Antimicrobial therapy analysis at the University Clinic Golnik

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ANTIMICROBIAL THERAPY ANALYSIS AT THE UNIVERSITY CLINIC GOLNIK

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1 INTRODUCTION

1.1 ANTIMICROBIAL AGENTS

Antimicrobial agents are drugs, chemicals or other substances that kill, inactivate, or slow the growth of microorganisms including bacteria, viruses, fungi and parasites. The term is derived from the Greek words *anti* (against), *micros* (little) and *bios* (life). Thus, antibiotic is a type of antimicrobial agent made from a mold or bacterium that kills or slows the growth of other bacteria (www.cdc.gov). Antimicrobials are responsible for the vast improvements in health and life expectancy, ever since first antimicrobial drug, named Salvarsan®, was synthesised in 1910, and they are among the most frequently prescribed classes of drugs. Throughout history, their effectiveness has been further confirmed by Alexander Fleming, who discovered penicillin (Aminov, 2010).

Code J is assigned to antimicrobial drugs as antiinfectives for systemic use, according to Anatomical Therapeutic Chemical classification system. Antibiotics are put in the therapeutic subgroup of antibacterials for systemic use, given the code J01 (www.jazmp.si).

There are several ways of classifying antibacterial agents, based on:

- The chemical structure of its pharmacophore.
  Some of the most used classes of antibiotics are beta-lactams (including penicillins, cephalosporins, carbapenems and monobactams), aminoglycosides, (fluoro)quinolones, macrolides, tetracyclines, glycopeptides, lincosamides ect.
- The biochemical pathway that an antibacterial agent interferes with.
  Different classes of antibiotics have different mechanisms of action on a bacterial cell, such as interfering with cell membrane permeability, or inhibition of enzymes involved in cell wall biosynthesis, nucleic acid metabolism and repair, and protein synthesis.
- The spectrum of activity of an antibacterial agent.
  The main distinction is between broad-spectrum drugs, usually used for empirical treatment, and narrow-spectrum drugs, which are targeting the bacteria known to cause the infection. Additionally, due to their pharmacokinetic properties, different antibiotics achieve greater concentrations in different pathological compartments. It is possible for an antibiotic to penetrate into the site of infection, rather than have systemic effect of the drug.
- The effect of an antibacterial agent on the bacteria.
  Bactericidal drugs, such as β-lactams and fluoroquinolones, are able to cause death of

the cell. Sulfonamides, tetracyclines and macrolides are bacteriostatic drugs which inhibit bacterial replication, relying on an immune system of the host to eliminate the bacteria and thus to clear the infection. This categorisation is not absolute, meaning that one drug can be both depending on the concentration of drug that is achieved safely in plasma (Goodman et al., 2017).

Antibiotics may be used prophylactically to prevent infection, pre-emptively to abort infection, empirically to provide initial control of an infection, in the absence of knowledge of its etiology, and definitively to cure infection of known etiology (Leekha et al., 2011).

By analysing the trends and drivers of antibiotic consumption, between 2000 and 2015, worldwide antibiotic consumption increased 65% (21.1–34.8 billion DDDs), and the antibiotic consumption rate increased 39% (11.3–15.7 DDDs per 1,000 inhabitants per day). The increase was driven by low- and middle-income countries. In high-income countries overall consumption increased modestly, but the antibiotic consumption rate decreased by 4%. It should also be noted that the usage of last-resort compounds, such as glycylcyclines, oxazolidinones, carbapenems, and polymyxins, also displays rapid increase (Klein et al., 2018). WHO has ranked antimicrobials according to their relative importance in human medicine in order to preserve the effectiveness of currently available antimicrobials. Another frightening data is on frequency of non-prescription use of antibacterials, rising to 50% worldwide (Morgan et al., 2011).

Total consumption (community and hospital sector) of antibiotics for systemic use in humans, in 2017 in Slovenia, was 14.0 DDD per 1 000 inhabitants per day, comparing to 23.4 DDD per 1 000 inhabitants per day in the EU/EEA countries (Table 1). Penicillins were the most frequently used antibiotics in the community in all countries, in Slovenia ranging up to 67% of the total consumption (ECDC).

Table 1. Trends in yearly consumption of antibacterials for systemic use in the community, in Slovenia, 2013–2017, expressed as DDD per 1 000 inhabitants per day (ECDC).

Year	2013	2014	2015	2016	2017
DDD per 1000 inhabitants per day	14.5	14.2	14.5	13.9	14.0

On the other hand, consumption of antibiotics in the hospital sector was 1.71 DDD per 1 000 inhabitants per day in 2017 in Slovenia, comparing to 2.03 DDD per 1 000 inhabitants per day in EU/EEA countries (Table 2). Penicillins were again the most frequently used antibiotics in the hospital sector in Slovenia, taking 45% of the total consumption (ECDC).

Table 2. Trends in yearly consumption of antibacterials for systemic use in hospital sector, in Slovenia, 2013–2017, expressed as DDD per 1 000 inhabitants per day (ECDC).

Year	2013	2014	2015	2016	2017
DDD per 1000 inhabitants per day	1.5	1.6	1.7	1.7	1.7

1.1.1. ANTIMICROBIAL RESISTANCE

Microorganisms are capable to adapt and overcome the obstacles they face in their surroundings, which also applies to antibacterial drugs, leading to prevalence increase of multi-drug resistant pathogens. The term ‘antimicrobial resistance’ (AMR) is defined as the ‘loss of effectiveness of any anti-infective medicine, including antiviral, antifungal, antibacterial and antiparasitic medicines’ (www.nice.org).

The most common bacteria with developed resistance to antibiotic are (Table 3):

- methicillin-resistant *Staphylococcus aureus* (MRSA)
  Better part of MRSA is resistant to beta-lactam antibiotics, as well as erythromycin and clindamycin. Often making glycopeptides (vancomycin, teicoplanin) the only therapeutic option .
- vancomycin-resistant *Enterococcus faecium* (VRE)
  At the moment, there is low percentage of VRE among the population, but it’s increase will leave no effective therapeutic options.
- extended spectrum beta-lactamase (ESBL) producing *Escherichia coli*
  Despite the low percentage (8.2%) of resistance, *E. coli* is the most common isolated bacteria in urinary tract infections, making it the most common resistant bacteria.
- extended spectrum beta-lactamase (ESBL) producing *Klebsiella pneumonia*
  Carbapenems are frequently recognized as the only therapeutic option, making the

appearance of carbapenem-resistant bacteria a high risk of resistance to all available antibiotics.

- carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
  Resistance to carbapenems is a result of different biochemical resistance mechanisms, leaving poor choice of effective antibiotic drugs, if any (Štrumbelj et al., 2018).

Table 3. Number and percentage of resistant isolates among samples taken in 2017, for each species of bacteria (Štrumbelj et al., 2018).

Species of bacteria / Resistance feature	Number of resistant samples	Percentage of resistant samples (%)
S. aureus / MRSA	640	7.7
E. faecium / VRE	112	0.6
E.coli / ESBL	2001	8.2
K. pneumoniae / ESBL	647	14.2
K. pneumoniae / CRE	16	0.4
P. aeruginosa / CRPA	198	4.2

The biochemical resistance mechanisms used by bacteria include reduction of entry of antibiotic into pathogen, enhanced export of antibiotic by efflux pumps, release of microbial enzymes that destroy the antibiotic, alteration of microbial proteins that transform pro-drugs to the effective moieties, alteration of target proteins and/or development of alternative pathways to those inhibited by the antibiotic. Once bacterium develops resistance through mutation, it can pass on this new feature through its genome vertically to daughter cells, or transfer it horizontally to susceptible recipient strains (Goodman et al., 2017).

Although this process occurs naturally, misuse and overuse of antimicrobials is accelerating this process (Bell et al., 2014). Therefore, in the shortage of the development of new antibiotic drugs, rational use of existing antibiotics is needed to ensure the long term availability of appropriate treatment for bacterial infections (Kaplan et al., 2004). In contrast to any other class of drugs, each antibiotic misuse has a potential public health consequence, since it increases the chances of bacteria becoming resistant to the antibiotic, harming not only the individual patient, but contributing to societal harm across the globe. And nowadays, owing to the increased mobility of the population, consequences of irrational use became a health threat without borders (McKenna, 2013). The lack of action in one country can

undermine progress in another. As a result, European Centre for Disease Prevention and Control (ECDC) manages regional networks on antimicrobial resistance, antimicrobial use, and healthcare-associated infections for countries of the European Union. On the global scale, Global antimicrobial resistance surveillance system (GLASS) is developed by World health organisation (WHO). Global action plan on antimicrobial resistance strives to ensure continuity of successful treatment and prevention of infectious diseases with effective and safe medicines by using them responsibly. It serves as a model on which all the countries are expected to rely on while developing their own national action plans on antimicrobial resistance (www.who.int).

