SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The role of the pharmacist in optimizing antibiotic use of inpatient care

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The Examination takes place at the Lecture Hall of Faculty of Pharmacy (Central Pharmacy Building first floor), University of Debrecen, 11 a.m. September 5, 2022.

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The PhD Defense takes place at the Lecture Hall of Faculty of Pharmacy (Central Pharmacy Building first floor), University of Debrecen, 1 p.m. September 5, 2022.

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1. Introduction

Antibiotics are one of the cornerstones of the modern medicine. The use of these agents is not only a cornerstone of the causal treatment of bacterial infections, but also contributes significantly to the success of surgical interventions by preventing wound infections. According to the estimation of the World Health Organization (WHO) the use of antibiotics has increased life expectancy by approximately 20 years, significantly reducing morbidity and mortality caused by infections.

Nowadays, antibiotic resistance (ABR) significantly threats the effectiveness of patient care. Excessive and unnecessary use of antibiotics has led to the emergence of multidrug-resistant (MDR) strains causing serious therapeutic problems, and even pan-resistant strains that have acquired resistance to all antibiotics and can no longer be treated with the antibiotics currently being on the market. If this process is not reversed, 10 million people will die each year from antibiotic-resistant infections by 2050, as bacteria that can resist the onslaught of antibiotics have a survival advantage over those that do not. Mortality and morbidity due to antibiotic-resistant infections has increased significantly in recent years compared to the antibiotic-sensitive infections. Consequently, length of hospital stay has increased placing a heavy financial burden on the health care system.

The Global Burden of Diseases (GBD) estimates that there were 1.27 million ABR-related deaths in 2019, and the highest mortality (1.5 million) was recorded for lower respiratory tract infections in the same year. However, in the survey lower respiratory and urinary tract infections were coded based on hospital discharge data, so it was not possible to distinguish between community-acquired and hospital-acquired infections.

ABR is a serious global public health problem that has become a major health challenge worldwide. Preserving modern medicine for the next generation means stopping and reversing the process, which requires clearly coordinated international cooperation. This is also shown by the fact that a number of international professional organizations, including the WHO, the Centres for Disease Control and Prevention (CDC) and the National Health Service (NHS), have made various recommendations to slow down this process. These recommendations also highlight the role of properly trained pharmacists in the management of ABR.

Recommendations include the following to deal with the crisis: increased surveillance of bacterial resistance, prevention of infections, and antibiotic stewardship program (ASP). ASP is a set of measures that aims the correct and responsible use of the antibiotic and the reduction of its overuse, to improve disease outcome, and to reduce ABR, health care-related infections, and health care costs. Optimizing antibacterial agents, while minimizing potential side effects, ensures access to properly prescribed, affordable, quality-guaranteed antibiotics.

The multidisciplinary antibiotic stewardship team (AST) has a key role in achieving the goals of ASP, in which, the pharmacist has also a significant contribution next to the infectologist and microbiologist. The appropriate antibiotic therapy of various diseases and the appropriate surgical prophylaxis calls for the support of specialists. This can improve not only the prescription of antibiotics (choice of agent, dosage, dosage form, duration), but also reduce the use of these agents. Nowadays, the importance of judging well the need for antibiotics used as life-saving medicines well has increased.

According to the WHO Regional Office for Europe, pharmacists can play an important role in combating antibiotic resistance providing adequate information on the correct use of antibiotics. It is within the pharmacist' or pharmacologist' competence to deal with antibiotics. In certain countries, a culture has already been established to perceive the community or institutional pharmacy not a "shop" or just a health care unit, but a pharmaceutical service. Guidelines developed jointly by the International Pharmaceutical Federation (FIP) and the WHO state that the pharmacists should be able to provide accurate information and advice on the appropriate use of antibiotics and encourage the prudent use of antibiotic among health professionals working with them.

