Practical application of antibiotic use data

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No conflict of interest
Questions for the ACASEM Survey

Question 1. Antimicrobial stewardship activities in hospitals should be combined with infection control interventions
True         False
Question 2. Point prevalence surveys can be used to assess

- Prevalence of antibiotic use
- Appropriateness of antibiotic therapy by diagnosis
- Appropriateness of antibiotic prescriptions according to the class of antibiotic
- Appropriateness of antibiotic therapy by medical specialization
- Dose and administration route
- All mentioned above
Question 3. Dose and length of antibiotic treatment is dependent on

Localization of disease
Type of microorganism
Speed of response to treatment
All the factors
Izmeklejamas materiāls

<table>
<thead>
<tr>
<th>Mikroorganisms</th>
<th>Antibiotikas nosaukums</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Ampicillin</td>
<td>R</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>Amoxicillin/Clavulanate</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Piperac/Tazobactam</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Aztreonam</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Imipenem</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Cephalothin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Cefoxitin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Cefoperazone</td>
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</tr>
<tr>
<td></td>
<td>Ceftriazone</td>
<td>R</td>
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<tr>
<td></td>
<td>Cefazidime</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
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<td>Ofloxacina</td>
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<tr>
<td></td>
<td>Norfloxacin</td>
<td>R</td>
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<td></td>
<td>Chloramphenicol</td>
<td>R</td>
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<tr>
<td></td>
<td>Clindamycin</td>
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<tr>
<td></td>
<td>Rifampin</td>
<td>R</td>
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<td></td>
<td>Doxycycline</td>
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</tr>
<tr>
<td></td>
<td>Tetracycline</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantion</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin/Sulbactam</td>
<td></td>
</tr>
</tbody>
</table>

Testēšanas pārskata izsniegās datuma 10.03.2011

Testēšanas rezultāti atiecās tikai uz noteiktu testēšanas objektu. Bez VSIA P.Stradiņa KUS CL mikrobioloģijas un serologijas aizpiedājumu nav iestājā testēšanas pārskata reproducēšana pilnā apjomā.
Exchange of resistance mechanisms and bacteria between different reservoirs

ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals
Healthcare-associated infections

Antimicrobial resistance

Community-acquired infections
Containment of spread of MDR pathogens

Development of resistance
Antibiotic Stewardship

Transmission
Infection control
Antimicrobial stewardship (AMS)

• Definition of AMS: a strategy aiming at promoting responsible antibiotic use

• AMS programme in hospitals= a set of interventions to fine tune antibiotic use in regards to
  – Efficacy
  – Toxicity
  – Resistance-induction
  – *Clostridium difficile* induction
  – IV to PO switch
  – Cost
  – Discontinuation
Contamination