In 2015, for EU countries, 671 689 infections with antibiotic-resistant bacteria were estimated, of which 63.5% were associated with health care. These infections are responsible for an estimated 33 110 deaths and 874 541 disability-adjusted life-years (DALYs) (Cassini et al., 2019). Hence, the results show a considerable human and economic cost. On top of that, initial research shows that a continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2-3.5% in Gross Domestic Product (GDP), costing the world up to 100 trillion USD (O'Neil, 2014).

1.2 ANTIMICROBIAL STEWARDSHIP

The term 'antimicrobial stewardship' is defined as 'an organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness (Morley and Wacogne, 2017). It aims to optimize antibiotic use, improve clinical outcomes, minimize toxicities and other adverse events, reduce microbial resistance, decrease the spread of infections caused by multidrug-resistant organisms, reduce hospital length of stay and overall cost of health care.

According to the Cochrane review, interventions in hospitals lead to more patients receiving the appropriate treatment while reducing duration of antibiotic treatment and length of stay. At the same time, mortality rate was unaffected, implying that antibiotic treatment is often misused, if not unnecessary (Davey et al., 2017).

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) present guidelines for developing institutional programs to enhance antimicrobial stewardship, which are intended to help creating an effective hospital-based

stewardship programs. The population targeted by these guidelines includes all patients in acute care hospitals. However, the guidelines are additionally adapted to each clinical setting according to the size of the institution, as well as their resources, and to local antimicrobial use and resistance (Dellit, 2007).

There are two core strategies that provide the foundation for an antimicrobial stewardship program. The first one relies on formulary restriction and preauthorization, meaning that a clinician needs to get approval for certain antibiotics before they are prescribed. Although it usually addresses empiric use, it can reduce initiation of unnecessary or inappropriate antibiotics. On the other hand, potential delay of therapy may be encountered, since a clinician loses autonomy in drug prescribing, while depending on the skill of the approver. And the second strategy is prospective audit of antimicrobial use with intervention and feedback. Incidence density rate of defined daily doses (DDD), days of therapy (DOT) or length of therapy (LOT), enable comparisons between time periods and across institutions and services, with different numbers of patients and different lengths of stay. That way is possible to monitor how often patients are getting an antibiotic and/or duration of antibiotic treatment. Each of these measurements provides different information, making the comparison more statistically accurate. WHO defined DDD as assumed average maintenance dose per day for a drug used for its main indication in adults (www.who.int). LOT is calculated as the number of calendar days' duration of therapy regardless of the number of agents used. On the other hand, DOT involves summing the total number of days that a patient received any number of doses of a drug.

Another measurement which should be collected and reported is an aggregate antimicrobial resistance. The first way to quantify this data is by expressing it as a period prevalence, the percentage of resistant or susceptible isolates over a defined period. Alternatively, resistance could be expressed as a rate, the number of resistant isolates divided by the number of admissions (Dellit, 2007).

It is also recommended to include additional strategies. Education of the whole medical staff, as well as medical and pharmacy students would provide them with knowledge and a sense of urgency on preventing the antimicrobial resistance. Medical staff competence is considered to have a critical role in patient's safety, thus the collaboration between the antimicrobial stewardship team, the hospital infection control, pharmacy and therapeutics committees, as well as the collaboration of hospital administration and medical staff leadership is essential. Health care information technology which includes electronic medical records and clinical

decision support can improve antimicrobial decisions. It provides information about the patient, the drug, and the pathogen, making it easier to obtain an appropriate therapy by regulating all the possible factors. Simultaneously, it enables collection of antimicrobial resistance patterns and monitoring nosocomial infections as a result (Dellit, 2007).

In 2008, Joseph and Rodvold wrote about the importance of considering 'the four Ds' for the appropriate antimicrobial therapy: right Drug, right Dose, De-escalation and right Duration of the therapy (Joseph and Rodvold, 2008).

Obtaining an accurate infectious disease diagnosis is crucial, taking into consideration determining the site of infection, defining the host, and establishing a microbial diagnosis. This applies to avoidance of antibiotic treatment for community-acquired, mostly viral, upper respiratory tract infections. Evidence-based practice guidelines and clinical pathways are to be used as a support system for a clinician while obtaining diagnosis and pharmacological therapy. Guidelines are not designed to replace the decision of a clinician, but rather to help identify opportunities and to add efficiency to the intervention process. Additional investigations are needed when the therapy is not beneficial. Antimicrobial therapy is firstly guided by the clinical presentation. Therefore, common approach is to use broad-spectrum antimicrobial agents as initial empiric therapy with the intent to cover multiple possible pathogens commonly associated with the specific clinical state or the previous exposure, for example while travelling, keeping in mind patient's present comorbidities and antimicrobial allergies. Hence, clinical microbiology laboratory plays a critical role in antimicrobial stewardship by providing patient-specific culture and susceptibility data to optimize individual antimicrobial management. Once microbiology results have identified the etiologic pathogen and/or antimicrobial susceptibility data are available, every attempt should be made to narrow the antibiotic spectrum. Re-evaluation of the therapy for potential de-escalation or elimination, prevents the development of resistance, reduces toxicity and costs. Dosing should be adapted to the patient's renal and/or hepatic function. Treatment that starts as intravenous therapy can be switched to oral therapy when there are clinical improvements, when the patient is hemodynamically stable, able to take oral medications, and has a normally functioning gastrointestinal tract. This is encouraged to reduce unnecessary hospital costs and hospital associated risks including iatrogenic complications and greater risk of antimicrobial resistance. Timing of initiation of antimicrobial therapy is guided by the urgency of the situation: empiric therapy initiated immediately after or concurrently with collection of diagnostic specimens in critically ill patients; in more stable patients, therapy should be

deliberately withheld until multiple specimens have been obtained. On the other hand, use of antibiotics for the shortest duration that is effective for the treatment of a particular diagnosis needs to be applied (Dellit, 2007).

Combination therapy is recommended when agents exhibit synergistic activity against a microorganism, when empiric therapy is urgent and required before microbiological etiology and/or antimicrobial susceptibility can be determined. Combination of two drug classes extends the antimicrobial spectrum for treatment of polymicrobial infections and prevents emergence of resistance (Dellit, 2007).

1.3 TREATMENT OF SPECIFIC INFECTIOUS DISEASES

1.3.1. PNEUMONIA

Pneumonia is an infection of the lung tissue. Diagnosis of pneumonia should be confirmed by a chest X-ray, after assessing clinical symptoms and signs of the infection. According to the site of presentation, pneumonia can be classified as community-acquired (CAP) or hospital-acquired (HAP) (www.nice.org.uk).

1.3.1.1 Community-acquired pneumonia

Community-acquired pneumonia (CAP) is defined as an acute symptomatic infection of the lower respiratory tract which in general develops outside a hospital or nursing home. The guidelines are intended for adult patients with CAP who present at the hospital and are treated as outpatients, as well as for hospitalised patients who present with the disease up to 72 hours after admission (Wiersinga et al., 2012).

Streptococcus pneumoniae is the most common cause of CAP and should be covered in the empirical treatment. Resistance of *S. pneumoniae* is highest against ciprofloxacin, erythromycin and clarithromycin, trimethoprim/sulfamethoxazole and doxycycline, while resistance against penicllins is low. *Legionella spp.* and *S. aureus* are more common in intensive care unit patients. In non-severe CAP it is not recommended to cover *S. aureus* by empiric antibiotic regimen. *Legionella* infections should be considered in patients with CAP who have recently travelled abroad, as well as penicillin resistance of *S. pneumoniae*. In up to 50% of CAP episodes, no causative microorganism can be identified (Wiersinga et al., 2012).

CURB-65 is validated scoring system for measuring the severity of disease in patients with community-acquired pneumonia, distinguishing mild, moderate-severe and severe CAP.

CURB-65 criteria include confusion, urea concentrations, respiratory rate frequency, blood pressure values and age above 65. Moreover, bacterial infections are generally associated with increased expression of procalcitonin (PCT) (Delèvaux et al., 2003).

Before starting antimicrobial therapy, blood and sputum specimens should be obtained for culture because this can enable streamlining of antibiotic therapy once a specific pathogen has been isolated. Additionally, it allows susceptibility testing. An urinary antigen test for *Legionella spp.* should be performed in all patients with moderate and severe CAP. The pneumococcal urinary antigen test may be included as well, but empiric therapy for CAP should always cover *S. pneumoniae*, independent of a negative or positive urinary test (Wiersinga et al., 2012).

According to CURB-65 score, there are three options for empiric antibiotic therapy:

a) Risk category I (mild CAP) refers to the outpatients and patients admitted to the hospital for other comorbidities.

