

PRINCIPLES OF ANTIMICROBIAL THERAPY

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Presentation overview

- **General principles**
- **Respiratory infections**
- **Urinary tract infections**
- **Skin and soft tissue infections**

Antimicrobials: Introduction

- Drugs affecting the growth of an microorganism
- They help the immune system to control the infection
 - Most mild and moderate infections
 - Significant portion of patients would recover without antimicrobial therapy
- In some infections the mortality rate is up to 100% without antimicrobials
 - Infective endocarditis, severe sepsis
- Relatively safe, non-toxic drugs
- Without antimicrobials there would be no „high-tech“ medicine
 - Major surgery, transplants, immunosuppression
- Antimicrobials are not antipyretics nor should they be used to treat „raised inflammatory markers“
 - Therapeutic plan: what are you treating, which drug you use, for how long
- Massive misuse of antimicrobials in clinical practice
 - „Patient with CRP of 150, let's start him on co-amoxicillin and we'll see“
- Real risk of widespread resistance and „postantibiotic era“

Antimicrobials: classification (1)

- **Origin**
 - Natural (produced by bacteria or fungi)
 - **Antibiotics (the correct use of this term!)**
 - Semisynthetic drugs
 - Synthetic drugs
 - **Chemotherapeutics (e.g. antimicrobial chemotherapy)**
- **Effect**
 - Bacteria: **antibiotics (the incorrect use of this term, but commonly used!), the correct term is antibacterial drugs**
 - Fungi: **antifungal drugs**
 - Viruses: **antiviral drugs**
 - Parasites: **antiparasitic drugs**

Antimicrobials: classification (2)

- **Molecular mode of action**
 - Cell wall, cell membrane, DNA replication, DNA transcription, translation
- **Spectrum**
 - Narrow, moderate, broad
- **Pharmacology (PK/PD)**
 - Time-dependent ($T > MIC$)
 - Concentration-dependent ($C_{max} > MIC$)
 - Exposure-dependent ($AUC > MIC$)

Antimicrobials: classification (3)

- **Toxicity**
 - Relatively toxic (aminoglycosides, glycopeptides)
 - Relatively nontoxic (beta-lactams)
- **Cost**
 - The older drugs are cheaper
- **Personal preferences**
 - Favourite antimicrobials
 - Partly influenced by Pharma lobby

How to „learn“ antimicrobials/ID

- No ideal/universal textbook!
- Textbooks, lectures, articles, guidelines, online guides, **SPC and clinical experience**
- Start by studying special chapters (infections by body systems and in different age groups/special hosts) and then go to general/introductory chapters (systematic bacteriology and overview of antimicrobial drugs)

Commonly used antibacterials

Antibacterials: classes and most commonly used drugs

Penicillins:	PNC-G, PNC-V, Procaine-PNC, Benzathine-PNC, amoxicillin, ampicillin, oxacillin, amoxicillin clavulanate, ampicillin sulbactam, piperacillin/tazobactam
Cephalosporins:	cefazolin, cefuroxime, ceftriaxone, ceftazidime, cefepime, ceftaroline
Carbapenems:	meropenem, imipenem, ertapenem
Aminoglycosides:	gentamicin, amikacin
Macrolides:	clarithromycin, azithromycin
Lincosamides:	clindamycin
Glycopeptides:	vancomycin, teicoplanin
Tetracyclines:	doxycycline. Rifamycins: rifampicin.
Fluoroquinolones:	ofloxacin, norfloxacin, ciprofloxacin, moxifloxacin
Nitroimidazoles:	metronidazole Sulfonamides: sulfamethoxazole Pyrimidines: trimethoprim.
Oxazolidinones:	linezolid. Lipopeptides: daptomycin. Lipoglycopeptides: telavancin, dalbavancin. Polymyxins: colistin. Glycylcyclines: tigecycline. Macrocyclics: fidaxomicin.

Principles of antibacterial therapy (1)

- **Diagnosis?**
 - **The most likely bug?**
 - **Community or healthcare-associated infection?**
 - Accurate history, physical exam, imaging, labs
 - **Microbiological tests**
 - Prior to antibacterial therapy
 - Gram stain, antigens, cultures, serology, molecular tests
 - **Differential diagnosis?**
 - What else could it be ? Non-infectious diagnosis? Worst-case scenario?

