Motto: „Every infection prevented is an antibiotic treatment avoided”

Basic principles of infectology - consultation

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Consultation - not an academic lecture!

- Brief history, why is it important to know a lot about this topic?
- ID - epidemiology
- Human-Microbe relationships
- Approach to a patient with ID
- Principles of anti-infective therapy

We focus on the general overview, the details come latter...
What we skip in the consultation: asepsis, antisepsis, antibiotic-stewardship
- Do you know how to wash your hands?
The brief history of infectious diseases

- mid-sixteenth century: communicable diseases were due to a *miasma* ("bad air")
- late-nineteenth century: Louis Pasteur and Robert Koch - germ theory of disease
  - 1882 Hans Christian Gram - Gram stain
- twentieth century: remarkable and fast advances in the field of infectious diseases
  - 1928 Alexander Flemming - penicillin
  - 1935 Clostridium difficile → 1970’s connection with pseudomembranosus colitis
  - elimination of smallpox
  - associations of *Helicobacter pylori* with peptic ulcer disease and gastric carcinoma
  - 1984 identifying HIV as the causative agent of AIDS
Why is it important? - the all known reasons:

- ~16% of all malignancies are now known to be associated with an infectious cause
- emerging and re-emerging infectious diseases continue to have a dire impact on global health: HIV/AIDS, pandemic influenza, severe acute respiratory syndrome (SARS)
- weaponizing pathogens for bioterrorism is ever present
- escalating antimicrobial resistance - appropriate stewardship is required
Leading causes of death (WHO) - ID are 2nd overall

Top 10 causes of death globally 2015

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Deaths in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>8</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
</tr>
<tr>
<td>Lower respiratory</td>
<td>4</td>
</tr>
<tr>
<td>Chronic obstructive</td>
<td>2</td>
</tr>
<tr>
<td>Trachea, bronchus</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td></td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Road injury</td>
<td></td>
</tr>
</tbody>
</table>

The top 10 causes of death in low-income economies 2015

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Deaths per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower respiratory</td>
<td>54</td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td>36</td>
</tr>
<tr>
<td>Stroke</td>
<td>35</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>26</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>18</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>18</td>
</tr>
<tr>
<td>Malaria</td>
<td>18</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>18</td>
</tr>
<tr>
<td>Birth asphyxi</td>
<td>18</td>
</tr>
<tr>
<td>Road injury</td>
<td>18</td>
</tr>
</tbody>
</table>
Most of infectious diseases are cureable!
ID - how much % of the book?

- There are 19 parts
- Part 8 is ID - 676 pages (of 2770 pages)
- 24% of the book
ID - epidemiology

1. Describe patterns of infection and disease occurrence in populations.
2. Identify outbreaks or unusual rates of disease occurrence.
3. Facilitate laboratory-based efforts to identify infectious agents.
4. Describe the occurrence of asymptomatic infection and the spectrum of disease associated with specific agents.
5. Provide population-based descriptions of clinical illness to improve the specificity of diagnosis for individual diseases.
6. Assist in the understanding of disease pathogenesis.
7. Identify and characterize factors in the chain of infection that contribute to agent transmission and the development of disease.
8. Develop and evaluate treatment protocols through clinical trials.
9. Develop and evaluate primary, secondary, and tertiary prevention and control measures for individuals.
10. Describe and assess the use of prevention measures on a community-wide basis.
Use the epidemiologic data!

- World: http://www.who.int/en/
- USA: https://www.cdc.gov/

Traveling information: https://wwwn.cdc.gov/travel/destinations/list/

National epidemiologic data is available!
As the currently dominant B/Yamagata virus is not included in the trivalent vaccines and there is no evidence of any reduced susceptibility, post-exposure of antiviral treatment with oseltamivir or zanamivir should be encouraged, particularly in high-risk patients.
Influenza in Europe
Data from EU and EEA countries for the 2017–18 season
Week 4 (22–28 January 2018)

Influenza viruses circulating in 2017–2018
Only sentinel specimens are included

- Subtype A(H1): 15.7%
- Subtype A(H3): 7.5%
- Type A unsubtyped: 9.1%
- Type B/Victoria: 0.9%
- Type B/Yamagata: 28%
- Type B: 38.8%