   The choice of a drug active against the most frequently occurring causative agent, *S. pneumonia*: Initial therapy with amoxicillin (1st choice) or doxycycline (2nd choice, because of the possible resistance of *S. pneumoniae*) for 5 days, in patients who have substantially improved after three days of treatment. If there is a penicillin allergy or it is not possible to administer doxycycline (for example, pregnancy or lactation), macrolides may be used.

b) Risk category II (moderate-severe CAP) refers to hospitalised patients on non-ICU ward. Initial 7- to 10-day course of therapy with beta-lactam monotherapy: intravenous penicillin or intravenous amoxicillin (1st choice). In case of a penicillin allergy, the best alternatives are a 2nd or 3rd generation cephalosporin or a 4th generation quinolone. Doxycycline and macrolides, as well as broad-spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone or cefotaxime, are not recommended. If Legionella antigen test is positive, therapy must be switched to monotherapy directed against *Legionella spp.*

c) Risk category III (severe CAP) refers to hospitalised patients at ICU ward. Patients requiring admission to an ICU are more likely to have risk factors for resistant pathogens. It is recommended to always cover *S. pneumonia* and *Legionella spp.*, this understands three acceptable choices with equally successful antimicrobial activity:
   1) Monotherapy with a 3rd of 4th generation quinolone (moxifloxacin or levofloxacin)
   2) Combination therapy with penicillin (or amoxicillin) and ciprofloxacin

3) Combination therapy with a 2nd and 3rd generation cephalosporin and a macrolide Legionella antigen test should be performed for all the patients (Wiersinga et al., 2012).

After an initial, empiric treatment, therapy should be streamlined to penicillin or amoxicillin. In the event of a culture-proven causative agent, pathogen-directed antibiotic treatment is always to be preferred. If *Legionella spp.* is detected, monotherapy with fluoroquinolone (levofloxacine) is required. Amoxicillin should be used against *S. pneumonia*e, and amoxicillin or co-amoxiclav against *Haemophilus influenzae* (Wiersinga et al., 2012).

1.3.1.2 Hospital-acquired pneumonia

Hospital-acquired pneumonia (HAP) is an acute symptomatic infection of the lower respiratory tract which develops 48 hours or more after hospital admission and that was not incubating at hospital admission. In this case, the infection is more likely caused by highly resistant pathogens, requiring the initial treatment with broad-spectrum antibiotics, targeting *P. aeruginosa* and β-lactamase producing bacteria, but still covering *S. pneumoniae.* Antibiotic therapy should initiate as soon as possible, lasting up to 10 days, and it should be based on patient characteristics until microbiology test results are available. However, using narrow-spectrum antibiotics, such as imipenem, meropenem, cefepime, piperacillin/tazobactam, levofloxacin or ceftazidime, is suggested in patients with suspected low risk of resistance and early-onset nosocomial pneumonia (Torres et al., 2017).

1.3.2. ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE and ACUTE BRONCHITIS

ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease are presented by the global initiative for chronic obstructive lung disease (GOLD). COPD is defined as preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Pharmacological therapy for COPD is used to reduce symptoms, but to also reduce the frequency and severity of future exacerbations. Initial therapy is based on symptoms, along with the frequency and severity of exacerbations. Hence, the importance of individualisation

of therapy is enhanced. Spirometry is measurement of airflow limitation, according to which the classification in four categories is made. Mild symptoms seek for treatment with bronchodilator, which can be either a short- or a long-acting. In more severe states, it is recommended to start therapy with long-acting muscarinic antagonist (LAMA), combination of LAMA and long-acting beta agonist (LABA) or combination of LABA and ICS.

Acute exacerbations, which are an important feature contributing to the morbidity and mortality, are usually caused by respiratory tract infections and require an additional therapy for both the treatment of current exacerbation and the prevention of subsequent events. Empirical antimicrobial treatment is an aminopenicillin with clavulanic acid, macrolide or tetracycline. Subsequently, therapy should be guided additionally by sputum tests for present or resistant pathogens. Recommended length of antibiotic therapy for acute exacerbations in COPD patients is 5 to 7 days (www.goldcopd.org).

ACUTE BRONCHITIS

Acute bronchitis in an inflammation of the large airways of the lung, commonly due to viruses and is usually self-limiting (Singh et al., 2019). Therefore, in the treatment of acute bronchitis, there is insufficient evidence to support the use of antibiotics, since the risk of potential adverse effects surpasses the benefits of assumed symptom relief (Smith et al., 2017). However, therapy with amoxicillin or doxycycline may be considered in patients with increased risk of subsequent pneumonia, such as patients with chronic conditions like COPD, asthma, cystic fibrosis or heart failure (www.nhs.uk).

1.3.3. URINARY TRACT INFECIONS

Diagnosis of urinary tract infections is based on the clinical state of the patient. Bacteriuria incidence increases with age for both sexes and it is common with patients with catheter. Additionally, microbiological test is used for identification of the pathogen and susceptibility testing. If the patient is not responsive to the treatment, urine culture should be performed, followed by a retreatment with another agent. Some of the tests performed are urine test strips (testing the presence of proteins, glucose, ketones, haemoglobin, bilirubin, nitrite, pH etc.), microscopic examination (provides the numbers and types of cells and/or materials present in urine), urine culture (detects germs) and blood testing.

E.coli is the causative organism in the most cases of both uncomplicated and complicated

urinary tract infections, followed by *Enterococcus spp*., *Proteus mirabilis*, and *K. pneumoniae*. *E.coli* have high resistance percentages to amoxicillin, amoxicillin with clavulanic acid, trimethoprim and trimethoprim-sulfamethoxazole, which makes them not suitable for the empirical treatment of complicated UTIs (Bonkat et al., 2019).

1.3.3.1. Uncomplicated urinary tract infections

The most common pathogen of uncomplicated UTIs is *E. coli*, therefore the empiric regimens are guided by the local susceptibility to *E. coli*.

a) First choice treatment for acute episode of uncomplicated cystitis in women are fosfomycin trometamol (3 g, single dose), pivmecillinam (400 mg, tid for 3 days) or nitrofurantoin macrocrystals (100 mg, bid for 5 days). Alternative choices include trimethoprim (200 mg, for 5 days) or combined with a sulphonamide as trimethoprim-sulfamethoxazole (160/800 mg bid for 3 days). Fluoroquinolones (levofloxacin or ciprofloxacin) in 3-day regimens may also be considered as an alternative.

   An acute episode of uncomplicated cystitis in men should be treated with trimethoprim-sulfamethoxazole for at least 7 days. Or alternatively, in case of resistance, with a fluoroquinolone (levofloxacin or ciprofloxacin).

b) For acute pyelonephritis and any type of complicated UTIs, a urine culture should be obtained before empiric therapy to optimize the definitive antibiotic regimen once the susceptibility results are available.

   In mild and moderate cases of acute uncomplicated pyelonephritis in women, a fluoroquinolone, such as ciprofloxacin (500-750 mg bid for 7-10 days) or levofloxacin (500 mg qd for 7-10 days, or 750 mg qd for 5 days) are recommended as first-line therapy if the resistance rate of *E.coli* is low. A third-generation oral cephalosporin for 10 days is used as an alternative. Trimethoprim-sulfamethoxazole might be prescribed if the pathogen is known to be susceptible. If that is not the case, initial empirical therapy with an aminoglycoside or carbapenem can be considered.

   Recommended treatment duration for men is 14 days, with fluoroquinolone (Bonkat et al., 2019).

1.3.3.2. Complicated urinary tract infections

The spectrum of bacteria causing a complicated urinary tract infection is much broader than in uncomplicated urinary tract infections. Furthermore, these are pathogens with a higher

prevalence of resistance against antimicrobials. Hence, optimal therapy depends on local resistance data and susceptibility results. If it is not possible to initiate the therapy with an antimicrobial agent based on the urine culture, a fluoroquinolone, 3rd generation cephalosoprine or an aminoglycoside are recommended. As an alternative, acylaminopenicillin, such as piperacillin plus a beta-lactamase inhibitor, or a carbapenem, with or without combination with an aminoglycoside, can be prescribed (Bonkat et al., 2019).

1.3.3.3. Asymptomatic bacteriuria

Asymptomatic bacteriuria is the occurrence of bacteria in the urine without causing symptoms. It should not be treated except in pregnant women, patients undergoing urologic procedures and patients who are in the first three months following renal transplantation. Duration for this kind of treatment should be for 3 to 7 days, along with at least one follow-up of urine culture to secure the treatment effect. General duration of the treatment is 7-14 days (Bonkat et al., 2019).

2 AIM OF THE STUDY

The aim of the study was to identify and descriptively describe the prescription patterns of antimicrobial prescribing for main infectious diagnoses at University Clinic of Pulmonary and Allergic Diseases Golnik – pneumonia, acute bronchitis, acute exacerbation of chronic obstructive pulmonary disease and urinary tract infections. Data was collected retrospectively, giving the pattern of prescribed antimicrobials, which will use as a base for implementation of activities recommended by Antimicrobial Stewardship. The focus of analysis was on initial antibiotic choice, route of delivery and time of intravenous to oral switch, duration, and de-escalation of therapy, as well as microbiology diagnostics performed to guide an antimicrobial treatment.