Colonisation

Local infection/Critical colonisation

Spreading invasive infection

Septicaemia
Unexposed

Colonization

Domination

Infection

Acquisition

Selection

Host factors

Prof. Dr. Jörg Vehreschild Personal communication
<table>
<thead>
<tr>
<th>Study setting</th>
<th>Number of studies</th>
<th>Incidence ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit</td>
<td>10</td>
<td>0.77 (0.66-0.89)</td>
</tr>
<tr>
<td>Medical ward</td>
<td>27</td>
<td>0.78 (0.66-0.91)</td>
</tr>
<tr>
<td>Surgical ward</td>
<td>5</td>
<td>0.76 (0.46-1.25)</td>
</tr>
<tr>
<td>Haematology- oncology ward</td>
<td>3</td>
<td>0.41 (0.20-0.85)</td>
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<tr>
<td>Co-implementation of ICMs</td>
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<td></td>
</tr>
<tr>
<td>ASP alone</td>
<td>23</td>
<td>0.81 (0.67-0.97)</td>
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<tr>
<td>ASP + ICMs</td>
<td>9</td>
<td>0.69 (0.54-0.88)</td>
</tr>
<tr>
<td>ASP + hand-hygiene intervention</td>
<td>5</td>
<td>0.34 (0.21-0.54)</td>
</tr>
<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic restriction</td>
<td>15</td>
<td>0.77 (0.67-0.89)</td>
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<tr>
<td>Audits/feedback</td>
<td>19</td>
<td>0.66 (0.52-0.83)</td>
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<tr>
<td>Antibiotic cycling</td>
<td>3</td>
<td>0.49 (0.34-0.72)</td>
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<tr>
<td>Year of study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-2000</td>
<td>5</td>
<td>0.90 (0.60-1.35)</td>
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<tr>
<td>2001-05</td>
<td>10</td>
<td>0.79 (0.69-0.90)</td>
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<tr>
<td>2006-13</td>
<td>17</td>
<td>0.58 (0.49-0.95)</td>
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<td>Infection and/or colonisation</td>
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<tr>
<td>Infection and colonisation</td>
<td>8</td>
<td>0.91 (0.60-1.37)</td>
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<tr>
<td>Infection</td>
<td>21</td>
<td>0.75 (0.66-0.85)</td>
</tr>
<tr>
<td>Colonisation</td>
<td>3</td>
<td>0.72 (0.41-1.25)</td>
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<td>Study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interrupted time-series studies</td>
<td>6</td>
<td>1.20 (0.97-1.50)</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>7</td>
<td>0.79 (0.61-1.02)</td>
</tr>
<tr>
<td>Before-after studies</td>
<td>18</td>
<td>0.56 (0.54-0.81)</td>
</tr>
</tbody>
</table>
Opportunities antibiotic stewardship policies

Diagnostic work-up for suspected infection
- Guidelines on testing
- Stewardship of laboratory testing
- Rapid diagnostics

Empirical therapy started
- Institutional guidelines
- Antibiogram available
- Computerized decision support
- Allergy testing
- Formulary restriction
- Prospective audit and feedback
- Automatic stop orders

Definitive therapy
- Prospective audit and feedback
- Antibiotic time-out
- Embedded ID or ASP provider
- Guidelines
- Cascade reporting
- Pharmacy interventions

Doemberg SB et al, 2017 Infectious Disease Clinics of Northern America
Where to start AMS activity?

• Clear opportunity to improve
  – PPS data
  – Laboratory surveillance reports
  – Healthcare associated infection surveillance
• Potential high impact on use and spread of resistance
  – Intensive care units
  – Transplantation
  – Nephrology
How to start?

• Start with friendly colleagues
• Frequent personal presence
• Start small
• Build on success
• Monitor your impact and adapt
• Avoid multiplicity of advisers for the same patient/department
• Feedback to colleagues
  – Short and easy to understand
  – Real time involvement
Planning stage

- Administrative support
- Creation of the team
- Choose monitoring system
- List of indicators
- Information for the department
How to measure and assess antibiotic use?

- Electronic records RDD or PDD
- Point prevalence surveys PDD
- Pharmacy
  - DDD/stays,
  - Packages
  - Grams
  - Euros
**DDD usefulness**

- Reduction in general consumption DDD/stays
- Reduction in consumption of selected antibiotics DDD/stays
- Replacement by different antibiotic DDD/stays

- Difficult due to patient mix
Point prevalence approach

• One day, one clinical unit
• All patients on antibiotics/all patients
  – Patient demographics
  – Reason for antibiotics
  – Antibiotic
  – Dose
What to include on antimicrobial section??