Pharmacist intervention in individual antibiotic therapy has been shown to improve disease outcome, reduce suboptimal drug concentrations, and reduce side effects (especially nephrotoxicity). Furthermore, by accessing patient-level data, the pharmacist can perform very accurate and detailed analyses on antibiotic use. By presenting the results of these analyses in the multidisciplinary team, the pharmacist can make suggestions for optimizing antibiotic use.

The Pharmacist Role in the Surgical Antibiotic Prophylaxis (SAP)

Joint arthroplasties are frequently performed life-enhancing procedures. The need for these surgical procedures continues to rise. Although arthroplasties belong to clean surgical procedures, surgical site infections (SSIs) are not uncommon. SSIs are defined as infections occurring after arthroplasties, and can involve superficial or deep tissues at the operation site. Furthermore, SSIs may result in periprosthetic joint infection (PJI). PJI is defined as infection involving the implants and adjacent tissues, which is one of the most threatening complications in orthopaedic arthroplasties, being responsible for excess morbidity and increased costs. Systemic antibacterial prophylaxis is a standard practice to prevent SSI, especially where implants are used. Inadequate Surgical Antibacterial Prophylaxis (SAP) can significantly increase antibiotic consumption in surgical wards. Inappropriate prophylaxis includes choosing an inappropriate drug, underdosing, as well as inadequate timing or prolonged administration, which also subsequently contribute to the development of antibiotic resistance. Adherence to the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery recommended by ASHP (American Society of Hospital Pharmacists) may be greatly enhanced by providing counselling for prescribers via consultation with pharmacists, who can play a vital role in controlling inappropriate prophylactic antibiotic usage and correcting suboptimal drug regimens.

Antibiotic Therapy in Patients Hospitalised with Community-Acquired Pneumonia (CAP)

European Centre for Disease Prevention and Control (ECDC) point prevalence survey data showed that antibiotic use for community acquired infections (CAIs) in Europe represented 69.9% of all antibacterial use in acute-care hospitals. In particular, more than one-third (35%) of CAIs were found to be respiratory tract infections (RTIs). In 2016, respiratory illnesses were the third most common cause of death in Europe, and accounted for 7.5% of all deaths, while in 2017 the corresponding number in Hungary was 6.2%. Community-acquired pneumonia (CAP) is one of the most common and potentially serious infectious diseases and is still one of the leading causes of morbidity and mortality worldwide, imposing a heavy economic burden on health systems even in developed countries. In European countries, CAP was responsible for almost 30% of mortality in the category of respiratory illnesses in 2015. Although CAP is often treated in ambulatory

settings, hospitalization rates range from 30% to 60%. Recent CDC data found that in the United States, 79% of all patients with CAP were treated inappropriately in the hospital setting. Inappropriateness of hospital treatment of CAP is associated with worse therapy outcomes, longer hospital stays, and higher cost of treatment. The National Institute for Health and Care Excellence/British Thoracic Society (NICE/BTS) and the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) have published official clinical CAP guidelines making recommendations for selection of initial empirical antibiotic therapy for patients hospitalized with CAP. A national CAP guideline has also been published by the Hungarian Professional Society of Infectious Diseases and Pulmonology.

Despite the importance and incidence of CAP, no field studies have been performed in Hungarian hospitals to assess the initiated antibiotic treatments.

2. Objectives

- To analyse the impact of pharmacist-led antibiotic stewardship interventions on compliance with SAP among patients undergoing joint arthroplasties, as well as antibiotic exposure and cost in SAP;
- To evaluate the characteristics and outcome of antibacterial drug use in patients admitted to hospital due to CAP;
- To evaluate adherence to national and international antibacterial CAP guidelines;
- To analyse the potential factors associated with mortality in CAP;
- To explore some basic characteristics of patients hospitalised with CAP and antibacterial treatments used in CAP.