Principles of antibacterial therapy (2)

- **Host?**
 - Newborns, infants, children, adults, elderly
 - Immunocompetent vs. immunocompromised
 - Obesity
 - Renal & liver function
 - Allergies
 - Pregnancy, breastfeeding
 - Genetics

Principles of antibacterial therapy (3)

- **Treatment strategy?**
 - **Empiric therapy** in severe infections
 - Bactericidal, broad-spectrum antibacterials, ASAP
 - Sepsis, meningitis
 - **Definitive therapy**
 - According to the susceptibility of the bug identified by culture
 - Penicillin G for pneumococcal pneumonia
 - **Observation**
 - „masterly inactivity“
 - Fever of unknown origin
 - **Prophylaxis**
 - Presurgical antibacterial prophylaxis

Principles of antibacterial therapy (4)

- **Which antibacterial drug?**
 - Choose the best option for the particular patient
 - Monotherapy (most cases)
 - Combinations
 - Empirical treatment in severely-ill patient
 - Septic shock, pneumonia, meningitis
 - Polymicrobial infections
 - Intra-abdominal infections
 - Synergistic activity
 - Enterococcal endocarditis
 - To prevent emergence of resistance
 - TB

Principles of antibacterial therapy (5)

Which route?

- Intravenous
 - Initial treatment of severe infections, IV/oral switch ASAP
 - In some infections IV administration is required for the duration of therapy (meningitis, endocarditis).
 - If there is no oral drug available
 - OPAT (Outpatient Parenteral Antibiotic Therapy)
- Intramuscular
 - Useful for outpatient treatment
 - Procaine-PNC, Benzathine PNC
- Oral therapy

Principles of antibacterial therapy (6)

Duration?

- In clinical practice: multiples of 5 and/or 7 (why?)
- Some data available
 - Sepsis 10-14 days
 - Osteomyelitis (adults) 42 days
 - Meningitis
 - Meningococcus and haemophilus 7 days
 - Pneumococcus 10-14 days
 - Listeria, Streptococcus spp., enteric bacteria 21 days
 - Pneumonia
 - Minimum duration 5 days (and the patient has been afebrile for at least 3 days)
 - Atypical pneumonia 7-14 days
 - Pyelonephritis
 - 14 days (ciprofloxacin 7 days, levofloxacin 5 days)

Antimicrobial therapy in practice

Key issues

Thorough diagnostic process, think outside the box
Microbiological tests prior to starting antibacterial treatment
Prescription of the particular drug, as much information as possible, check allergy history, check SPC, think of possible pregnancy
As narrow-spectrum drug as possible, guided by sensitivity results
IV/Oral switch as soon as feasible
Duration of treatment
No clinical response after 2-3 days: step back and think. Why?
Antimicrobial team: ID, Microbiology, Pharmacology, Infection control

Common mistakes

- No cultures taken!!!
- Frequent change of antibiotics in case of non-response
 - Think of undrained collection of pus, „Ubi pus, ibi evacua“
 - Resistant bug?
 - Wrong dose/route of the antibacterial drug
- Non-infectious diagnosis treated with antibacterials
 - Vasculitides, tumours, thrombo-embolic diseases, drug fever, ...
- Colonisation treated with antibacterials
- No de-escalation
- Presurgical antibacterial prophylaxis continued after the surgery
- Overprescription of some antimicrobials

Pneumonia

- Bacterial (viral)
- Certain microorganisms in certain age groups/ susceptible hosts
- Subjective complaints: cough, chest pain, fever, shivers, headache
- Physical exam
 - Inspection (chest expansion)
 - Palpation (fremitus pectoralis)
 - Percussion (dull percussion note)
 - Auscultation (vocal fremitus, reduced breath sounds, crackles, wheeze)
- CXR
- Point of care CRP
- Microbiological test (sometimes not helpful)
- Antibacterials
- Outpatient versus inpatient management

Pneumonia: aetiology

- **COMMUNITY-ACQUIRED PNEUMONIA**
 - Streptococcus pneumoniae, Haemophilus influenzae
 - Mycoplasma pneumoniae, Chlamydia pneumoniae
 - Gram negative rods (alcoholics, pulmonary pathology)
 - Legionella pneumophila
 - Staphylococcus (superinfection- influenza)
 - Anaerobes (aspiration pneumonia)
 - Viruses (influenza, parainfluenza, RSV)
- **HOSPITAL-ACQUIRED PNEUMONIA**
 - Gram negative rods, Staphylococcus aureus (MSSA, MRSA)

CURB-65 Severity Score

- **Confusion**
- **Urea** above 7 mmol/l
- **Respiratory Rate** 30/min and above
- **BP** syst 90 mmHg and under or BP diast 60 mmHg and under
- **65** years and above
- **0-1**: outpatient treatment (30-day mortality 3%)
- **2**: consider inpatient treatment or outpatient with close follow-up (7%)
- **3-5**: inpatient treatment with possible intensive care admission (14-30%)

Pneumonia: diagnosis

- **CXR**
- **Sputum** culture
- **Blood cultures** (positive in 20 %)
- **Urinary antigens** (Legionella, pneumococcus)
- **PCR sputum, throat swab** (respiratory viruses, legionella, chlamydia, mycoplasma)
- Full blood count + differential
- BUN, creatinin, electrolytes, liver function tests, CRP
- **Serology** (mycoplasma, chlamydia)
 - Paired sera

