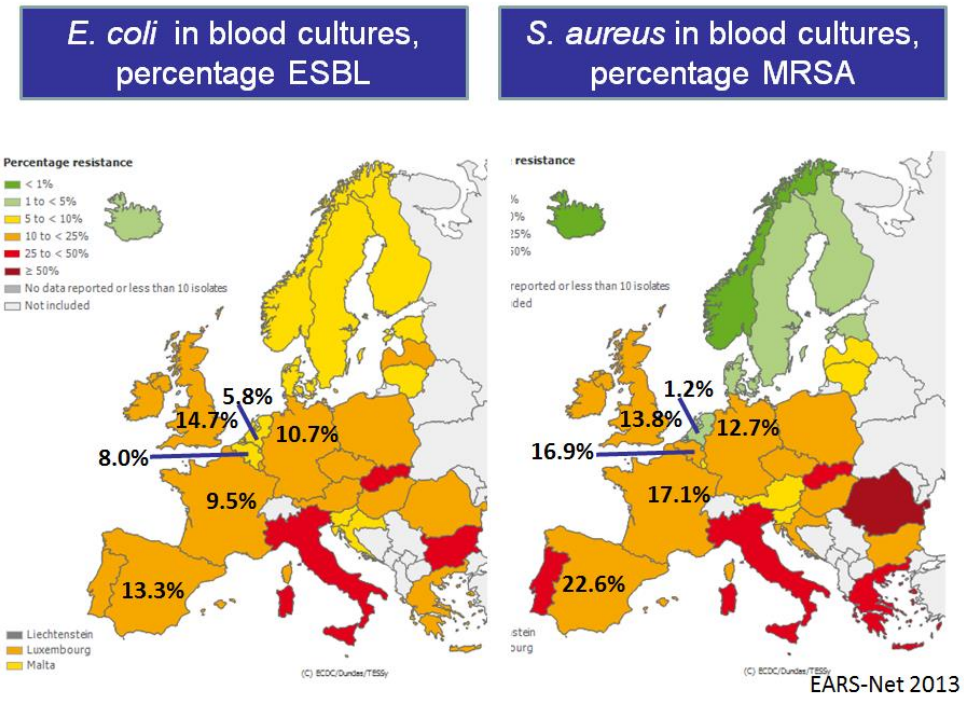
Focus of nosocomial infections

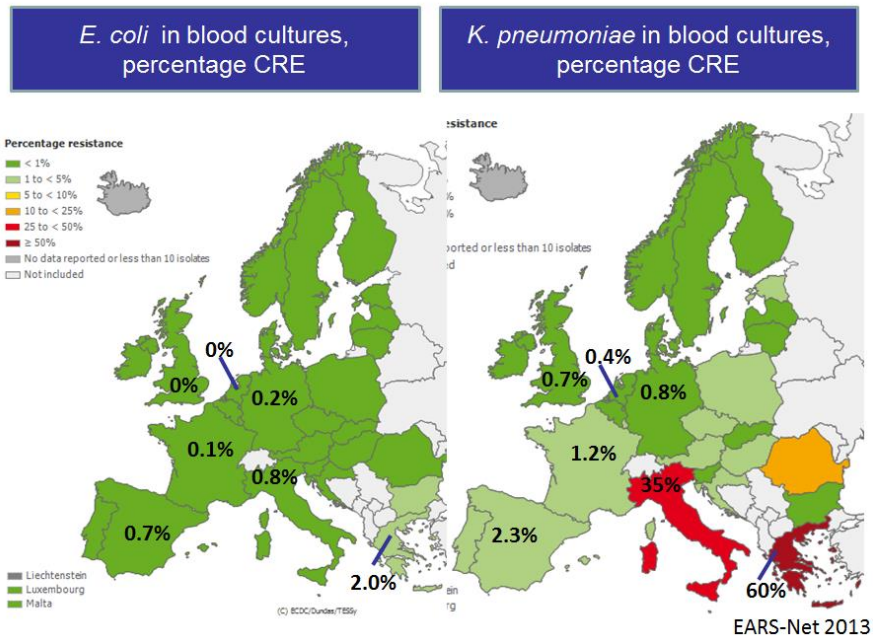
As stated above, there are hardly any epidemiological data on focus of sepsis. In a prevalence study conducted at the UMC Utrecht (all admitted patients screened on a random day for nosocomial infections), the most frequent infections were surgical site infections (in surgical patients). The percentage of patients with urinary tract infections, respiratory infections, line-associated infections and "other" infections was approximately equal.

Resistance of pathogens in sepsis, implications for choice of empirical therapy

In The Netherlands *Staphylococcus aureus* and pneumococci are only very rarely resistant against the beta-lactam antibiotics used as empirical therapy for sepsis. In a large study from 2005 to 2007 only 0.11% of the patients admitted to Dutch hospital was carrier of MRSA. Issues with resistance here are mainly due to enterobacteriaceae, in particular ESBL-positive *E. coli* and *Klebsiella spp*. After a steady increase in the last decade from 0.1% of isolates to 5-6% of *E. coli* blood culture isolates harboring ESBL, this percentage now appears to have stabilized over the last few years. However, 2nd and 3rd generation cephalosporins do often remain the antibiotics of first choice, because (1) most patients are already known to be ESBL-positive from previous cultures, or (2) have defined risk factors, and (3) many suffer urinary tract infections, which may initially still respond to therapy due to the high urine concentration reached with these agents. Dutch guidelines have been adapted to the increase in ESBL-infections, which has led to an increase in the empirical use of combination therapy with aminoglycosides or of carbapenems.