3. Materials and Methods

The Effect of Pharmacist-Led Intervention on Surgical Antibacterial Prophylaxis (SAP) at an Orthopaedic Unit

This was a single centre study including a retrospective observational part (pre-intervention period) and a prospective intervention part (intervention period). The study was conducted at an Orthopaedic Department of a tertiary-care centre in Hungary. The pre-intervention period was 12 months while the intervention phase 7 months. The pre-intervention period was merely an observational period, when the clinical pharmacist was present in limited hours in the ward compared to the intervention period, and collected data retrospectively from all patients receiving an antibiotic. The intervention period was a prospective phase, when the clinical pharmacist spent six hours a day in the ward

Study Population

The study population included all the hospitalized patients receiving SAP for primary THA (Total Hip Arthroplasty), TKA (Total Knee Arthroplasty), and revision arthroplasty (surgery performed to replace the worn-out joint) at the aforementioned Department.

Exclusion Criteria

All patients admitted from another ward/hospital who were on antibiotic treatment, patients receiving preoperative empirical antibacterial therapy due to various suspected or proven infections, or targeted antibacterial therapy, or SAP for other operations than THA and TKA, as well as patients readmitted due to SSI or PJI (primary TKA, THA, or revision arthroplasty) were excluded from the study.

Pre-Intervention and Intervention Period

The data obtained in the pre-intervention period were analysed by the pharmacist, who later provided feedback to prescribers. Taking into account the HOA (Hungarian Orthopaedic Association) national guideline and the clinical practice guidelines for SAP published by ASHP, problems related to the appropriate use of SAP (choice of agent, timing, dosing, and duration) were discussed. The clinical pharmacist's interventions consisted of the following: proactively controlling the antibiotic therapy every day on an individual level to ensure compliance with SAP (agent, dosage, and duration) guidelines, attending afternoon surgical ward visits twice a week, and discussing their findings with the anaesthesiologist and surgeons in cases when SAP guideline deviations were observed. Moreover, the pharmacist was involved in antibiotic related decisions and provided continuous counselling service continuously. The obtained data were compared to determine the results of the pharmacist led intervention.

Data Collection

All hospitalized patients receiving antibiotics for SAP were identified and their medical records were retrieved. Demographics (age, gender), clinical characteristics (weight, date of hospital admission and discharge, surgical diagnosis, date and type of surgery, LOS, antibiotic allergy, clinical signs of SSIs including redness, delayed healing, fever, pain, tenderness, warmth, swelling, and presence of pus produced by wound were observed on surgical ward round), symptoms: fever > 37.5 ◦C, C-reactive protein > 5 mg/L, positive blood culture or micro-organism isolated from wound, bone, or synovial fluid samples), data on antibacterial administration (indication, agents, dose, route of administration, frequency, duration of antibacterial treatment, antibiotic generic substitution/combination), and cost (cost of antibiotic agents) were recorded on data collection forms. LOS was calculated by subtracting day of admission from day of discharge, and refers to the number of days that patients spent in hospital. Both the admission and discharge day were counted as one day. Patients were anonymized, and thus made unidentifiable in the study.

Data Analyses

We compared prophylactic antibiotic use regimen, namely the number of prescribed antibiotics (single agent or combination), active agent(s), dosage, and duration of prophylaxis, as well as and rate of guideline adherence, antibiotic exposure: DDD/patient, antibiotic costs, and clinical outcomes (LOS, number of surgical site infections) during the two study periods using chi-square, Fisher exact, and Mann-Whitney tests, as appropriate, using R statistical environment. To measure the antibiotic consumption, we applied the World Health Organization's ATC/DDD index (version 2020). Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. Antibiotic costs were calculated based on actual prices obtained from the central hospital pharmacy. Values of equal or less than 0.001 (multiple comparison method) were considered statistically significant

Impact of Guideline Adherence on Outcomes in Patients Hospitalized with Community-Acquired Pneumonia (CAP) in Hungary: A Retrospective Observational Study

Study Design and Setting

A 1-year (January–December 2017) retrospective observational study was conducted at the 110-bed internal medicine unit of the University of Debrecen, which is a tertiary care teaching hospital.