Influenza intensity in week 4
based on sentinel reports of influenza-like illness and/or acute respiratory infections

Bubble size is indicative of country population

Influenza trend
based on the percentage of sentinel specimens found positive, by week

2016–2017
2017–2018
### Surveillance Atlas of Infectious Diseases

#### Tuberculosis

<table>
<thead>
<tr>
<th>Region</th>
<th>Reported cases (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/EEA</td>
<td>56994</td>
</tr>
<tr>
<td>Austria</td>
<td>654</td>
</tr>
<tr>
<td>Belgium</td>
<td>1249</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>1603</td>
</tr>
<tr>
<td>Croatia</td>
<td>460</td>
</tr>
<tr>
<td>Cyprus</td>
<td>63</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>516</td>
</tr>
<tr>
<td>Denmark</td>
<td>330</td>
</tr>
<tr>
<td>Estonia</td>
<td>192</td>
</tr>
<tr>
<td>Finland</td>
<td>126</td>
</tr>
<tr>
<td>France</td>
<td>4958</td>
</tr>
<tr>
<td>Germany</td>
<td>5915</td>
</tr>
<tr>
<td>Greece</td>
<td>443</td>
</tr>
<tr>
<td>Hungary</td>
<td>766</td>
</tr>
<tr>
<td>Iceland</td>
<td>6</td>
</tr>
<tr>
<td>Ireland</td>
<td>338</td>
</tr>
</tbody>
</table>

#### Reported cases (%)

Value range: 5 - 22595

#### Yearly reported cases

- **EU/EEA**

#### Distribution by age

- 0-4
- 5-14
- 15-24
- 25-64
- 45-64
- 65+
## Surveillance Atlas of Infectious Diseases

### Antimicrobial resistance

<table>
<thead>
<tr>
<th>Region</th>
<th>Resistant (R) isolates proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>1.1</td>
</tr>
<tr>
<td>Belgium</td>
<td>0.4</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>21.2</td>
</tr>
<tr>
<td>Croatia</td>
<td>21.9</td>
</tr>
<tr>
<td>Cyprus</td>
<td>40.0</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>0.8</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.4</td>
</tr>
<tr>
<td>Estonia</td>
<td>0.0</td>
</tr>
<tr>
<td>Finland</td>
<td>0.0</td>
</tr>
<tr>
<td>France</td>
<td>0.1</td>
</tr>
<tr>
<td>Germany</td>
<td>0.7</td>
</tr>
<tr>
<td>Greece</td>
<td>-</td>
</tr>
<tr>
<td>Hungary</td>
<td>0.0</td>
</tr>
<tr>
<td>Iceland</td>
<td>0.0</td>
</tr>
<tr>
<td>Ireland</td>
<td>0.0</td>
</tr>
<tr>
<td>Italy</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### Resistant (R) isolates proportion, by age

- <2%
- 1-5%
- 5-10%
- 10-25%
- 25-50%
- 50-75%
- >=75%
Traveler’s health - https://wwwnc.cdc.gov/travel

22-year-old woman traveled to Thailand. Spent 1 week there. (Took preventive measures against yellow fever, malaria) After arriving back to Budapest she developed high degree fever (39 Celsius) and a skin rush. Was admittited to the ID ward and empirically imipenem/cilastatin was started. At 48hs procalcitonin was still negativ, AB was stopped. And a presumptive diagnosis was made.
Traveler’s health - [https://wwwnc.cdc.gov/travel](https://wwwnc.cdc.gov/travel)

- Serology and control for Dengue fever was positive: IgM seroconversion between paired acute and convalescent phase
- Critical phase has not developed
Human-Microbe relationships: microbiota

- “supra-organism” in which microbial symbionts outnumber human cells by 10-fold
- co-evolution, co-adaptation, co-dependency
  - facilitates nutrient acquisition and energy extraction from food
  - stimulates both the innate and adaptive immune systems
  - provides “colonization resistance” against pathogen invasion
- not all pathogens have an equal probability of causing clinically apparent disease
  - Virulence provides a quantitative measure of pathogenicity
  - Virulence factors refer to the properties