In countries where MRSA and ESBL are more frequent, empiric therapies have to be adapted. Resistance to carbapenems is low in most European countries, but is steadily rising, and may require adaptations of the chosen therapy in specific situations / centers.





Choice of empiric antibiotic therapy in sepsis

Based on epidemiological data (the expected pathogens with their susceptibility profile) empirical treatment regimes have to be established for septic patients. These may vary between hospitals, due to epidemiological and "cultural" factors (i.e. what are the doctors used to). General guidelines for The Netherlands have been defined by SWAB. These recommendations of course change once a likely focus of infection has been defined, or if colonization with other pathogens (*P. aeruginosa*, *A. baumannii*) has been demonstrated.

SWAB-guideline empirical antibiotics in community-acquired sepsis	
Sepsis e.c.i.:	- cefuroxime, +/- gentamicin or tobramycin OR: - ceftriaxone, +/- gentamicin or tobramycin OR: - augmentin + gentamicin or tobramycin
Recent use fluoroquinolones or cephalosporins	One of the above combinations including gentamicin or tobramycin
Demonstrated ESBL-colonization	Carbapenem (imipenem, meropenem, ertapenem)

SWAB-guideline empirical antibiotics in nosocomial sepsis	
Sepsis e.c.i.:	- cefuroxime + gentamicin / tobramycin OR: - ceftriaxone + gentamicin / tobramycin / ciprofloxacin OR: - piperacillin-tazobactam + gentamicin / tobramycin / ciprofloxacin
High suspicion of ESBL	Consider carbapenem

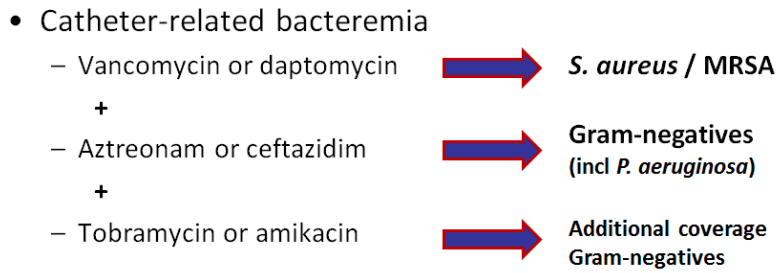
UMC Utrecht / Maastricht UMC policy:

At the UMCU / MUMC the policy is dependent on the severity of the sepsis. Stable patients, without risk factors for enterobacteriaceae resistant to 3rd-generation cephalosporins are treated empirically with ceftriaxone (1 dd 2 gram). In cases of severe sepsis gentamicin (5-7 mg/kg once a day) is added, often as a single dose. If risk factors *are* present gentamicin is added as a standard to the ceftriaxone. In cases of demonstrated colonization with enterobacteriaceae resistant to 3rd-generation cephalosporins empirical therapy is started with a carbapenem (meropenem). In principle, no distinction is made between the choice of agents for community-acquired and nosocomial sepsis.

Antibiotic policy for sepsis of unknown origin UMCU / MUMC	
Sepsis e.c.i.	Ceftriaxone 1 dd 2 gram
Severe sepsis / septic shock	Ceftriaxone 1 dd 2 gram + gentamicin 5-7 mg/kg
Recent use fluoroquinolones or cephalosporins	Ceftriaxone 1 dd 2 gram + gentamicin 5-7 mg/kg
Demonstrated colonization ESBL or AMP-C producing enterobacteriaceae (enterobacters, citrobacters, serratia, morganella)	Meropenem 3 dd 1 gram
Clinical deterioration on antibiotic therapy	Consult clinical microbiologist or ID-specialist

Spanish SEIMC recommendations

Spanish guidelines for sepsis are difficult to find, but the Spanish society for Clinical Microbiology and Infectious Disease does have guidelines for catheter related bacteremia. These cover a wide spectrum of pathogens which will certainly cover most cases of nosocomial sepsis



IDSA-recommendation

The IDSA has endorsed the "Surviving Sepsis campaign" which recommends "one or more drugs that have activity against all likely pathogens".

Sanford Guide recommendation:

- 1st Vancomycin PLUS meropenem / imipenem / piperacillin-tazobactam
- Alternative: daptomycin PLUS cefepime / piperacillin-tazobactam

Treatment of multi-drug resistant (MDR) pathogens

Increased (sometimes imprudent) antibiotic use, and at times failure to contain outbreaks with resistant pathogens has led to a steady increase in resistance and the emergence of multi-resistant outbreak clones. In the past it was believed that carrying resistance genes would make these bacteria less "fit to survive" giving them an evolutionary disadvantage compared to more susceptible clones, and that they would only be capable of persisting in hospital environments under antibiotic pressure. This has proven largely untrue, with many resistant bacteria, such as ESBL and CA-MRSA now being widespread in certain communities. Also, although some resistant bacteria appear to have lost (part of) their virulence, eventually many either acquire virulent properties or pass their resistance genes on to clones which *are* virulent.

In treating resistant bacteria three general options are available: using second line antibiotics, using higher dosages, and using combination therapy – and sometimes a combination of these.

Any bacterium may finally become resistant to any antibiotic, but some resistances have been defined as especially problematic: the resistances for first choice (empiric) therapies, and those to antibiotics seen as "last resort". Most of these involve resistance to beta-lactam antibiotics, but also resistance to vancomycin, fluoroquinolones or aminoglycosides may be reason for more concern and measures. Surveillance systems (such as EARS-Net and ISIS-web) usually focus on these micro-organisms.