PROPHYLAXIS
Day before survey
8:00 AM - 8:00 AM
day of survey

TREATMENT
Planned at time of survey
If stopped before survey do not include

INTERMITTENT
PLANNED TREATMENT
e.g. alternate day

Carl Suetens. Personal communication
### European Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use

**Form A. Patient-based data (standard protocol)**

**Patient data (to collect for all patients)**

- Hospital code
- Ward name (abbr.)/Unit Id
- Ward specialty
- Survey date: ___ / ___ / _______  (dd/mm/yyyy)
- Patient Counter: 
- Age in years: ___ yrs;  Age if < 2 year old: _____ months
- Sex: M  F
- Date of hospital admission: ___ / ___ / ____
- Consultant/Patient Specialty:
- Surgery since admission:
  - O No surgery
  - O NHSN surgery
  - O Unknown
- McCabe score:
  - O Non-fatal disease
  - O Ultimately fatal disease
  - O Rapidly fatal disease
  - O Unknown
- Central vascular catheter:
  - O No
  - O Yes
  - O Unk
- Peripheral vascular catheter:
  - O No
  - O Yes
  - O Unk
- Urinary catheter:
  - O No
  - O Yes
  - O Unk
- Intubation:
  - O No
  - O Yes
  - O Unk
- Patient receives antimicrobial(s): O No
- Patient has active HAI: O No

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### Antimicrobial (generic or brand name)

- Route
- Indication
- Diagnosis
- Notes
- Reason in

<table>
<thead>
<tr>
<th>Antimicrobial (generic or brand name)</th>
<th>Route</th>
<th>Indication</th>
<th>Diagnosis</th>
<th>Notes</th>
<th>Reason in</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Case definition code**

<table>
<thead>
<tr>
<th>Case definition code</th>
<th>HAI 1</th>
<th>HAI 2</th>
<th>HAI 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant device in situ before onset[3]</td>
<td>O Yes</td>
<td>O No</td>
<td>O Yes</td>
</tr>
<tr>
<td>Present at admission</td>
<td>O Yes</td>
<td>O No</td>
<td>O Yes</td>
</tr>
<tr>
<td>Date of onset[4]</td>
<td>___ / ___ / ____</td>
<td>___ / ___ / ____</td>
<td>___ / ___ / ____</td>
</tr>
<tr>
<td>Origin of infection</td>
<td>O current hospital</td>
<td>O other hospital</td>
<td>O other origin/ unk</td>
</tr>
</tbody>
</table>

**Microorganism 1**

**Microorganism 2**

**Microorganism 3**

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(1) At the time of the survey, except for surgical prophylaxis 24h before 8:00 AM on the day of the survey; if yes, fill antimicrobial use data; (2) [infection with onset ≥ Day 3, OR SSI criteria met (surgery in previous 30d/1yr), OR discharged from acute care hospital <28 days ago OR onset < Day 3 after invasive device/procedure on D1 or D2] AND [HAI case criteria met on survey day OR patient is receiving (any) treatment for HAI AND case criteria are met between D1 of treatment and survey day]; if yes, fill HAI data

(3) relevant device use (intubation for PN, CVC for BSI, urinary catheter for UTI) in 48 hours before onset of infection (even intermittent use), 7 days for UTI; (4) Only for infections not present/active at admission (dd/mm/yyyy); (5) C-CVC, C-PVC, S-PUL, S-UTI, S-DIG, S-SSI, S-SST, S-OTH, UO, UNK; (6) AMR marker 0,1,2 or 9, see table
# GLOBAL-PPS PATIENT Form

(Please fill in one form per patient on antimicrobial treatment/prophylaxis)

<table>
<thead>
<tr>
<th>Ward Name/code</th>
<th>Activity (M, S, IC)</th>
<th>Patient Identifier</th>
<th>Survey Number</th>
<th>Patient Age</th>
<th>Gender M or F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Years (if ≥ 2 years)</td>
<td>Months (1-23 month)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antimicrobial Name</th>
<th>Single Unit Dose (g, mg, or IU)</th>
<th>Doses/day</th>
<th>Route (P, O, R, I)</th>
<th>Diagnosis (see appendix II)</th>
<th>Type of indication (see appendix III)</th>
<th>Reason in Notes (Yes or No)</th>
<th>Guideline Compliance (Y, N, NA, NI)</th>
<th>Is a stop/review date documented? (Yes or No)</th>
<th>Treatment (E: Empirical; T: Targeted)</th>
<th>Treatment based on biomarker data? (Yes or No)</th>
<th>If yes, on which biomarker? (fill in: CRP, PCT or other)</th>
<th>Targeted treatment choice based on microbiology data (Yes, No)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.</td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