<table>
<thead>
<tr>
<th>Transient</th>
<th>A microorganism that we encounter in our food or elsewhere in our environment. In general, it is just “passing through” and of little consequence; however, regular encounters over extended periods of time might lead to host adaptation or even dependence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commensal</td>
<td>A microorganism that is a normal inhabitant of the human body. In commensal relationships, either the microbe or host derives benefit; in mutualistic relationships, both derive benefit.</td>
</tr>
<tr>
<td>Pathogen</td>
<td>A microbe that may or may not be a member of the indigenous microbiota, but it regularly causes disease in apparently normal individuals.</td>
</tr>
<tr>
<td>Opportunistic pathogen</td>
<td>A microbe that causes disease only in humans who are in some way compromised in their normal defense mechanisms.</td>
</tr>
<tr>
<td>Accidental pathogen</td>
<td>A microorganism that is encountered by accidental contact with animals, insects, or the environment. These microorganisms are often deadly in humans and sometimes the causative agent of disease in other animals. These microbes are often distinguished from human-specific pathogens because they are not directly or readily transmissible from human to human.</td>
</tr>
</tbody>
</table>
The Human Microbiome Project (HMP)

- canonical pathogens are generally absent from the human microbiome in healthy individuals (exceptions were the well-known pathogens *Staphylococcus aureus* and *Escherichia coli*)
- opportunistic pathogens are widely distributed in healthy adults
- each primary body habitat in the healthy human microbiome contains a distinctive microbial community
- a single microbe is the etiologic agent of infection \(\rightarrow \leftarrow\) the pathogenesis and pathophysiology of infection can be viewed within the context of the microbiome and human biology
  - shifts the focus to the global balance of our microbiota
  - human microbiome as „metagenomic medicine” (e.g., recurrent *Clostridium difficile* colitis)
Microbial pathogens

1. enter the human host
2. become established, which includes successful competition with indigenous microbes
3. acquire nutrients
4. avoid or circumvent the host’s innate defenses and a powerful immune system
5. above all, replicate
6. disseminate if necessary to a preferred site
7. eventually be transmitted to a new susceptible host

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>VIRULENCE FACTOR</th>
<th>BIOLOGIC FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasmid Encoded</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic <em>Escherichia coli</em></td>
<td>Heat-labile, heat-stable enterotoxins</td>
<td>Activation of adenylate/guanylate cyclase in the small bowel, which leads to diarrhea</td>
</tr>
<tr>
<td>Extraintestinal <em>E. coli</em></td>
<td>CFA/I and CFA/II</td>
<td>Adherence/colonization factors</td>
</tr>
<tr>
<td><em>Shigella</em> spp. and enteroinvasive <em>E. coli</em></td>
<td>Gene products involved in invasion</td>
<td>Induces internalization by intestinal epithelial cells</td>
</tr>
<tr>
<td><em>Yersinia</em> spp.</td>
<td>Adherence factors and gene products involved in invasion</td>
<td>Attachment/invasion</td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>Edema factor, lethal factor, and protective antigen</td>
<td>Edema factor has adenylate cyclase activity; lethal factor is a metalloprotease that acts on host signaling molecules</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Exfoliative toxin</td>
<td>Causes toxic epidermal necrosis</td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Tetanus neurotoxin</td>
<td>Blocks the release of inhibitory neurotransmitter, which leads to muscle spasms</td>
</tr>
</tbody>
</table>

| **Phage Encoded**               |                                   |                                                                                    |
| Corynebacterium diphtheriae     | Diphtheria toxin                    | Inhibition of eukaryotic protein synthesis                                        |
| *Streptococcus pyogenes*        | Erythrogenic toxin                  | Rash of scarlet fever                                                             |
| *Clostridium botulinum*         | Botulism neurotoxin                 | Blocks synaptic acetylcholine release, which leads to flaccid paralysis           |
| Enterohemorrhagic *E. coli*     | Shiga-like toxin                    | Inhibition of eukaryotic protein synthesis                                         |
| *Vibrio cholerae*               | Cholera toxin                       | Stimulates adenylate cyclase in host cells                                         |
Approach to a patient with ID (sepsis?)