In general it is prudent to consult a specialist – a clinical microbiologist or ID-specialist – to decide the antibiotic regimen in such patients. Below we will mark a couple of current options for the main (multi-drug) resistant pathogens

Penicillin-resistant pneumococci (PrP)

Increased MIC to penicillin, not fully resistant.

- First choice is higher dosage of antibiotics: General recommendation is to increase the dose of iv penicillin to 6 dd 4 MU. Plasma and tissue levels of ceftriaxone are probably also usually adequate.
- Alternative is to change to non-betalactam therapy with respiratory fluoroquinolones, vancomycin or linezolid.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Presence of an additional PBP which confers resistance to all beta-lactam antibiotics except the 5th generation cephalosporins. Nosocomial clones are usually resistant to antibiotics such as clindamycin, co-trimoxazole and tetracyclines.

- First choice iv-therapy is vancomycin. In some hospitals linezolid or daptomycin have been chosen. Some hospitals (mainly USA) use tigecycline.
- First choice oral options are co-trimoxazole, clindamycine or doxycycline, if (expected) susceptible. An alternative is linezolid.

Vancomycin-resistant *Staphylococcus aureus* (VRSA)

Resistance conferred through adaptation in the cell wall (low-level resistance) or acquisition of a vancomycin-resistance gene from enterococci (VanA, VanB). Higher dosage of vancomycin is not a therapeutic option (does not increase the effect in these strains). Cross-resistance with daptomycin has been described. Since these strains are still quite infrequent (in Europe almost non-existent) clinical evidence is very limited. Possible options could be linezolid, daptomycin (if tested susceptible), 5th generation cephalosporins (although little to no clinical evidence at this moment).

Vancomycin-resistant enterococci (VRE)

The denomination "VRE" is usually reserved for those strains resistant to both penicillins (amoxicillin, piperacillin) and vancomycin. VRE's are seldom very pathogenic, as they almost always belong to the less virulent species *E. faecium* (instead of *E. faecalis*). Sometimes VRE is still susceptible to teicoplanin, although clinical efficacy is difficult to establish. Daptomycin or linezolid would probably be considered first choice, if needed combined with an aminoglycoside for true, severe infections.

Extended-spectrum beta-lactamase (ESBL)- producing enterobacteriaceae

ESBLs confer resistance to most penicillins and cephalosporins, although the level of resistance for the antibiotics will vary: ESBLs are a large family of different hydrolytic enzymes with different affinities for the different compounds. Aminoglycosides, fluoroquinolones and co-trimoxazole may have retained their activity, but cross-resistance is frequent.

- For proven infections with ESBL-positive pathogens in severely ill patients carbapenems should be used.
- If there is only the possibility of an ESBL-infection (not yet proven) use of an aminoglycoside in combination therapy may be adequate.
- Once tested susceptible, fluoroquinolones and co-trimoxazole are good antibiotic options in stable patients.
- Combinations of penicillins / cephalosporins with a beta-lactamase inhibitor may be effective. In a restrospective study use of augmentin, if the strain was tested susceptible, did not give a worse outcome than carbapenems.

AMP-C producing enterobacteriaceae

AMP-C enzymes are present in all Enterobacters, Serratia's and Morganella's and in most Citrobacter species. As ESBL they provide resistance to most penicillins and cephalosporins (cefepime may still be active). Clavulanic acid does not lower the MIC of AMP-C producing strains, but the novel beta-lactamase inhibitor avibactam does appear to do so.

- For proven infections with AMP-C-positive pathogens in severely ill patients carbapenems should be used.
- If there is only the possibility of an AMP-C-positive pathogen causing the infection (but not yet proven) use of an aminoglycoside in combination therapy may be adequate.
- Once tested susceptible, fluoroquinolones and co-trimoxazole are good antibiotic options in stable patients.

Carbapenemase-producing enterobacteriaceae (CRE)

Carbapenemase-producing enterobacteriaceae usually also harbor ESBL- enzymes and/or AMP-C-enzymes. In general this will confer high-level resistance to almost all beta-lactam antibiotics. Depending on the exact carbapenemase (these are divided into class A - D) aztreonam may still be active (against class B and class D). The novel combination ceftazidime-avibactam may also be active against some of these bacteria (class A and C). The options for treatment are more or less the following (adequate evidence is lacking):

- For low-level carbapenem resistance, high dosed slow infusions of meropenem can be used in combination with at least one other active drug (usually an aminoglycoside, colistin or fosfomycin).
- For higher-level carbapenem resistance (meropenem MIC >8 mg/l) carbapenems are not an option. A combination of at least two active antibiotics should be given if at available. Options include colistin, aminoglycosides, fosfomycin and very rarely fluoroquinolones, tigecycline or co-trimoxazole.
- The new combinations ceftazidime-avibactam or ceftolozane-tazobactam could be tried (although registration issues and availability may be a problem), if tested susceptible (not a generally available susceptibility test).
- In case reports combination therapy with two carbapenems (ertapenem + meropenem, or ertapenem + doripenem) has been found to retain some action against these pathogens. The idea being that ertapenem binds the carbapenemase allowing the other carbapenem to act on the bacteria.