3 MATERIALS AND METHODS

3.1 ENROLLED PATIENTS

Retrospective audit of antimicrobial prescriptions included all the patients over the age of 18, dismissed from the wards (100, 200, 300, 600 and 700) in University Clinic of Pulmonary and Allergic Diseases Golnik, in time period 18th of November to 17th of December 2019. Of 118 identified patients, 106 were included in the analysis, after exclusion of four patients with incomplete documentation, seven patients with complicated/severe diseases and one tuberculosis patient.

Patients were identified from hospital's electronic data "BIRPIS" and patient's medical charts based on the International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10). All of them were treated with antibiotic therapy for at least one of the following discharge diagnoses:

J12 Viral pneumonia, not elsewhere classified
J13 Pneumonia due to *Streptococcus pneumonia*
J14 Pneumonia due to *Haemophilus influenzae*
J15 Bacterial pneumonia, not elsewhere classified
J16 Pneumonia due to other infectious organisms, not elsewhere classified
J18 Pneumonia, organism unspecified
J20 Acute bronchitis
J21 Acute bronchiolitis
J43 Emphysema
J44 Other chronic obstructive pulmonary disease
J96 Respiratory failure, not elsewhere classified
N10 Acute pyelonephritis
N30 Cystitis
N39 Other disorders of urinary system
A40 Streptococcal sepsis
A41 Other sepsis

Ethics approval was obtained from the National Medical Ethics Committee of the Republic of Slovenia (approval number: 0120-570/2019/9; Attachment 1).

3.2 DATA COLLECTION AND ANALYSIS

Data were collected on patient demographics, presence of cardinal symptoms, cumulative dose of corticosteroid used as a part of a treatment of acute exacerbation of COPD, as well as antibiotic use, including those used prior to admission and those prescribed on discharge from hospital, focusing on the choice and duration of antibiotic prescribed, timing of intravenous to oral switch. Laboratory values on admission and during hospitalization allow rough assessment of the severity of disease and time of clinical response, dividing patients to quick and slow responders. Quick response is defined as an improvement in clinical status based on recorded parameters, such as arterial blood pressure, heart rate, temperature, need for supplemental oxygen, white blood cells level, CRP/procalcitonin drop, in 3-4 days after initiation of antimicrobial therapy. Collecting microbiology data provides information on type of performed microbiology tests, timing of specimen withdrawals and results. Length of therapy (LOT), calculated as the number of calendar days' duration of therapy regardless of the number of agents used, and days of therapy (DOT), which involves summing the total number of days that a patient received any number of doses of a drug, were also documented. Comorbidities were recorded to enable the assessment of CURB-65 in patients with pneumonia.

Statistical analyses were completed using descriptive statistic tools in Excel.

Table 4. For each main discharge diagnosis, following parameters are to be described separately.

Discharge diagnosis	Parameters to be described with descriptive data analysis
Pneumonia	The choice of antimicrobial medication in empiric treatment, expressed in proportions for different antimicrobial agents
	Number of samples on which some type of microbiology test was performed (blood culture, sputum test, urine antigen test, Sanford urine analysis, PCR for viral infection and atypical bacteria)
	Percentage of patients with some type of positive microbiological culture test
	Length of therapy (LOT) and days of therapy (DOT) with first-line and subsequent antimicrobial drugs
	Proportion of patients receiving macrolide in combination with beta lactam antibiotics
	Median time of parenteral to oral switch expressed in days, if the initial therapy was administered parenterally
	Proportion of patients without documented penicillin allergy who were prescribed a fluoroqinolone as first-line treatment
	Proportion of patients without documented penicillin allergy who were prescribed a macrolide as a first-line treatment for low-severity CAP
	Proportion of de-escalated therapies after laboratory results which would enable the use of narrow-spectrum antimicrobials and the number of extra non de-escalated days of broad-spectrum therapy
Acute exacerbations of COPD and acute bronchitis	The choice of antimicrobial medication in empiric treatment, expressed in proportions for different antimicrobial agents
	Length of therapy (LOT) and days of therapy (DOT) with first-line and subsequent antimicrobial drugs
	Proportion of patients which were treated with systemic glucocorticoids for acute exacerbations
	Length of therapy (LOT) with systemic glucocorticoids prescribed to patients for acute exacerbations expressed in days, including the

	medications prescribed at discharge
	Median of cumulative systemic glucocorticoid dose
	Median time of parenteral to oral switch expressed in days, if the initial therapy was administered parenterally
	Number of samples on which some type of microbiology test was performed (blood culture, sputum test, urine antigen test, Sanford urine analysis, PCR for viral infection and atypical bacteria)
	Percentage of samples positive for some type of microbiological culture
	Proportion of de-escalated therapies after laboratory results which enabled the use of narrow-spectrum antimicrobials and the number of extra non de-escalated days of broad-spectrum therapy
Uncomplicated or complicated urinary tract infections	The choice of antimicrobial medication in empiric treatment, expressed in proportions for different antimicrobial agents
	Number of performed Sanford urine analyses and proportion of samples which were collected before the initiation of empiric therapy
	Number of blood culture tests performed and proportion of samples which were collected before the initiation of empiric therapy
	Percentage of samples positive for some type of microbiological culture
	Proportion of de-escalated therapies after laboratory results which enabled the use of narrow-spectrum antimicrobials and the number of extra non de-escalated days of broad-spectrum therapy
	Median time of parenteral to oral switch expressed in days, if the initial therapy was administered parenterally
	Length of therapy (LOT) and days of therapy (DOT) with first-line and subsequent antimicrobial drugs

4 RESULTS AND DISCUSSION

4.1. RESULTS

106 patients were included in the analysis: 56 patients with pneumonia, 23 patients with acute exacerbations of chronic obstructive pulmonary disease, 15 patients with acute bronchitis, 9 patients with uncomplicated urinary tract infection, 3 patients with complicated urinary tract infection.

Total male to female ratio was 51 to 55, with median age of 70.5 years (IQR=17; Q1=64, Q3=81). Meanwhile, median hospitalization days for this group of patients was 7 (IQR=6; Q1=6, Q3=12).

4.1.1. PNEUMONIA

56 (52.83%) patients with pneumonia as discharge diagnosis were treated with antibiotic therapy (Table 5). Median patients' age was 66 years (IQR = 21.5; Q1=57.75, Q3=79.25)**,** with a range from 22 to 97 years. Most of the patients were already treated for some type of chronic disease (Table 6). Median hospitalization duration was 7 days (IQR=6; Q1=5, Q3=11). 1 patient died during hospitalization.

Table 5. Distribution of different types of pneumonia among the patients with pneumonia as discharge diagnosis.

Type of pneumonia	Number of patients	Percentage of patients
Pneumonia, unclassified	14	25.00%
Pneumonia, bacterial	19	33.93%
Pneumonia (*S.pneumoniae*)	9	16.07%
Pneumonia (*M.pneumonia*)	7	12.50%
Other	7	12.50%

Table 6. Additional comorbidities recorded in patients with pneumonia.

Comorbidity	Number of patients	Percentage of patients	Comorbidity	Number of patients	Percentage of patients
COPD	17	30.36%	Type II diabetes	7	12.50%
Asthma	9	16.07%	Carcinoma	9	16.07%
Heart failure	3	5.36%	Immobility	1	1.79%
Dementia	4	7.14%	Bronchiectasis	6	10.71%
Emphysema	1	1.79%	IBS	16	28.57%
Congestive heart failure	13	23.21%	No chronic diseases	8	14.29%

Since guidelines on antibiotic therapy in pneumonia depend on the severity of the disease, the assessment of CURB-65 is needed. However, available clinical parameters were not sufficient for accurate evaluation in 11 (19.64%) patients. Most of the patients had mild pneumonia (67.86%), while only one patient was considered to have severe disease.

4.1.1.1.Diagnostic microbiology

Viral infection identification with PCR was performed in 32 (57.14%) patients, but in 3 patients sample was taken twice, counting up to 35 tested samples. Results were positive 7 (20.00%) times for *Influenza A* and 2 (5.71%) times for *Rhinovirus*. One sample was positive for *Parainfluenza virus*, and one for *Coronavirus* (Table 7).

Table 7. Distribution of test results for samples on which viral infection identification with PCR was performed, in patients with pneumonia.

Test result	Number of samples	Percentage of samples
Negative result	24	68.57%
Influenza A	7	20.00%
Rhinovirus	2	5.71%
Parainfluenza virus	1	2.86%
Coronavirus	1	2.86%

Blood culture analysis was performed once in 19 (33.93%) and twice in 4 (7.14%) patients, with total number of 27 samples. 8 (29.63%) of them were performed after antibiotic therapy

had been initiated. Median time to results was 6 days (IQR=1; Q1=6, Q3=7). Results were mostly negative (88.89%), while 2 patients were positive for *S. pneumoniae*, and 1 was positive for *H. influenzae*.