The patient is stable - we have time.
- whole and detailed H&P

The patient is instable - we are under pressure.
- focused H&P - ABCDE SBAR

How should anyone know?
Approach to a patient with ID

Whole and detailed H&P:

- an exposure history that may identify microorganisms
  - Previous infections: microorganisms, resistant microorganisms, colonizations - surveillance
  - Social history: IV drug use, alcohol, tobacco, occupational exposures
    /in 2009 in which a laboratory researcher died of a *Yersinia pestis* infection acquired during his work/
  - Dietary habits: raw or undercooked meat (Shiga toxin-producing strains of *Escherichia coli* and *Toxoplasma gondii*); unpasteurized milk, developing diarrhea after eating ...
  - Animal exposures: cats - Bartonella henselae; reptiles - Salmonella etc.
- Travel history
- Developing lobar pneumonia after taking care of a grandchild ...

- host-specific factors that may predispose to the development of an infection
  - Neutropenic/immunocompromised patients - related opportunistic infections
  - Age related infections
Approach to a patient with ID

Physical examination:

- Vital signs
- Lymphatics - presenting with lymphadenopathy, 75% have localized findings
- Skin: distal extremities - splinter hemorrhages, Janeway lesions, or Osler’s nodes; pressure ulcers
  - Fever and rash
- Foreign bodies: biofilm infections, catheter associated infections
Approach to a patient with ID - diagnostic tests

- **WBC**
  - Elevations in the WBC count are often associated with infection, though many viral infections are associated with leukopenia.
  - Assess the WBC differential: bacteria are associated with an increase in polymorphonuclear neutrophils; viruses are associated with an increase in lymphocytes; certain parasites are associated with an increase in eosinophils.

- **ESR** - very slow, measure it weekly only, low specificity.

- **CRP** - more rapid, can be measured daily, low specificity.
  - Specificity for diagnosis of sepsis is rather low and its peak plasma levels do not indicate the severity.
  - Increase to peak levels of CRP may take several days, the decline of its increased plasma levels may also take up to one or two weeks.

- **PCT** - very rapid, more specific for bacteria and fungi, it’s place in diagnostics and treatment is debated.
  - Lag time for PCT induction is approximately 2 to 4 hr after the onset of sepsis.
  - Peak levels of PCT occur at 24 to 48 hrs after sepsis.
  - Antibiotic prescription rates were significantly reduced by the use of PCT.
Approach to a patient with ID - diagnostic tests

- Radiology
  - CXR
  - Abdominal US
  - Contrast CT/MR
  - SPECT/PET

Each has different sensitivity/specificity: neutropenic patient’s lower airway infections are not gonna be seen on CXR only on CT.

They do not overrule the findings on physical examination: auscultation over lung becomes positive in pneumonia faster than CXR.
Approach to a patient with ID - diagnostic tests

- Cultures
  - Hemocultures +/- Gram stain, agglutination
  - Urine, sputum, purulence from wound, BAL etc.
- Pathogen specific testing
  - Serology, antigen test, PCR

When to collect?
How to collect?
How many to collect?

Sensitivity and specificity? - blood cultures are estimated to be positive for *S. pneumoniae* in less than 10% of patients who actually have pneumococcal pneumonia.
Approach to a patient with ID - microbiology laboratory

The clinician and the microbiologist must actively work together to maximize the clinical value of diagnostic microbiology testing:

- immediate telephone notification of critical laboratory results
- hospital surveillance program can monitor infection rates and noncompliance with established infection prevention policies

Clinician’s Responsibilities:

- Maintain knowledge of the laboratory test menu and specimen collection and transport guidelines (influenza, CDI)
  - Selection of the appropriate specimen and test for the detection of an organism responsible for the patient’s disease is the ultimate objective
- Alert the laboratory when a specific organism is sought (e.g., slow growing organism)
- Prioritize test requests when a limited quantity of specimen can be collected
- Establish an open communication with the laboratory director when testing needs are not satisfied by the available test menu or special handling of a specimen is required
Approach to a patient with ID - microbiology laboratory

Result:
- Potential pathogen(s)
- Antimicrobial susceptibility
- Additional information

The results should be interpreted!
- this is a point where lots of clinicians fail
Principles of anti-infective therapy—Identification of the Infecting Organism

- identity of the **infecting organism must be known** or (→ **definitive therapy**)
- it must be possible to arrive at a **statistically reasonable guess** as to its identity on the basis of clinical information (→ **empiric therapy**)