Multi-drug resistant (MDR) *Pseudomonas aeruginosa* and *Acinotobacter baumannii*

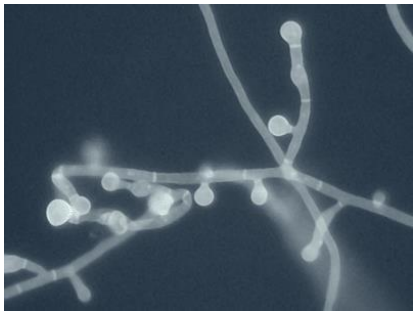
The *P. aeruginosa* and *A. baumannii* strains classified as multi-drug resistant generally are resistant to all beta-lactam options (penicillines, cephalosporins and carbapenems) and fluoroquinolones

(ciprofloxacin). Aminoglycosides may still be active, but should not be used as monotherapy and will generally be combined with a beta-lactam antibiotic for which the strains were tested resistant. The hope is to gain some synergistic effect from the combination. The last option is colistin, which also is generally combined with a beta-lactam even if resistance to all beta-lactams has been demonstrated. Resistance to colistin may ultimately develop, but is generally not a stable trait in these bacteria.

Fungal infections

Fungi are eukaryotic micro-organisms that have both mitochondria and a cell wall. They can reproduce either sexually or asexually (through spores), and may exist as multicellular organisms or unicellular organisms (=yeasts). Approximately 150 fungal species have been implicated in human disease, of which 15 relatively frequently. Fungi are divided into hyphe-forming fungi or molds, and the unicellular fungi or yeasts, but this division is not absolute. Under certain circumstances yeasts may produce "pseudohyphes" and some molds may grow as yeasts.

Molds include, amongst others, the Aspergillus spp, Fusarium spp, Scedosporium spp and the mucorales (previously: zygomycetes). Well known yeasts are the Candida spp, cryptococci and (the non-pathogenic) Saccharomyces species (baker's yeast).



Hyphae, calcofluor white stain

Fungal growth on agar plate

The following techniques may be used to diagnose fungal infections:

Direct microscopy: in particular for dermatomycoses (with KOH). Diverse stains are available, including calcofluor white and blancophor stains.

Culture:

When an (invasive) fungal infection is suspected, this should be mentioned in the test order, as the material will need to be processed differently. Fungi grow more slowly than bacteria and are therefore incubated for a longer time. Overgrowth of more rapidly growing micro-organisms may occur, reason for which they are cultured on special selective media (generally containing antibiotics). Some fungi grow better (or only) at lower temperatures; cultures are therefore often also incubated at 20˚-25˚ C. Due to the fragility of the hyphae, tissues cultured for fungi require a more delicate treatment. In invasive infections fungi often only grow filamentously (without producing spores) which may make them more difficult to culture.

Swabs, in principle, are unfit for culture of fungi. For some fungi, such as Pneumocystis, no culture methods are available.

Antigen tests:

-*Aspergillus fumigatus*: Galactomannan. Expensive, labor intensive test which can be performed on serum and on bronchoalveolar lavages (BAL). The sensitivity of the serum-test is high for invasive aspergillosis in neutropenic patients, but limited in other patient groups. The sensitivity of galactomannan in BAL-fluids is high for pulmonary aspergillosis.

-Cryptococcal antigen: a latex agglutination test. May be used for serum and for cerospinal fluid.

-Candida: antigen test in serum. Limited use.

PCR (Polymerase Chain Reaction):

-Widely used for diagnosis of dermatomycoses.

-Increasingly used to diagnose Pneumocystis infection.

-Still in development for *Aspergillus fumigatus*.

Antifungal therapy

Polyenes: Amphotericin B as desoxycholate or as lipid / liposomal / colloidal suspension

Amphotericin B for systemic use can only be administered intravenously. The desoxycholate drug may cause severe nephrotoxicity and hematologic toxicity, limiting its use and its dosage. This toxicity is reduced when the drug is administered as a lipid complex, a colloid dispersion or a liposomal formulation. No differences in efficacy have been demonstrated between the different formulations. Liposomal amphotericin B causes the least renal toxicity and infusion-related toxicity, but it is also the most expensive formulation.

Azoles: fluconazole, itraconazole, voriconazole, posaconazole, miconazole, ketoconazole, clotrimazole, sulconazole

Azoles are highly resorbed and may be administered orally and intravenously for systemic use. The azoles available for systemic therapy are fluconazole, itraconazole, voriconazole and posaconazole. Fluconazole is only active against yeasts. Itraconazole, voriconazole and posaconazole are also effective against molds (such as *A. fumigatus*). Posaconazole is the only azole with activity against zygomycetes. Some of the azoles are applied topically for the treatment of dermatomycoses.

Echinocandins: caspofungin, anidulafungin, micafungin

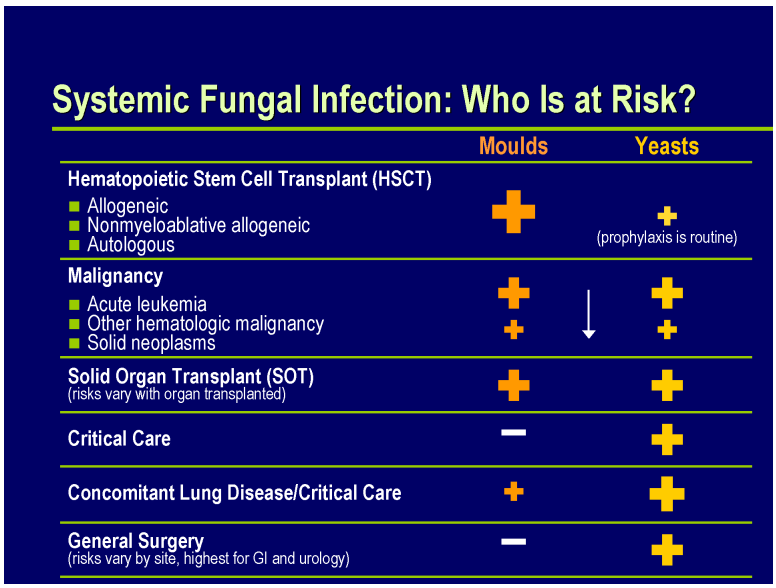
Echinocandins are only available as intravenous solutions. There are differences between the available echinocandins in registration and interactions, but in general they are regarded as clinically equally