IF YES: (This section is to be filled in only if the treatment choice is based on microbiology data AND the organism is one of the following)

- MRSA (Yes or No)
- MRCoNS (Yes or No)
- VRE (Yes or No)
- ESBL-producing Enterobacteriaceae (Yes or No)
- 3rd generation cephalosporin resistant Enterobacteriaceae non-ESBL producing
Prevalence survey

Intervention
Plan
Analyze
Interventions measured by point prevalence (Process measures)

- New formulary and education
- New guidelines and education
- Shortened laboratory reports
- Switch from IV to oral
Funnel plot comparing hospital prescribing in the UK using proportion of children on antibiotics.
Appropriateness of use of AMT (95% confidence interval) in six surveys between 2001 and 2004.
Appropriateness of antibiotic prescriptions assessed with point prevalence survey

• Appropriateness of antibiotic prescriptions according to the class of antibiotic
• Appropriateness of antibiotic therapy by diagnosis
• Appropriateness of antibiotic therapy by medical specialization
High quality of each prescription: ultimate goal of all AMS programmes.
Figure 1: The 22 domains of responsible antibiotic use identified through a systematic review. On the right side of the figure are the domains affecting the individual patient and on the left of the figure are the societal domains.
Impact of diagnostic testing

- Accurate identification of bacterial infection and rapid identification and susceptibility testing can improve antibiotic use and clinical outcomes.

- Negative test results can assist providers with stopping antibiotics.

- Cascade reporting of antibiotics may improve appropriate selection of antibiotics.
Resistance testing

- Strains are sorted according to level of Minimal Inhibitory Concentration (MIC) versus reference breakpoints
- \( c \) and \( C \) are the minor and major breakpoints

<table>
<thead>
<tr>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{MIC} &lt; c )</td>
<td>( c \leq \text{MIC} &lt; C )</td>
<td>( C \leq \text{MIC} )</td>
</tr>
</tbody>
</table>
Breakpoints

Breakpoints are determined using two approaches

• Pharmacological concept
• Clinical and epidemiological concept

• Breakpoints are the expression of a consensus among the scientific community at a given time in a country or region
The epidemiological concept for breakpoints

Wild type

Inherited resistance mechanism

MIC
Dosages

EUCAST Clinical Breakpoint Tables v. 7.1, valid from 2017-02-16

EUCAST breakpoints are based on the following dosages (see section 8 in Rationale Documents).