Sputum sample was taken 33 times, in 30 (53.57%) patients. 23 (69.70%) samples were taken after, and 9 (27.27%) samples were taken before antibiotic therapy had been initiated. 21 out of 33 samples (63.64%) were appropriate for the analysis. Median time to results was 3 days (IQR=1, Q1=3, Q3=4). Most results (66.67%) were negative (Table 8).

Table 8. Distribution of test results of analyzed sputum samples.

Test result	Number of samples	Percentage of samples
Normal mixed flora	14	66.67%
S. pneumoniae	1	4.76%
H. influenzae β-	1	4.76%
S. pneumonia, H. influenzae β-	1	4.76%
P. mirabilis	1	4.76%
P. aeruginosa	1	4.76%
E. coli	1	4.76%
MSSA, K. pneumoniae	1	4.76%

Urine antigen testing for both *S. pneumoniae* and *Legionella* was performed in 21 (37.50%) patients, while in 2 (3.57%) patients only infection with *Legionella* was tested. Result was 6 (28.57%) times positive for *S. pneumoniae*, and once (4.35%) for *Legionella*.

Atypical bacteria were analyzed with PCR in 28 (50.00%) patients, while in one patient test was performed two times. 6 (20.69%) results were positive for *Mycoplasma*, and 1 (3.45%) for *Chlamydia*.

Sanford urine analysis was performed 21 times in 19 (33.93%) patients. 10 (42.86%) samples were taken after antibiotic therapy had been initiated. Median time to results was 2 days (IQR=1.5; Q1=1.5, Q3=3). Results were mostly negative (80.95%), while they were positive once (4.76%) for *Enterococcus faecalis* and *Morganella morganii*, and positive for *Candida* in 2 (9.53%) patients.

In 27 (48.21%) patients, isolates were positive, and pathogen was identified (Table 9).

Table 9. Types of microbiological isolates found in patients with pneumonia.

Microbiological isolate	Number of patients	Percentage of patients
None	29	51.79%
Bacteria	16	28.57%
Virus	8	14.29%
Bacteria + virus	3	05.36%

4.1.1.2.Antimicrobial therapy

45 (80.36%) patients were treated with only one type of antibiotic. In others, different types of antibiotic were used consecutively or simultaneously as a combination.

Amoxicillin with clavulanic acid was most commonly used as a first line therapy, in 23 (41.07%) patients, followed by moxifloxacin, prescribed in 16 (28.57%) patients (Table 10). 7 (12.50%) patients were treated with combination of β-lactam antibiotic with azithromycin. Hence, macrolide was given to 11 (19.64%) patients, with median length of therapy with macrolide was 5 days (IQR=2.25; Q1=3.75, Q3=6). Only one of these patients had previous allergy to penicillin described in their medical chart. 12 patients were treated with 3rd generation fluoroquinolone even though no prior allergies to other antibiotic drugs were recorded. In only one out of 4 patients with recorded allergies, type of allergic reaction was described in the medical chart. One patient treated with moxifloxacin, started to develop urticaria as an allergic skin reaction to the drug. Median days of first line therapy was 7 (IQR=5; Q1=5, Q3=10).

Table 10. Antibiotics prescribed as first line therapy in patients with pneumonia.

First line antibiotic	Number of patients	Percentage of patients
Penicillin + azithromycin	2	3.57%
Amoxicillin /clavulanic acid	23	41.07%
3rd gen cephalosporin	1	1.79%
3rd generation fluoroquinolone	16	28.57%
Amoxicillin/clavulanic acid + azithromycin	4	7.14%
3rd gen cephalosporin + azithromycin	1	1.79%
Azithromycin	4	7.14%
Piperacillin/tazobactam (/8h)	5	8.93%

39 (69.64%) patients received some form of intravenous antibiotic treatment (Table 11), and of that group, 29 (74.36%) therapies were switched to oral route, after 4 median days (IQR=3; Q1=3, Q3=6) (Table 12).

Table 11. Route of first line antibiotic administration among patients with pneumonia.

Route of administration	Number of patients	Percentage of patients
Intravenous route	36	64.29%
Oral route	17	30.36%
Both oral and iv route	3	5.36%

Table 12. Recorded switches from intravenous to oral route in patients with pneumonia who were primarily treated with intravenous administered first line antibiotics.

Switch from iv to oral route	Number of patients	Percentage of patients
Yes	29	74.36%
No	8	20.51%
Antibiotic discontinued (in max 3 days)	2	5.13%

Antibiotic therapy was changed in 6 (10.71%) patients. 2 patients were treated with azithromycin, while moxifloxacin, levofloxacin, piperacillin/tazobactam and sulfamethoxazole/trimethoprim were prescribed once (Table 13). In 3 (50%) patients antibiotic was applied by intravenous route, which was switched to oral route only once, after 4 days, when the patient was discharged from the hospital. Median duration of second line therapy was 5.5 days (IQR = 2.5; Q1=4.25, Q3=6.75).

Table 13. Antibiotics prescribed as second line therapy in patients with pneumonia.

Second line antibiotic	Number of patients	Percentage of patients
3rd generation fluoroquinolone	2	33.33%
Azithromycin	2	33.33%
Piperacillin/tazobactam (/8h)	1	16.67%
SMX+TMP	1	16.67%

Third line therapy was needed in two patients. One was prescribed with amoxicillin with clavulanic acid for 5 days after discharge and the other with imipenem/cilastatin intravenously for 14 days after poor response to previous therapy. Median duration of third line therapy was 9.5 days (IQR=4.5).

Median DOT in patients with pneumonia was 9 days (IQR=5; Q1=7, Q3=12). Median LOT in patients with pneumonia was 8.5 days (IQR=4.25; Q1=7, Q3=11.25). Median LOT at the clinic was 6 days (IQR=3; Q1=5, Q3=8), which was longer than median LOT at home, 3.5 days (IQR=3.75; Q1=2, Q3=5.75). Additionally, 7 (12.50%) patients were transferred from another hospital, therefore median LOT which was prescribed and taken there was 1 day (IQR=1.5; Q1=1, Q3=2.5). 24 (42.86%) patients were treated for 10 or more days.

After a rough assessment of the collected data, it is estimated that with, at least, 6 patients therapy was not appropriately de-escalated or discontinued, after laboratory results were reached. Resulting in at least 50 cumulative days when an antibiotic therapy was needlessly received.

Antimicrobial therapy was inappropriate in 28 (50.00%) patients with pneumonia, mostly because the patient was treated longer than recommended. Additionally, in some patients,

switch to oral route of drug administration was performed later than needed, or the empiric antibiotic was not de-escalated properly.

4.1.2. ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE and ACUTE BRONCHITIS

23 (60.53%) out of 38 patients were treated with antibiotic therapy for an acute exacerbation of COPD, and 15 (39.47%) of them for acute bronchitis. 21 (55.26%) patients were male, while 17 (44.74%) patients were female, comorbidities were often present in both (Table 14). Median age for this group is 72 years (IQR=12; Q1=68, Q3=80), with a ratio from 21 to 93 years. 1 patient died while staying at intensive care unit.

18 (47.37%) patients were treated with systemic glucocorticosteroid (methylprednisolone), in duration of 8 median days, with median cumulative dose of 192mg. Only 2 out of 15 patients with acute bronchitis used methylprednisolone as a part of a therapy for asthma, while 2 patients were treated for COPD. Remaining 14 patients were all hospitalized and treated for AE of COPD.

Table 14. Additional comorbidities in patients with acute exacerbation of COPD and acute bronchitis.

Comorbidity	Number of patients	Percentage of patients	Comorbidity	Number of patients	Percentage of patients
COPD	27	71.05%	Diabetes 2	10	26.32%
Asthma	7	18.42%	Carcinoma	6	15.79%
Heart failure	3	7.89%	Bronchiectasis	4	10.53%
Congestive heart failure	7	18.42%	Irritable bowel syndrome	1	2.63%
Emphysema	5	13.16%	Chronic kidney disease	2	5.26%
Dementia	1	2.63%	No chronic diseases	4	10.53%

4.1.2.1.Diagnostic microbiology

In 20 (52.63%) patients PCR was used to identify a viral infection. All of 6 (30.00%) positive results were positive for rhinovirus/enterovirus.

The blood culture was taken at least once in 4 (10.53%) patients. 3 (60.00%) samples were taken after antibiotic therapy had been initiated, however neither patient was positive.

Sputum sample was taken 33 times, in 26 (68.42%) patients. Therefore, test was performed twice in 7 (26.92%) of these patients. 16 (50.00%) samples were taken after, and 16 (50.00%) before antibiotic therapy had been initiated. 24 out of 33 samples (72.72%) were appropriate for the analysis, and mostly positive (Table 15). Median days between taking appropriate samples and getting the results was 4 days (IQR=1; Q1=3, Q3=4).