active. In principle, echinocandins are only used for yeast-infections; in exceptional cases they may be used as salvage-therapy for infections with *Aspergillus fumigatus*.

Other antimycotics: flucytosine, terbinafine, gentian violet

Spectrum of activity antifungal agents

	C.albicans	*C.krusei*	*C.glabrata*	*A.fumigatus*	*Fusarium*	Mucorales
Fluconazole	++	-	-	--	--	--
Voriconazole	++	++	- / -/+	++	+/-	--
Posaconazole	+	+	-/+	+	-	+/-
Flucytosine	+	+	+	-	-	--
Amfo B	+	+	+	+	+	+
Echinocandins	++	++	++	+/-	-	--



Invasive opportunistic mycoses

Organism(s)[b]	No. of cases/ million/yr	Case/fatality ratio (%)
Yeasts		
Candida species	72.8	33.9
C. albicans		
C. glabrata		
C. parapsilosis		
C. tropicalis		
C. krusei		
C. lusitaniae		
C. rugosa		
C. guilliermondii		
C. inconspicua		
C. norvegensis		
Cryptococcus species	65.5	12.7
Other yeasts		
Hyaline molds		
Aspergillus species	12.4	23.3
Zygomycetes	1.7	30.0
Other hyalohyphomycetes	1.2	14.3
Dematiaceous molds	1.0	0
Pneumocystis jiroveci		

Pfaller e.a., Clin. Micro. Rev. 2007

Choice of antifungal therapy for the most common mycoses

Dermatomycoses / onychomycoses

Dermatomycoses are preferably treated topically with an azole or terbinafine. In case of a deep mycosis of the skin, topical therapy is not adequate and oral treatment with terbinafine or an azole is required.

Onychomycoses usually respond poorly to topical therapy. When treatment is indicated (the indication is often purely cosmetic) longterm treatment with oral terbinafine or oral itraconazole may be attempted; such treatments yield a cure-rate of approximately 50-70%.

Oral candidiasis: First choice: oral nystatin. Alternative: oral gentian violet.

Candidemia

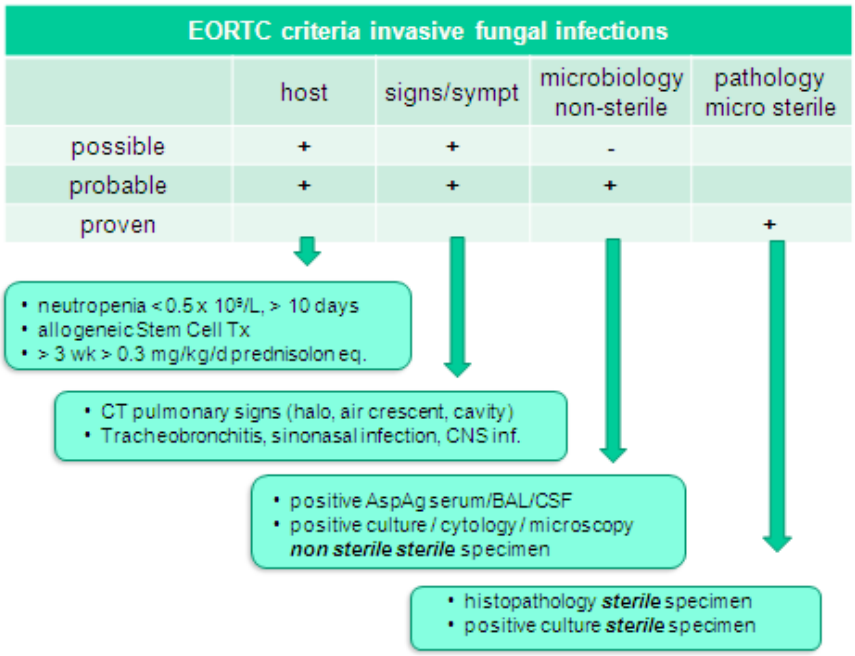
The susceptibility of Candida species tot azoles is largely dependent on the species. C. glabrata is often resistant to fluconazole, C. krusei is universally resistant. In severely ill patients with candidemia echinocandins appear to provide a survival benefit. Therefore, in case of (suspicion of) candidemia, echinocandins are the first choice therapy when a patient has been previously treated with azoles, is known to be colonized with a resistant species, or when the patient is hemodynamically unstable. In other cases fluconazole is also an option. Once a patient is stabilized and the susceptibilitiy pattern of the yeast is known, therapy may be switched to fluconazole.

Invasive aspergillosis

First choice of treatment for invasive aspergillosis is voriconazole. In case of resistance to azoles or when azoles (second choice azoles are itraconazole or posaconazole) are not tolerated amphotericin B is the drug of choice. Due to a lack of clinical evidence of efficacy, echinocandins are only used as salvage-therapy.