Rapid identification: Gram stain, ELISA or latex agglutination, PCR, NAAT
Definitive identification: culture

- in most cases, it is impossible to determine the exact nature of the infecting organisms before the institution of antimicrobial therapy

Statistically reasonable guess: epidemiologic data, H&P, surveillance data

  - **bacteriologic statistics** refers to the application of knowledge of the organisms most likely to cause infection in a given clinical setting
Principles of anti-infective therapy-
Determination of Antimicrobial Susceptibility of Infecting Organisms

- if the pathogen is isolated from a culture, it can be subjected to direct susceptibility testing
- the lowest concentration of the antimicrobial agent that prevents visible growth, usually after an 18- to 24-hour incubation period, is the minimal inhibitory concentration (MIC)
- antimicrobial agents is to exert selective pressure that results in the emergence of resistant organisms
  - in some cases, the organisms are naturally resistant to the antibiotic used
  - acquired genes encoded on transposons or plasmids that enable them to resist antimicrobial inhibition
- There are very few examples of organism-antibiotic combinations for which susceptibility can be predicted: Group A and other β-hemolytic streptococci - penicillins
<table>
<thead>
<tr>
<th>ORGANISMS</th>
<th>NATURAL RESISTANCE AGAINST:</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobic bacteria</td>
<td>Aminoglycosides</td>
<td>Lack of oxidative metabolism to drive uptake of aminoglycosides</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td>Metronidazole</td>
<td>Inability to anaerobically reduce drug to its active form</td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>Aztreonam (a beta-lactam)</td>
<td>Lack of penicillin binding proteins (PBP) that bind and are inhibited by this beta lactam antibiotic</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>Vancomycin</td>
<td>Lack of uptake resulting from inability of vancomycin to penetrate outer membrane</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>Ampicillin (a beta-lactam)</td>
<td>Production of enzymes (beta-lactamases) that destroy ampicillin before the drug can reach the PBP targets</td>
</tr>
<tr>
<td><em>Stenotrophomonas. maltophilia</em></td>
<td>Imipenem (a beta-lactam)</td>
<td>Production of enzymes (beta lactamases) that destroy imipenem before the drug can reach the PBP targets.</td>
</tr>
<tr>
<td>Lactobacilli and <em>Leuconostoc</em></td>
<td>Vancomycin</td>
<td>Lack of appropriate cell wall precursor target to allow vancomycin to bind and inhibit cell wall synthesis</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Sulfonamides, trimethoprim, tetracycline, or chloramphenicol</td>
<td>Lack of uptake resulting from inability of antibiotics to achieve effective intracellular concentrations</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Aminoglycosides</td>
<td>Lack of sufficient oxidative metabolism to drive uptake of aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>All cephalosporins</td>
<td>Lack of PBP that effectively bind and are inhibited by these beta lactam antibiotics</td>
</tr>
</tbody>
</table>
Principles of anti-infective therapy - Host Factors

- history of previous adverse reactions
- age
  - gastric acidity varies with age: absorption of a number of antimicrobials administered via the oral route depends on their acid stability and the pH of gastric secretions
    - orally administered β-lactam antibiotics is probably also enhanced in achlorhydric patients; however, evidence is convincing only in the case of the penicillins
- renal function
- age related contraindications
  - tetracyclines are avidly bound to developing bone and tooth structures
  - quinolone antimicrobials have been shown to cause cartilage damage and arthropathy in young animals
Principles of anti-infective therapy - Host Factors

- **Genetic or metabolic abnormalities - interactions**
  - Number of antimicrobial agents have been shown to be capable of provoking hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, including the sulfonamides, dapsone (a sulfone), nitrofurantoin.
  - Diabetes mellitus - such as the sulfonamides can potentiate the hypoglycemic activity of sulfonylurea hypoglycemic agents.
  - Cephalosporins, isoniazid, nitrofurantoin, penicillin, streptomycin, and the tetracyclines can all cause false-positive test results when urine sugar levels.
  - Rifampin and other rifamycins may increase the hepatic metabolism and therefore decrease the effect of oral anticoagulants, oral contraceptives, barbiturates, and a number of other drugs, including the protease inhibitors.
  - Macrolides, fluoroquinolones, and antifungals, can potentially prolong the cardiac QTc interval.
Principles of anti-infective therapy - Host Factors - pregnancy