Table 15. Distribution of test results among analyzed sputum samples in patients with acute exacerbations of COPD and acute bronchitis.

Test result	Number of samples	Percentage of samples
Normal mixed flora	7	29.17%
S. pneumoniae	2	8.33%
H. influenzae β-	3	12.50%
Moraxella catarrhalis	2	8.33%
P. aeruginosa	2	8.33%
E. coli	1	4.17%
Serratia marcescens	1	4.17%
MSSA	1	4.17%
Multiple isolates	5	20.83%
S. pneumoniae + *M. catarrhalis*	1	4.17%
P. aeruginosa + *M. catarrhalis*	1	4.17%
H. influenzae + *M. catarrhalis*	1	4.17%
H. influenzae + *M. catarrhalis* + *E. cloaceae*	1	4.17%
MSSA + *Citrobacter brakii* + *Achromobacter spp.*	1	4.17%

Urine antigen test, for both *S. pneumoniae* and *Legionella*, was performed in 3 (08.11%) patients, while atypical bacteria were analyzed with PCR in 11 (28.95%) patients. All the results were negative.

Sanford test was performed in 6 (15.79%) patients, while in one of these patients two samples were analyzed. 2 (28.57%) samples were taken after antibiotic therapy had been initiated. Median time to results was 2 days (IQR=0.75; Q1=2, Q3=2.75). Result was positive in 3 (50.00%) patients, once for *E. coli*, *E. coli ESBL* and *Streptococcus agalactiae*.

Some type of pathogen was identified in 19 (50.00%) patients, 5 of them viral, 13 bacterial, while one patient was infected with both virus and bacteria.

4.1.2.2.Antimicrobial therapy

Most of the patients (89.47%) were treated with only one type of antibiotic drug. Others had either two or antibiotics consecutively, or the combination of two classes of antibiotic drugs.

As first line of antibiotic therapy, 23 patients (60.53%) received amoxicillin with clavulanic acid. Azithromycin and 3rd generation fluoroquinolone was prescribed to 6 (15.79%) and to 5 (13.16%) patients, respectively (Table 16). Fluoroquinolone or macrolide was chosen as empiric therapy in 8 (61.54%) patients who did not have any record of allergies to penicillin.

Table 16. Antibiotics prescribed as first line therapy in patients with AE of COPD and acute bronchitis.

First line antibiotic	Number of patients	Percentage of patients
Amoxicillin/clavulanic acid	23	60.53%
3rd generation fluoroquinolone	5	13.16%
Ciprofloxacin	1	2.63%
Amoxicillin/clavulanic acid + azithromycin	1	2.63%
Azithromycin	6	15.79%
Piperacillin/tazobactam (/8h)	1	2.63%
Nitrofurantoin	1	2.63%

Most of the patients (89.47%) received antimicrobial orally. In 3 out of 4 patients (75.00%), drug that was given intravenously was switched to oral route, after 5 median days (IQR=0.5, Q1=4.5, Q3=5). Median duration of first line antibiotic given to these patients was 7 days (IQR=3; Q1=5, Q3=8).

For 3 (7.89%) patients, therapy was de-escalated to another antibiotic drug, all of which were administered via intravenous route (Table 17). Median duration of second line therapy was 14 days (IQR=4.5, Q1=12, Q3=16.5).

Table 17. Antibiotics prescribed as second line therapy in patients with AE of COPD and acute bronchitis.

Second line antibiotic	Number of patients
Ciprofloxacin + TMP/SMX + Pip/tazo (/12h)	1
Imipenem/cilastatin	1
Piperacillin/tazobactam (/8h)	1

Median DOT in patients with acute exacerbations of COPD and acute bronchitis was 7 days (IQR=2.5; Q1=6.25, Q3=8.75), which also equals to median LOT. Meanwhile, median LOT at Golnik was 5 days (IQR=4; Q1=3, Q3=7), as well as at home (IQR=3.5; Q1=2.75, Q3=6.25), while median LOT at transfer was 2 days (IQR=2.25; Q1=1, Q3=3.25). 4 (10.53%) patients were transferred from/to and treated in another hospital.

After a rough assessment of the collected data, it is estimated that with, at least, 8 patients therapy was not appropriately de-escalated or discontinued, after laboratory results were reached. Resulting in at least 39 cumulative days when an antibiotic therapy was needlessly received. Antimicrobial therapy was inappropriate in 19 (50.00%) patients, mostly because the patient was treated longer than recommended, considering the guidelines and patients' clinical response.

4.1.3. URINARY TRACT INFECTIONS

12 patients were treated with antibiotic therapy for urinary tract infection (UTI), 9 (75.00%) of them were diagnosed with uncomplicated and 3 (25.00%) with complicated UTI. Most

patients (83.33%) were female, and only 2 (16.67%) were male, all of them already had some type of chronic disease (Table 18). Median age for this group of patients is 85 (IQR=10.75; Q1=77.75, Q3=88.5), both the youngest (52 years) and the oldest (92 years) were female.

Median duration of antibiotic therapy for both uncomplicated and complicated UTI was 7 days (IQR=2.5; Q1=6; Q3=8.5). Meanwhile, median time during which patients received antibiotic therapy was equal in both hospital and at home, which is 6 days.

Table 18. Additional comorbidities recorded in patients with urinary tract infection.

Comorbidity	Number of patients with uncomplicated UTI	Percentage of patients with uncomplicated UTI	Number of patients with complicated UTI	Percentage of patients with complicated UTI
COPD	2	22.22%	0	0.00%
Asthma	2	22.22%	0	0.00%
Heart failure	0	0.00%	3	100.00%
Congestive heart failure	4	44.44%	1	33.33%
Immobility	2	22.22%	1	33.33%
Diabetes type II	4	44.44%	2	66.67%
Carcinoma	0	0.00%	1	33.33%
Chronic kidney disease	1	11.11%	1	33.33%

4.1.3.1. Uncomplicated urinary tract infections

Blood culture was taken in 2 (22.22%) patients, and for both of them test was performed before antibiotic therapy had been initiated, yet neither had positive blood culture test.

Sanford test was performed in all 9 (100%) patients. Total number of tests performed was 11, since the samples were taken twice in two patients, and only in these two patients test was performed after antibiotic therapy had been initiated. Median time to result was 2 days (IQR=2; Q1=1, Q3=3). Result was positive for 8 out of 9 patients (88.89%), mostly for *E. coli* (Table 19).

Table 19. Distribution of test results among samples analyzed with Sanford urine test in patients with uncomplicated urinary tract infection.

Sample result	Number of samples	Percentage of samples
Negative	1	11.11%
E. coli	4	44.44%
E. coli ESBL	2	22.22%
P. mirabilis	1	11.11%
Raoultella ornithinolytica	1	11.11%

Amoxicillin with β-lactamase inhibitor was prescribed as first line therapy in 5 (55.56%) patients, with median length of 6 days (IQR=1; Q1=6, Q3=7). From other antibiotics, nitrofurantoin was used twice (22.22%), while 2nd generation cephalosporin and combination of trimethoprim with sulfamethoxazole were prescribed in one patient (11.11%). Six (66.67%) therapies were initiated orally, while all 3 (33.33%) intravenous therapies were switched to oral route. Median days when switch occurred was 4 (IQR=1; Q1=3.5, Q3=4.5).

None of the first line therapy was changed or discontinued. Therefore, median length of first line therapy equals to median LOT, and since all of them were prescribed as monotherapy, it also equals to total median DOT, which is 6.5 days (IQR=1.25; Q1=6, Q3=7.25). However, data is missing for 1 patient. Meanwhile, median LOT in hospital was equal to median LOT, which is 6 days.

Antibiogram was available for 8 (88.89%) patients. Median days antibiogram was available after taking the sample was 2 (IQR=2; Q1=1, Q3=3). According to antibiogram results, therapy should have been deescalated in 3 (33.33%) patients. Sum of days when therapy could have been deescalated in these patients was 21 days.

By the rough assessment of the collected data, it is estimated that with at least three (33.33%) patients therapy was not properly de-escalated, after an antibiogram on identified pathogen's susceptibility was available, resulting in 16 cumulative days of inadequate therapy.

4.1.3.2. Complicated urinary tract infections

In two of three (66.67%) patients, complications occurred, both of them included sepsis.

The blood culture was taken in 3 (100%) patients. However, for one patient only one sample was taken, while for other two, only one sample was taken before antibiotic therapy was initiated. Only one patient (33.33%) had positive blood culture test, and it was positive for *E. coli*. Results were available 6 days after taking blood sample.

Sanford test was performed before antibiotic therapy had been initiated in 3 (100%) patients, and all of them were positive (Table 20). Median time to result was 5 days (IQR=1.5; Q1=3.5, Q3=5).

Table 20. Distribution of test results among samples analyzed with Sanford urine test in patients with complicated urinary tract infection.