Pneumonia: empiric treatment (1)

- **Outpatients (CURB 0-2)**
 - **AMOXICILLIN** 1-1.5 g TDS +/- clarithromycin
 - **CLARITHROMYCIN** 500 mg BD
 - Penicillin allergy
 - Strong clinical suspicion of atypical pneumonia
 - **(doxycycline** 100 mg BD)
- **Inpatients (CURB 3-5)**
 - **CO-AMOXICILLIN** 1.2 g TDS IV + **CLARITHROMYCIN** 500 mg BD IV
 - **Ceftriaxone** + **clarithromycin** (PNC allergy, severe pneumonia)
 - **(Vancomycin) + FQ** (severe PNC allergy- anaphylaxis, severe pneumonia, MRSA, ...)

Pneumonia: empiric treatment (2)

- **Aspiration pneumonia (anaerobes)**
 - Co-amoxicillin
 - Ceftriaxone + metronidazole (PNC allergy)
 - Vancomycin + metronidazole + ciprofloxacin (severe PNC allergy)
- **HAP (PSAE, MRSA, other MDR bacteria)**
 - Piperacillin/tazobactam +/- vancomycin
 - Meropenem +/- vancomycin
 - Vancomycin + FQ (PNC allergy)

Pneumonia: definitive treatment

- **Pneumococcus**
 - Amoxicillin, penicillin
- **Haemophilus influenzae, Moraxella catarrhalis**
 - Amoxicillin, co-amoxicillin
 - Cefuroxime (2nd generation)
- **Legionella pneumophila**
 - Clarithromycin or FQ
 - + rifampicin
- **Chlamydia/ Mycoplasma**
 - Clarithromycin/ doxycycline

Common misuse of antibacterials

- **Upper respiratory infections (viruses!!!)**
 - Viruses are NOT susceptible to antibacterials
- **Exceptions**
 - Protracted sinusitis with systemic upset (i.e. bacterial superinfection)
 - Acute exacerbation of COPD (Pneumococcus, Haemophilus, Moraxella, Staphylococcus, G negative rods)
 - Pertussis (Bordetella pertussis)
 - (Protracted bronchitis with systemic upset)

Urinary tract infections

- **Uncomplicated UTIs**
 - ▣ Normal urinary tract, normal immune system
 - ▣ Young women (some young men)
- **Complicated UTIs**
 - ▣ Abnormal urinary tract
 - ▣ And/or abnormal immune system
 - ▣ Also UTIs in children, men and pregnant women
- **Urethritis, Cystitis, Prostatitis, Pyelonephritis**

Cystitis

- **E. coli, enterococci, Staphylococcus saprophyticus**
 - ▣ (Gram negative rods, Pseudomonas aeruginosa)
- Suprapubic discomfort, dysuria, frequency, urgency, hesitancy, incontinence, hematuria, smelly urine, (low grade fever)
- Urinalysis (leucocytes, erythrocytes, bacteria, nitrites, high pH)
- **Urine culture**
 - ▣ 100 000 CFU/ ml
- **Nitrofurantoin** 100 mg BD 5 days
- (Trimethoprim, cotrimoxazole, co- amoxicillin, cefuroxime)
- **Complicated cystitis: urinary tract imaging, immunology tests,...**
- **Differential diagnosis: urethritis (STG- gonococcal, non-gonococcal), gynae infections, adenovirus cystitis**

Prostatitis

- Dysuria, pelvic/perineal pain, systemic upset
- Extremely tender prostate on rectal exam
- Sepsis
- **Gram negative rods** (E. coli, Enterobacter, Proteus, Klebsiella), STD (gonococcus, chlamydia)
- Urine culture, blood culture
- **FQ 2 (-4) weeks!!!**
- (Trimethoprim)
- STD: Ceftriaxone 1 dose IM + doxycycline 10 days

Pyelonephritis

- Ascendent spread of infection from lower urinary tract, BUT sometimes without prior LUT symptoms, sometimes hematogenous spread from distant focus
- **E. coli**, other Gram negative rods, enterokoky
- Fevers, nausea, vomiting, diarrhoea, flank pain, +/- dysuria
- SIRS
- **Urinalysis, urine culture, blood culture**
- **Co-amoxiclav** 1.2 g TDS i.v. +/- gentamicin
- Ciprofloxacin 400 mg i.v. á 12 hod (or 500 mg p.o. á 12 hod.) +/- gentamicin
- **14 days (7 days ciprofloxacin, 5 days levofloxacin)**