Mucormycosis (zygomycosis)

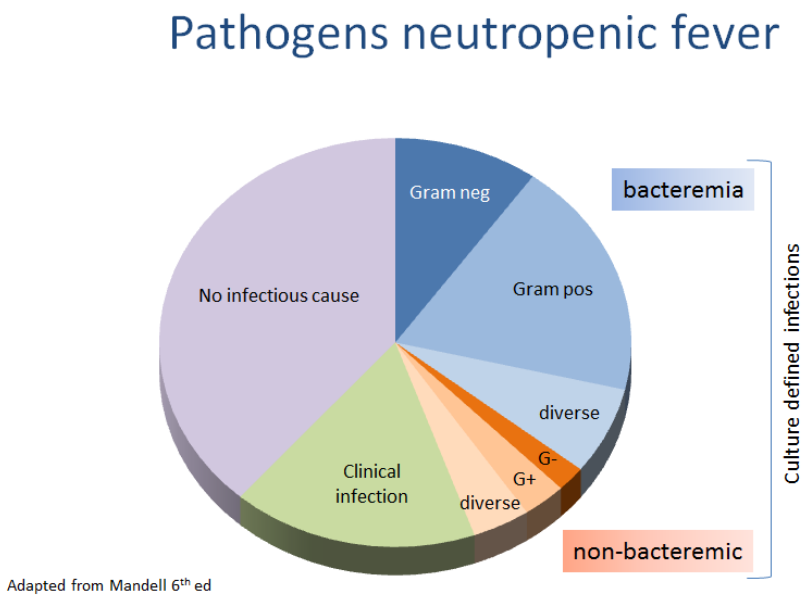
Mucorales (previously “zygomycetes”) are intrinsically resistant to voriconazole and echinocandins. The first choice of treatment is therefore amphotericin B, with as alternative (if susceptible) posaconazole. Treatment of a mucormycosis will nearly universally require surgical intervention.


EORTC criteria invasive fungal infections
host
signs/sympt
microbiology non-sterile
pathology micro sterile
possible
+
+
-
probable
+
+
+
proven
+
• neutropenia < 0.5 x 10⁹/L, > 10 days
• allogeneic Stem Cell Tx
• > 3 wk > 0.3 mg/kg/d prednisolon eq.
• CT pulmonary signs (halo, air crescent, cavity)
• Tracheobronchitis, sinonasal infection, CNS inf.
• positive AspAg serum/BAL/CSF
• positive culture / cytology / microscopy
non sterile sterile specimen
• histopathology sterile specimen
• positive culture sterile specimen

Neutropenic fever associated with chemotherapy

Patients receiving chemotherapy often suffer episodes of fever, in particular patients who are being treated for hematological malignancies. Mucositis, as a result of the chemotherapy, may lead to disruption of the anatomical barriers in the whole gastro-intestinal tract, and to subsequent translocation of mucosal and intestinal bacteria. Also the presence of a central venous catheter is a risk factor for infection.

Approximately 1/3 of the hematological patients with neutropenic fever suffer a bacteremia. Another 1/3 suffers an infection without bacteremia, and in 1/3 no infectious explanation is found for the fever. If the fever persists for more than 5 days, invasive fungal infections should be considered.



The chance that an infection will occur during neutropenia is considered to be so high in hematological patients, that usually antibiotic prophylaxis is prescribed for that period. Prophylaxis is then aimed at Gram-negatives and yeasts, for instance with a combination of ciprofloxacin and fluconazole. An alternative is co-trimoxazole, colistin and fluconazole (all three oral). In case of severe mucositis additional coverage of viridans streptococci is given, for instance with cefazolin, penicillin or clindamycin. Although prophylaxis has been demonstrated to decrease the number of infectious episodes, no effect on mortality has been observed. Therefore, since the microbial flora of the patients may rapidly grow resistant, and since broadspectrum antibiotics are started in case of fever, the IDSA advises to exercize restraint in prescribing prophylaxis.

The occurance of fever during neutropenia (with or without prophylaxis) is considered an alarming symptom and is always reason for initiation of empirical antibiotic therapy, or to switch from prophylaxis to therapy. The choice of empirical antibiotics depends on risk stratifications, as for instance the MASCC score. Virtually all hematological patients will qualify as high-risk and will therefore require iv-treatment with broadspectrum agents. Patients treated for solid tumors, mostly fall in the low-risk group, for whom oral treatment may be justified. Empirical treatment is aimed at both Gram-negatives, including *P. aeruginosa*, and virulent Gram-positives, as *S. aureus* and streptococci. Naturally, patient culture results are also taken into consideration.

The choice of antibiotic regimen for high-risk patients differs from center to center. Common regimes include:

- carbapenems (imipenem, meropenem)
- piperacillin/tazobactam
- ceftazidime

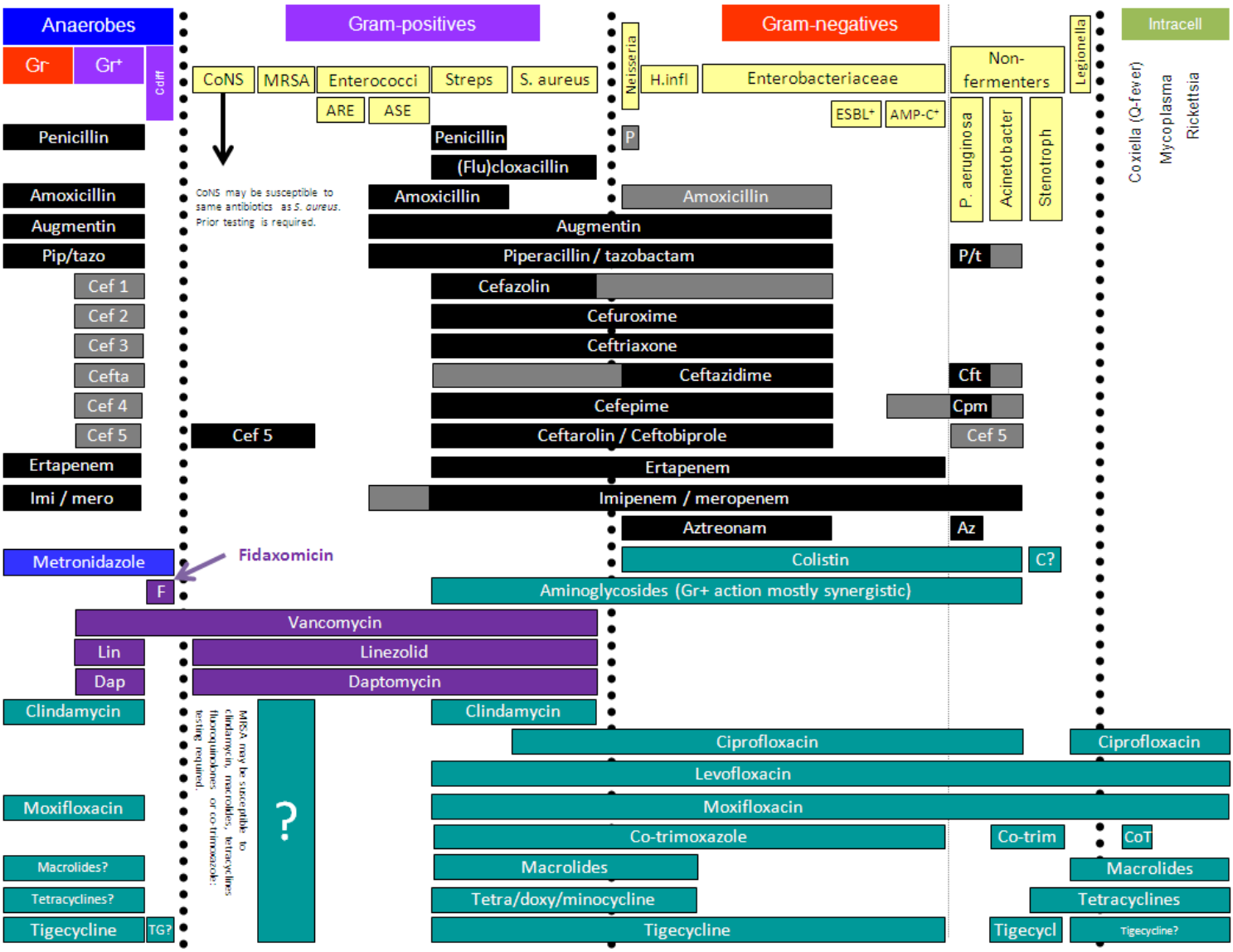
These antibiotics may or may not be combined with vancomycin (in particular if ceftazidime is chosen) and/or with an aminoglycoside.

Low-risk patients with neutropenic fever may be treated with oral antibiotics or be switched to oral therapy after a short iv-course. A commonly used oral regime is augmentin + ciprofloxacin.

The duration of empiric therapy is a matter of much debate. Some Dutch centers base the duration on the severity of illness, on the presence of a plausible focus of infection and on whether the patient has bacteremia. At the UMC Utrecht hemodynamically stable patients, without a focus and with negative blood cultures, are switched back to oral prophylaxis.

A consequence of the precautionary initiation of antibiotics in *all* patients with neutropenic fever, in daily practice leads to gross antibiotic overtreatment of this group. Even in this vulnerable group of patients it should be attempted to limit antibiotic use to what is truly indicated in terms of duration and spectrum, once more certainty has been gained as to the cause of the fever.

Overview of antibiotic spectra



This figure is a general representation of clinical activity of antibiotics frequently used in hospital practice. It may be used to understand choices of antibiotic therapy, but is not intended to establish therapy in individual patients. Epidemiological data of a center or country, susceptibility testing in the patient, outcome of clinical studies, PK/PD-considerations and guidelines need to be taken into account. Choices to designate a micro-organism / antibiotic combination are at some points arbitrary. Unclear activity and highly variable susceptibility indicated with a question mark. A >50% expected resistance has been generally depicted as "inactive" (no bar). A high expected resistance or decreased activity has for beta-lactams been depicted in grey. These may be very variable between different regions and different hospitals. Furthermore, the following considerations apply:

Notes per antibiotic group:

Penicillins: Spectrum of oxacillin, cloxacillin, flucloxacillin, dicloxacillin and nafcillin is similar.

Cephalosporins: increased activity from 1st to 4th generation against enterobacteriaceae, with significant drop in MICs, especially from 1st to 2nd and from 2nd to 3rd generation. 1st generation: cefazolin, cefalotin, cefalexin. 2nd generation: cefuroxime. 3rd generation: ceftriaxone and cefotaxim have similar activity, ceftazidim also has activity vs *P. aerurginosa*,

but is less active against Gram-positives. 4th generation in vitro active against enterobacter-group / AMP-C positive enterobacteriaceae, however, with scarce if any evidence of clinical activity.