Sample result	Number of patients	Percentage of patients
E.coli	1	33.33%
E.coli ESBL	1	33.33%
K. oxytoca, E.coli	1	33.33%

All patients were treated with antibiotics intravenously (Table 21). In two of them (66.67%) therapy was changed to oral route. In case of piperacillin/tazobactam, therapy was switched to cefuroxime, accordingly. Median days when switch occurred was 7 days (IQR=3, Q1=5.5, Q3=8.5).

Median length of first line therapy equals to median LOT, and since all of them were prescribed as monotherapy, it also equals to total median DOT, that is 14 (IQR=4.5; Q1=10, Q3=14.5). Median LOT in the hospital (6 days; IQR=2; Q1=5.5, Q3=7.5) was slightly shorter than LOT prescribed at home (7.5 days; IQR=1.5).

Table 21. Antibiotics prescribed as first line therapy in patients with complicated urinary tract infection.

First line therapy	Number of patients	Percentage of patients
Amoxicillin with clavulanic acid	1	33.33%
Ciprofloxacin	1	33.33%
Piperacillin/tazobactam 4,5/12h	1	33.33%

Antibiogram was available for every patient. Median days antibiogram was available after taking the sample was 5 (IQR=1.5, Q1=3.5, Q3=5). By the rough assessment of the collected data, and taking the antibiogram results into an account, therapy was properly de-escalated in one patient, while two therapies were already adequate. However, two (66.67%) therapies were prescribed for more days than needed, according to both presented guidelines and patients' clinical responses.

4.2.DISSCUSION

Microbiological tests were not performed in 26 (27.66%) patients with pneumonia, acute exacerbations of COPD or acute bronchitis, such as analyzing swab or sputum samples, and/or urinary antigens. Yet, all patients treated for UTI were subjected to Sanford urine test. Moreover, blood, sputum and urine samples in 33 (35.11%) patients with pneumonia, AE of COPD and acute bronchitis were taken after the therapy was initiated, while in patients with UTI all Sanford tests were performed promptly. General principles of AMS point out the importance of properly obtained and promptly submitted diagnostic specimens to the microbiology laboratory, in order to direct an antimicrobial agent with a narrower spectrum at the identified pathogen, or discontinue the therapy after bacterial infection was not confirmed (Leekha et al., 2011). On the contrary, 62 (58.49%) patients received some kind of antibacterial therapy even though bacterial infection was not confirmed by performed microbiological tests, while in 13.83% of patients results showed viral respiratory infection, both implying the overuse of antibiotics.

Most common choice of empiric therapy was amoxicillin with clavulanic acid, in 52 (49.06%) patients, which corresponds only to current guidelines for managing AE of COPD (www.goldcopd.org). In other observed indications, use of amoxicillin-clavulanate is justified only after certain pathogens are identified (Wiersinga et al., 2012). 3rd generation fluoroquinolone, which is recommended as a first line therapy in hospitalized patients with severe CAP (Wiersinga et al., 2012), was correspondingly prescribed in 16 (28.57%) patients with pneumonia.

24 (25.53%) patients received fluoroquinolone for respiratory infection or macrolide for pneumonia, even though no previous allergies to penicillin were recorded. Furthermore, 13 (12.26%) patients claimed they had experienced allergic reaction to an antibiotic drug. Since studies showed that up to 90% of patients who reported a history of penicillin allergy can in

fact be treated with penicillin (Khan and Solensky, 2010), additional allergological tests are needed to confirm the suspicion and provide more detailed information on the severity of the reaction. Also, great share of patients with confirmed IgE-mediated penicillin allergy lose their sensitivity after 10 years (Khan and Solensky, 2010) .

49 (46.23%) therapies were administered intravenously, whereupon 38 (77.55%) of them were switched to oral route, while one empirical therapy was rightfully discontinued within three days, once microbiological results showed viral infection. Administration route was switched after 4.5 median days (IQR=3, Q1=3.25, Q3=6). This implies good practice, since this conversion has many advantages as fewer complications, less healthcare costs and earlier hospital discharge (Cyriac and James, 2014). Only 9 (8.49%) empiric therapies were switched to another antimicrobial.

Median length of therapy (LOT) was 7 days (IQR=4, Q1=6, Q3=10). Yet, 34 (32.08%) patients took antibiotics for more than 10 days, which is recommended duration of therapy in patients with severe CAP (Wiersinga et al., 2012), while for AE of COPD and UTIs it is even shorter, up to 7 days (www.goldcopd.org; Bonkat et al., 2019). To avoid excessive duration of therapy in the future, it is needed to take action, both in patients not responsive to the current therapy and with patients whose clinical condition shows no sign of on-going infection. Randomized trial in 2018 in patients hospitalized with urinary infections, mainly caused by *Enterobacteriaceae*, proved that an antibiotic course of 7 days was not inferior to 14 days, when the clinical stability of the patients was achieved before day 7 (Yahav et al., 2018).

Overall rough assessment of collected data, discharge letters and clinical parameters and diagnostics results, shows that at least 52 (49.06%) patients were not appropriately treated according to the guidelines, indicating a scope for future interventions and implying the necessity of implementing AMS programme.

Additionally, it is needed to highlight the importance of accurate and more detailed notes in electronic medical records and discharge letters, since that type of documentation is much more accessible than physical medical charts. 27 (25.47%) electronic medical records did not have all the crucial information on prescribed antimicrobial therapy, including the choice of the drug, route of administration and duration of therapy. Implementation of a separate segment on antimicrobial therapy into medical chart may reduce inadequate fulfilment of medical documentation, needed patient data and enhance the importance of pharmacist's role in optimizing antimicrobial therapy. The proposed approach would lead to more efficient therapy for an individual patient, and a decrease in the occurrence of antimicrobial resistance.

Furthermore, detailed data base on applied antimicrobial therapies for different clinical indications can be developed, giving the pattern of resistant bacteria present in the clinic, which would enable formation of the clinic's local guidelines.

5 CONCLUSIONS

Antimicrobial therapy was analyzed retrospectively among 106 patients in order to propose the interventions necessary to provide more efficient therapy for the patient, while simultaneously preventing antimicrobials' overuse and development of bacterial resistance. Diagnostic test that could confirm and identify bacterial infection, such as analyzing swab or sputum samples and/or urinary antigens, was not performed in 27.66% of patients with respiratory infection, meanwhile 58.49% of patients received antibiotic without bacterial pathogen being confirmed. Amoxicillin-clavulanate was used in 49.06% of empiric therapies, despite current guidelines recommending otherwise. Good practice was shown in switching for intravenous to oral route of drug administration, which occurred in 77.55% of patients. Even though median length of therapy was 7 days, 32.08% of patients were treated for longer than 10 days, which may be linked with low occurrence of therapy streamline (8.49%). Overall rough assessment of collected data shows that almost one half of patients did not receive appropriate therapy. We believe that more detailed electronic medical charts could provide more accurate and easier accessible data for future analyses and optimization of the antibiotic therapy.

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7 SAŽETAK

Prekomjerno i neprikladno propisivanje antimikrobnih lijekova u bolnicama dovodi do pojave nuspojava i antimikrobne rezistencije, što rezultira produljenjem hospitalizacije bolesnika i povećanjem troškova u zdravstvu. Zbog toga je program *Nadzora korištenja protumikrobnih lijekova* (engl. *Antimicrobial stewardship,* AMS) implementiran u brojne institucije u cijelom svijetu, s naglaskom na racionalnu upotrebu antimikrobnih lijekova. Kako bi uspostavili ključne aktivnosti AMS programa u Klinici Golnik, potrebno je prikupiti podatke o propisanim antimikrobnim terapijama. Stoga je cilj ovog rada bio identificirati i opisati uzorke propisivanja antimikrobnih lijekova za glavne infektivne dijagnoze na klinici – upalu pluća, akutno pogoršanje KOPB-a, akutni bronhitis i urinarne infekcije. Podaci su prikupljeni i analizirani retrospektivno među 106 pacijenata, pokazujući trend propisivanja antimikrobnih terapija i dajući sljedeće rezultate: nepotpuna dokumentacija kod 25,47% pacijenata je istaknula potrebu za unošenjem detaljnijih podataka u medicinske kartone. 58,49% analiziranih pacijenata je primalo antimikrobnu terapiju iako testiranjem nije potvrđena bakterijska infekcija. Gotovo polovica empirijskih terapija je uključivala amoksicilin s klavulanskom kiselinom. Štoviše, prema gruboj procjeni sakupljenih podataka, skoro polovica terapija nisu bile u skladu sa smjernicama i/ili pacijentovim kliničkim stanjem. Iako je medijan trajanja terapije iznosio 7 dana, 32,08% pacijenata je bilo liječeno duže od 10 dana, što je vjerojatno povezano s niskom stopom sužavanja spektra djelovanja antibiotika (8,49%). Dobra praksa je primjenjena kod zamjene parenteralnog s oralnim putem administracije lijeka, kod 77,55% pacijenta. Vjerujemo da bi detaljniji elektronički medicinski kartoni pacijenata pružili točnije i dostupnije podatke za buduće analize i optimizaciju antibiotske terapije.