UTIs: special problems

- **Asymptomatic bacteriuria**
 - ▣ Significant bacteriuria + NO symptoms
 - ▣ +/- leucocyturia
 - ▣ Screen and treat only pregnant women and patients before urinary tract surgery
- **Catheter associated UTIs**
 - ▣ Treat only symptomatic patients
 - ▣ Asymptomatic bacteriuria and leucocyturia is VERY common
 - ▣ Rate of catheter colonisation up to 8% per day!
 - ▣ Change catheter, take urine culture from the newly inserted catheter, then start antibacterials

UTIs: clinical pearls

- **Staph aureus in urine culture. What does it mean?**
 - ▣ Usually NOT na UTI
 - ▣ Marker of Staph bacteraemia
- **Leucocyturia, low pH, negative urine culture. Flank pain, weight loss. What does it mean?**
 - ▣ Renal TB
- **2 or more bacteria species in urine culture. What does it mean?**
 - ▣ Contamination. Repeat urine culture.
- **Batson plexus. What is that?**
 - ▣ Batson's venous plexus is a system of paravertebral veins that connect pelvic and thoracic vessels to the intraspinal (basivertebral) veins
 - ▣ Possible route of spread of pelvic infections (UTI, gynae infection, diverticulitis,...) to the spine (vertebral osteomyelitis)

Skin and soft tissue infections

- **Erysipelas**
 - Superficial infection of the skin and dermis
 - Lymphatic spread (lymphangitis, lymphadenopathy)
 - Bright red discoloration, sharply demarcated, elevated, warm to touch, tender
 - In some patients bullous erysipelas
 - Sudden onset
 - Prodromal symptoms: nausea, vomiting, shivers, fevers
 - Streptococcus pyogenes
- **Cellulitis**
 - Deeper layers of dermis and hypodermis
 - Not sharply demarcated, sometimes purulent secretion
 - Prodromal symptoms are not usually present
 - Onset is gradual
 - Staphylococcus, streptococcus, (mixed flora, Clostridium perfringens)
- **Terminology and classification very confusing**

Erysipelas/cellulitis

- **Risk factors: lymphoedema, obesity, tinea, varices, diabetes mellitus, previous lower limb surgery, previous trauma, skin diseases (eczema, psoriasis), skin ulcers**
- **Diagnosis: clinical**
- (Blood culture, pus, ulcer swab)
- **Léčba: PNC (erysipelas), oxacillin/cefazolin (cellulitis), (ceftriaxone, vancomycin, daptomycin, clindamycin)**

Severe SSTIs (deep-seated infections)

- **Necrotising fasciitis**
 - Dermis, hypodermis, fascia, muscles
 - **Type 1: mixed flora (G-, G+, anaerobes), diabetes mellitus**
 - Lower limbs, deep neck spaces (Ludwig angina), perineum (Fournier gangrene)
 - Usually following injury or surgery
 - **Type 2: Group A Streptococcus („flesh-eating bacteria“)**
 - Injury (even on minor one!), chickenpox!!!
 - Sometimes + toxic shock syndrome!
- Life-threatening infection, excruciating pain with only mild local signs (oedema), later erythema, livid discolouration, bullae, SIRS, coma, death
- **Treatment: intensive care, urgent surgery**
- **Blood cultures, tissue samples + pus for culture, Gram stain**
- **Antibacterials**
 - PNC + Oxacillin + Gentamicin + Clindamycin + Metronidazole
 - Meropenem + Clindamycin

Myonecrosis (gas gangrene)

- **Clostridium perfringens, C. septicum**
- Following penetrating injury, abdominal surgery, sometimes translocation from the gut in the setting of bowel tumour (local invasion or hematogenous spread)
- Excruciating pain, pale skin, bronze discolouration, bullae, crepitation, SIRS, MODS
- **Gas seen on XR (CT)**
- **Toxins: microvascular thrombosis, haemolysis, reduced myocardial contractility, cytokine storm**
- **Intensive care, urgent surgery**
- **Gram stain (to guide antibiotic therapy)**
- **Sometimes difficult to distinguish from Nec Fasc**
- **ATB: PNC+ Clindamycin**

SSTIs: clinical pearls

- **Which bacterium causes erysipeloid?**
 - Erysipelothrix rhusiopathiae (water, animals)
 - G+ rod, fishermen/butchers/farmers
 - Tender lesions on hands
 - PNC OR CLINDAMYCIN OR CIPROFLOXACIN
- **What is a fish tank granuloma?**
 - Mycobacterium marinum
 - Indolent granulomas on hands (aquarists)
 - Clarithromycin for 3 months
- **What is a rose-thorn disease?**
 - Sporotrichosis (fungus)
 - Erythema, oedema, ulcers, nodular lymphangitis
 - Itraconazole

Thank you. Any questions?