Carbapenems: Meropenem is the carbapenem most active against *P. aeruginosa*. Imipenem is the carbapenem most active against enterococci, but still considered inferior to other active treatments (in particular inferior to amoxicillin and piperacillin).

Aminoglycosides: Inferior to beta-lactams, not to be used as monotherapy (except for urosepsis). Gentamicin considered the most active aminoglycoside against Gram-positives and least active aminoglycoside against *P. aeruginosa*.

Polymyxins (colistin, polymyxin B): *Proteus, Morganella, Serratia* and *Providencia* spp are intrinsically resistant. Inferior to beta-lactams, not to be used as monotherapy (except for urosepsis).

Fluoroquinolones: Ciprofloxacin is the most active fluoroquionolone against *P. aeruginosa*, but it has limited activity vs streptococci / pneumococci. Norfloxacin and ofloxacin have similar activity to ciprofloxacin. Norfloxacin achieves low tissue levels and is therefore not deemed appropriate for infections other than UTI. Levofloxacin (and to a lesser degree: moxifloxacin) considered as alternative in the treatment of *S. maltophilia;* this is based on data from susceptibility testing, without clinical data. Moxifloxacin considered the only fluoroquinolone with significant activity against anaerobic bacteria. High regional differences in susceptibility of gonococci for fluoroquinolones; resistance of up to 50% has been reported. Beware of resistance induction in *S. aureus* and *P. aeruginosa* when treating with fluoroquinolone monotherapy.

Daptomycin: inactivated by lung surfactant, not to be used for respiratory infections.

Macrolides: In vitro activity against many anaerobes (Gram-postives > Gram-negatives); however, not used in the treatment of such infections.

Glycopeptides: Vancomycin and teicoplanin have (nearly) identical spectra of activity. Considered inferior to beta-lactam antibiotics in the treatment of *S. aureus* (MSSA).

Tetracyclines / glycylcyclines: minocycline, doxycycline and tigecycline may be considered alternatives for infections with *S. maltophilia* when first choice treatmen (i.e. co-trimoxazole) is not an option. Clinical activity has however not been established. Tigecycline is the only tetracycline with established clinical efficacy against anaerobic intra-abdominal infections. Cases of *C. difficile* infections successfully treated with tigecycline have been reported.

The activity of tigecycline against enterobacteriaceae is variable, with reduced activity against particular species (Proteus, Morganella). It is considered less active than beta-lactam antibiotics against enterobacteriaceae (when strains are tested susceptible to both). There is insufficient evidence for use of tigecycline in atypical pneumonia and against intracellular pathogens. Doxycycline may be active against Acinetobacter, but clinical experience is lacking.

Notes per micro-organism:

Clostridium difficile: May be susceptible to many antibiotics, including clindamycin, fluorquinolones and beta-lactam antibiotics. However, clinical epidemic strains are generally resistant to these antibiotics.

Enterobacteriaceae: *Proteus, Morganella* and *Serratia* spp are intrinsically resistant to colistin. *Proteus* and *Morganella* spp have increased MICs to tigecycline and imipenem. Providencia spp have increased MICs to imipenem.

Abbrevations:

Gr-	: Gram-negative bacteria	P	: Penicillin
Gr+	: Gram-positive bacteria	P/t	: Piperacillin/tazobactam
C. diff	: Clostridium difficile	Cef 1	: 1st generation cephalosporins
CoNS	: Coagulase-Negative Staphylococci	Cef 2	: 2nd generation cephalosporins
MRSA	: Methicillin-Resistant Staphylococcus aureus	Cef 3	: 3rd generation cephalosporins
ARE	: Ampicillin-Resistant Enterococci	Cefta, Cft	: ceftazidime
ASE	: Ampicillin-Sensitive Enterococci	Cef 4	: 4th generation cephalosporins / cefepime
Streps	: Streptococci	Cef 5	: Ceftaroline
S. aureus	: *Staphylococcus aureus*	Az	: Aztreonam
H. infl	: *Haemophilus influenza*	Lin	: Linezolid
ESBL+	: Extended Spectrum Beta-Lactamase	Dap	: Daptomycin
Amp-C+	: Amp-C beta-lactamase	CoT	: Co-trimoxazole
Stenotroph:	*Stenotrophomonas maltophilia*	TG	: Tigecycline
Intracell	: Intracellularly growing bacteria		

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Evaluation course "Antibiotic use in Practice"

Would you please grade the different topics from (bad / not useful) to 5 (very good / very usuful)?

Introduction microbiology

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

PK/PD

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Beta-lactam antibiotics

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Tetracyclines , macrolides, clindamycin

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Pneumonia (CAP / HAP / VAP)

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Fluoroquinolones, co-trimoxazol, nitrofurantoin, fosfomycin

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Urinary tract infections

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Interactive questions Wednesday

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Microbiological diagnostics

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Aminoglycosides and polymyxins

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Vancomycine, linezolid, daptomycin

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Clostridium, intra-abdominal infections, metronidazole

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Fever in the neutropenic patient

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Endocarditis

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Sepsis and catheter-associated bacteremia

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Case discussions Thursday

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Interactive questions Thursday

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Fungal infections and antifungal agents

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Infections of skin and soft tissue

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Case discussions Friday

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

Interactive questions Friday

Contents	1	2	3	4	5
Presentation	1	2	3	4	5

I would award the course as a whole the following grade (from 1 to 10): …….

What I missed in this course was:

……

……

……

Other comments:

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