- Category A: adequate studies in pregnant women, no risk
- Category B: animal reproduction studies, no fetal risk; no controlled studies in pregnant women
- Category C: animal reproduction studies shown fetal adverse effect; no controlled studies in humans; potential benefit may warrant use despite potential risk
- Category D: evidence of human fetal risk; potential benefit may warrant use despite potential risk
- Category X: animal and human studies demonstrates fetal abnormalities; risks in pregnant women clearly exceed potential benefits
Principles of anti-infective therapy -
Host Factors

Renal and hepatic function

- the ability of the patient to **metabolize or excrete** antimicrobial agents is one of the most important host factors to consider.

- doses for drugs that require alteration in patients with impaired renal function can be found.

- agents that require no dosage change in patients with impaired renal function are excreted effectively by extrarenal routes, usually the hepatobiliary system (doxycycline, moxifloxacin).

- certain antimicrobial agents, including erythromycin, azithromycin, chloramphenicol, lincomycin, and clindamycin, should be used with caution in patients with impaired hepatic function.
Principles of anti-infective therapy-
Host Factors

Site of infection

- for antimicrobial therapy to be effective, an adequate concentration of the drug must be delivered to the site of infection
- local concentration of the antimicrobial agent should at least equal the MIC
- monitoring of serum concentrations is routinely performed only for a limited number of antimicrobials, such as vancomycin, aminoglycosides
- therapeutic drug monitoring has an increasing role in the management of fungal infections (interpersonal variability is high)
- penetration of antimicrobial agents into interstitial fluid and lymph is related to protein binding

Blood/brain barrier crossing: lipid-soluble agents, such as chloramphenicol, rifampin, trimethoprim, and isoniazid, are all more efficient in penetrating membranes. + ceftriaxone, ampicillin, meropenem
Principles of anti-infective therapy - Host Factors

**Blood/brain barrier crossing:** lipid-soluble agents, such as chloramphenicol, rifampin, trimethoprim, and isoniazid, are all more efficient in penetrating membranes + ceftriaxon, ampicillin, meropenem

**Agents that are excreted by the liver and are concentrated in the bile:** ampicillin, doxycycline, ceftriaxon

**Bone:** new fluoroquinolones may owe some of their effectiveness in the treatment of osteomyelitis to their ability to achieve superior concentrations in bone

**Prostate:** new fluoroquinolones

**Abcesses:** bad penetration by antibiotics - surgical drainage is imperative

**Significant hematoma:** penicillins and tetracyclines are bound by hemoglobin and thus may be less effective
Principles of anti-infective therapy-pharmacokinetics

- **Duration of therapy**: shortest effective duration
  - For the most indication the duration is getting shorter
    - CAP 5 days (even 3 can be enough)

- **Pharmacokinetics**
  - In severe infection the aim is to reach high enough concentration at the site of infection
  - State of metabolism: kidney, liver
  - Distribution and penetration in tissues
  - Beta-lactams T>MIC at least 70%
  - Aminoglycosides Cmax/MIC 8-12
  - Fluorokinolons, vancomycin AUC/MIC

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**Figure 170-2**: Pharmacokinetic and pharmacodynamic model predicting efficacy of antibacterial drugs. AUC, area under the time–concentration curve; C\(_{\text{max}}\), peak serum concentration of drug; MIC, minimal inhibitory concentration; T>MIC, duration of drug concentrations above the MIC.
**Principles of anti-infective therapy - basics**

- **Definitive therapy**: infecting organism must be known
- **Empiric therapy**: statistically reasonable guess (80% for stable patients, 95% for instable patients)
- **Prophylactic therapy**: aims at preventing an infection in a high risk scenario
  - IE profilaxis as example
- **Escalation / De-escalation**
Take home messages

- Take your time for learning the basics of ID because
  - you gonna face them a lot
  - most of the time these are curable disease

- When facing an ID patient
  - get as much information as you can (H&P, epidemiology, resistance data...)
  - make a statistically reasonable guess (what can be the microorganism - local resistance)
  - work together with the Microbiology Department
  - always interpret the results

- When something is not clear ask for a consult with a specialist

- Whenever it is possible, try to prevent the infections!

Homework: look through the antiinfective agent groups!