Ključne riječi: antimikrobni lijekovi, antimikrobna rezistencija, program Nadzora korištenja protumikrobnih lijekova

8 SUMMARY

Excessive and inappropriate prescribing of antimicrobial drugs in hospitals leads to emergence of adverse reactions and antimicrobial resistance, which results in the prolongation of in-patient hospitalizations and increase of healthcare expenses. For that reason, *Antimicrobial stewardship* (AMS) programme was implemented in numerous institutions worldwide focusing on the rational use of antimicrobials. In order to implement the core elements of AMS programme in the University clinic Golnik, the collection of data on prescribed antimicrobial therapies is needed. Therefore, the aim of this study was to identify and descriptively describe the prescription patterns of antimicrobial prescribing for main infectious diagnoses at the University Clinic Golnik – pneumonia, acute bronchitis, acute exacerbation of chronic obstructive pulmonary disease and urinary tract infections. Data were collected and analyzed retrospectively among 106 patients, showing the trend of prescribed antimicrobials and providing the following results: incomplete data on 25.47% of patients pointed out the necessity for entering more detailed notes in medical records. 58.49% of analyzed patients received antimicrobial therapy even though bacterial infection was not confirmed. Almost half of empiric therapies included amoxicillin-clavulanate. Moreover, rough assessment of collected data shows that almost one half of therapies were not appropriate according to the guidelines and/or patients' medical condition. Even though median length of therapy was 7 days, 32.08% of patients were treated for longer than 10 days, which may be linked with low occurrence of therapy streamline (8.49%). Good practice was shown in switching for intravenous to oral route of drug administration, which occurred in 77.55% of patients. We believe that more detailed electronic medical charts could provide more accurate and easier accessible data for future analyses and optimization of the antibiotic therapy.

Key words: antimicrobials, antimicrobial resistance, Antimicrobial Stewardship

9 ATTACHMENT

Attachment 1: Ethics approval from the National Medical Ethics Committee of the Republic of Slovenia

REPUBLIKA SLOVENIJA
MINISTRSTVO ZA ZDRAVJE
Komisija Republike Slovenije za medicinsko etiko

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Številka: 0120-570/2019/9
Datum: 24. marec 2020

Zadeva: Ocena etičnosti predložene raziskave

Spoštovani,

Komisija Republike Slovenije za medicinsko etiko (v nadaljevanju KME RS) je dne 21. 2. 2020 (datirano z datumom 6. 2. 2020) od vas prejela vlogo za oceno etičnosti raziskave z naslovom "Pregled uporabe protimikrobnih zdravil v Kliniki Golnik".

Gre za retrospektivno raziskavo, ki bo potekala v okviru vaše magistrske naloge na Kliniki Golnik pod mentorstvom izr. prof. dr. Mojce Kerec Kos, mag. farm. in somentorstvom Tine Morgan, mag. farm., spec. .

KME RS je na dopisni seji 17. marca 2020[1] obravnavala prejeto vlogo in ugotovila, da je vaša vloga popolna ter ocenila, da je raziskava etično sprejemljiva. S tem vam za njeno izvedbo izdaja svoje soglasje.

P.S.: Pri morebitnih nadaljnjih dopisih v zvezi z raziskavo se obvezno sklicujte na številko tega dopisa.

S spoštovanjem,

Pripravil/-a:
Maja Žejn
svetovalka III

dr. Božidar Voljč, dr. med.,
predsednik KME

[1]Seznam članov KME, ki so odločali o vlogi, in izjava, da KME deluje v skladu z zadevnimi zakoni in priporočili, sta na voljo na spletni strani MZ (zavihek "O Ministrstvu – Komisija Republike Slovenije za medicinsko etiko", rubrika "Seje Komisije").

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Temeljna dokumentacijska kartica

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Diplomski rad

Analiza antimikrobne terapije na Klinici Golnik

Kata Sekulić

SAŽETAK

Prekomjerno i neprikladno propisivanje antimikrobnih lijekova u bolnicama dovodi do pojave nuspojava i antimikrobne rezistencije, što rezultira produljenjem hospitalizacije bolesnika i povećanjem troškova u zdravstvu. Zbog toga je program *Nadzora korištenja protumikrobnih lijekova* (engl. *Antimicrobial stewardship*, AMS) implementiran u brojne institucije u cijelom svijetu, s naglaskom na racionalnu upotrebu antimikrobnih lijekova. Kako bi uspostavili ključne aktivnosti AMS programa u Klinici Golnik, potrebno je prikupiti podatke o propisanim antimikrobnim terapijama. Stoga je cilj ovog rada bio identificirati i opisati uzorke propisivanja antimikrobnih lijekova za glavne infektivne dijagnoze na klinici – upalu pluća, akutno pogoršanje KOPB-a, akutni bronhitis i urinarne infekcije. Podaci su prikupljeni i analizirani retrospektivno među 106 pacijenata, pokazujući trend propisivanja antimikrobnih terapija i dajući sljedeće rezultate: nepotpuna dokumentacija kod 25,47% pacijenata je istaknula potrebu za unošenjem detaljnijih podataka u medicinske kartone. 58,49% analiziranih pacijenata je primalo antimikrobnu terapiju iako testiranjem nije potvrđena bakterijska infekcija. Gotovo polovica empirijskih terapija je uključivala amoksicilin s klavulanskom kiselinom. Štoviše, prema gruboj procjeni sakupljenih podataka, skoro polovica terapija nisu bile u skladu sa smjernicama i/ili pacijentovim kliničkim stanjem. Iako je medijan trajanja terapije iznosio 7 dana, 32,08% pacijenata je bilo liječeno duže od 10 dana, što je vjerojatno povezano s niskom stopom sužavanja spektra djelovanja antibiotika (8,49%). Dobra praksa je primjenjena kod zamjene parenteralnog s oralnim putem administracije lijeka, kod 77,55% pacijenta. Vjerujemo da bi detaljniji elektronički medicinski kartoni pacijenata pružili točnije i dostupnije podatke za buduće analize i optimizaciju antibiotske terapije.

Rad je pohranjen u Središnjoj knjižnici Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta.

Rad sadrži: 42 stranice, 21 tablice i 34 literaturna navoda. Izvornik je na engleskom jeziku.

Ključne riječi: antimikrobni lijekovi, antimikrobna rezistencija, program Nadzora korištenja protumikrobnih lijekova

Mentor: **Dr. sc. Maja Ortner Hadžiabdić**, *docentica Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta*

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Dr. sc. Anita Hafner, *izvanredna profesorica Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta*

Rad prihvaćen: rujan 2020

Basic documentation card

University of Zagreb
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Centre for Applied Pharmacy
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Diploma thesis

Antimicrobial therapy analysis at the University Clinic Golnik

Kata Sekulić

SUMMARY

Excessive and inappropriate prescribing of antimicrobial drugs in hospitals leads to emergence of adverse reactions and antimicrobial resistance, which results in the prolongation of in-patient hospitalizations and increase of healthcare expenses. For that reason, *Antimicrobial stewardship* (AMS) programme was implemented in numerous institutions worldwide focusing on the rational use of antimicrobials. In order to implement the core elements of AMS programme in the University clinic Golnik, the collection of data on prescribed antimicrobial therapies is needed. Therefore, the aim of this study was to identify and descriptively describe the prescription patterns of antimicrobial prescribing for main infectious diagnoses at the University Clinic Golnik – pneumonia, acute bronchitis, acute exacerbation of chronic obstructive pulmonary disease and urinary tract infections. Data were collected and analyzed retrospectively among 106 patients, showing the trend of prescribed antimicrobials and providing the following results: incomplete data on 25.47% of patients pointed out the necessity for entering more detailed notes in medical records. 58.49% of analyzed patients received antimicrobial therapy even though bacterial infection was not confirmed. Almost half of empiric therapies included amoxicillin-clavulanate. Moreover, rough assessment of collected data shows that almost one half of therapies were not appropriate according to the guidelines and/or patients' medical condition. Even though median length of therapy was 7 days, 32.08% of patients were treated for longer than 10 days, which may be linked with low occurrence of therapy streamline (8.49%). Good practice was shown in switching for intravenous to oral route of drug administration, which occurred in 77.55% of patients. We believe that more detailed electronic medical charts could provide more accurate and easier accessible data for future analyses and optimization of the antibiotic therapy.

The thesis is deposited in the Central Library of the University of Zagreb Faculty of Pharmacy and Biochemistry.

Thesis includes: 42 pages, 21 tables and 34 references. Original is in English.

Keywords: antimicrobials, antimicrobial resistance, Antimicrobial Stewardship

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The thesis was accepted: September 2020