<table>
<thead>
<tr>
<th>Penicillins</th>
<th>Standard dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzylenicillin</strong></td>
<td>0.6 g x 4 iv</td>
<td>2.4 g x 6 iv</td>
</tr>
<tr>
<td><strong>Ampicillin</strong></td>
<td>0.5-1 g x 3-4 iv</td>
<td>1.2 g x 4-6 iv</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>3 g x 3 iv</td>
<td>4 g x 3 iv</td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>0.5 g x 3 iv</td>
<td>2 g x 6 iv</td>
</tr>
<tr>
<td><strong>Amoxicillin-clavulanic acid</strong></td>
<td>(1 g amoxicillin + 0.2 g clavulanic acid) x 3 iv</td>
<td>(2 g amoxicillin + 0.2 g clavulanic acid) x 3 iv</td>
</tr>
<tr>
<td><strong>Piperacillin</strong></td>
<td>4 g x 3 iv</td>
<td>4 g x 4 iv</td>
</tr>
<tr>
<td><strong>Piperacillin-tazobactam</strong></td>
<td>(4 g piperacillin + 0.5 g tazobactam) x 3 iv</td>
<td>(4 g piperacillin + 0.5 g tazobactam) x 4 iv</td>
</tr>
<tr>
<td><strong>Ticarcillin</strong></td>
<td>3 g x 4 iv</td>
<td>3 g x 6 iv</td>
</tr>
<tr>
<td><strong>Ticarcillin-clavulanic acid</strong></td>
<td>(3 g ticarcillin + 0.1 g clavulanic acid) x 4 iv</td>
<td>(3 g ticarcillin + 0.1 g clavulanic acid) x 6 iv</td>
</tr>
<tr>
<td><strong>Temocillin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenoxymethylpenicillin</strong></td>
<td>0.5-2 g x 3-4</td>
<td>None</td>
</tr>
<tr>
<td><strong>Oxacillin</strong></td>
<td>Clinical breakpoints not available</td>
<td>Clinical breakpoints not available</td>
</tr>
<tr>
<td><strong>Cloxacinil</strong></td>
<td>0.5 g x 4 oral or 1 g x 4 iv</td>
<td>1 g x 4 oral or 2 g x 6 iv</td>
</tr>
<tr>
<td><strong>Dcloxacillin</strong></td>
<td>0.5-1 g x 4 oral or 1 g x 4 iv</td>
<td>2 g x 4 oral or 2 g x 6 iv</td>
</tr>
<tr>
<td><strong>Fluoxacinil</strong></td>
<td>1 g x 3 oral or 2 g x 4 iv</td>
<td>1 g x 4 oral or 2 g x 6 iv</td>
</tr>
<tr>
<td><strong>Mecillinam</strong></td>
<td>0.2-0.4 g x 3 oral</td>
<td>None</td>
</tr>
</tbody>
</table>
Microorganism | Antibiotic | MIC<sub>50</sub> (mg L<sup>-1</sup>) | MPC<sub>50</sub> (mg L<sup>-1</sup>)
--- | --- | --- | ---
Pseudomonas aeruginosa | Imipenem | 2 | 32
| Meropenem | 0.5 | 8
| Doripenem | 0.5 | 4

Escherichia coli | Imipenem | 0.25 | 0.5
| Meropenem | 0.03 | 0.06
| Doripenem | 0.03 | 0.125

Modified from Credito et al. (2010)
THE GLOBAL DEFINITION OF RESPONSIBLE ANTIBIOTIC USE: THREE HIGHLIGHTS

• Education
• Duration
• Access and availability
When the antibiotic treatment should be stopped

- When the benefit to the patient (but also for society) no longer outweighs the potential harm
What are the harms of inappropriately prolonged antibiotic therapy?

- Antimicrobial resistance
- Altered microbiome
- Costs
- Adverse events
Antibiotic resistance selection pressure
Macroepidemiological considerations

- Penicillins
- Aminoglycosides
- Nitrofurantoin, trimetroprim
- First generation cephalosporins
- Second generation cephalosporins
- Tetracyclines
  - Macrolides
  - 3rd generation cephalosporins
  - Fluoroquinolones
  - Carbapenems
From: Emergence and spread of antibiotic resistance following exposure to antibiotics
How to stop antibiotics earlier?

- Reduction in procalcitonin and CRP
- No fever for 2-3 days
- Feeling well, eating well
Conclusions

• AMS interventions should be targeted and well planned
• Different methods can be used to asses the impact of AMS activities
• Microbiology laboratory support is essential to assure quality of AMS
• Selection of optimal treatment regimen for each patient is essential for credibility of AMS programmes
Questions for the ACASEM Survey

Question 1. Antimicrobial stewardship activities in hospitals should be combined with infection control interventions

True
Point prevalence surveys can be used to assess impact of AMS interventions

- Prevalence of antibiotic use
- Appropriateness of antibiotic prescriptions according to the class of antibiotic
- Appropriateness of antibiotic therapy by diagnosis
- Appropriateness of antibiotic therapy by medical specialization
- All mentioned above
Dose and length of antibiotic treatment is dependent on

- Type of disease
- Type of microorganism
- Speed of response to treatment
- All of the factors