Data Collection

Data for all inpatients receiving antibacterial therapy during the hospital stay were recorded by the ward pharmacist. All patient and therapy related data were collected manually from medication charts and discharge letters using the e-MedSolution Hospital Information System. Data collection forms were developed and the following data were extracted: patient age, sex, weight, date of hospital admission and discharge, comorbidities, discharge type. Clinical outcome (30-day mortality) and laboratory test results on the day of admission (white blood cell count, CRP, eGFR—estimated

glomerular filtration rate) were also collected. In relation to the antibacterial therapy, the following data were collected: pre-hospital antibiotic therapy, drug allergy, indication of antibiotic treatment, empirical antibiotic choice, dosage, route of administration, and duration of antibacterial therapy during hospital stay. Only adult (18 years or above) patients who started their first empirical antibacterial therapy for community acquired pneumonia were included in the study. Empirical treatment was defined as antibacterial therapy without pathogen identification and susceptibility testing.

Patients' general condition was evaluated using the Charlson comorbidity index (CCI). eGFR on admission was used to assess dose appropriateness for drugs excreted renally. To reveal the antibiotic exposure of patients, the World Health Organization's ATC/DDD index (version 2021) was applied. Defined daily dose (DDD) refers to the assumed average maintenance dose per day for a drug used for its main indication in adults. Regarding antibiotics, DDD refers to infections of moderate severity. Our analysis focused on systemic antibacterial drugs (ATC: J01). LOS refers to the number of days that patients spent in hospital. Both the admission and discharge day were counted as a separate day.

Main Outcome Measures

The primary outcome measure was guideline adherence to the national (published by Hungarian Professional College of Infectious Diseases and Pulmonology) and two international (ATS/IDSA-American Thoracic Society/Infectious Diseases Society of America, BTS/NICE-British Thoracic Society/National Institute for Health and Care Excellence) CAP guidelines, in terms of choice of empirical antibiotic(s) and dosing. Therefore, empirical treatment was considered guideline adherent when complying with the recommendations. Secondary outcome measures included antibiotic exposure (DDD/patient), and clinical outcome (30-day mortality rate). Furthermore, demographic (age, gender) and clinical characteristics (CCI, CRP) of patients with CAP in the 30-day mortality and 30-day survivor groups were compared. Significant p values were defined as below 0.05.

4. Results

Results obtained in the surgical antibacterial prophylaxis

In the pre-intervention (12 months) and the intervention period (7 months) data of 525 and 210 patients, respectively, were collected. Of them, 130 patients were excluded in the pre-intervention period and 28 patients in the intervention period, due to various reasons.

Patient's Characteristics

Although the number of patients differed, no significant differences were found regarding their age, gender, median body weight, and diagnosis for primary arthroplasty between the two periods. In both periods almost two thirds of the patients were female, and the number of THAs was also higher than the number of TKAs.

SAP Characteristics and Pharmacist intervention

Agent Selection, Dosage

Cefuroxime was used for prophylaxis in both periods in the vast majority of arthroplasties (88.1% vs. 87.9%). Ciprofloxacin was and remained the most frequently used non-recommended agent (5.6% vs. 7.1%), even in beta-lactam allergy, when vancomycin or clindamycin were recommended by guidelines. No significant changes in the use of guideline non-adherent combinations with metronidazole (5% vs. 2.2%, $p > 0.05$) were observed between the two periods. However, the use of the guideline adherent combination of cefuroxime and amikacin slightly increased (from 0.5% to 2.2%, $p > 0.05$) in the intervention period. Data show no differences in dose and frequency of antibiotics used for SAP.

Timing and Duration of SAP

No data on the timing of the first dose of SAP were collected. Considering all arthroplasties together, we found a significant difference in the mean duration of SAP between the two periods (42.9%, pre-intervention: 4.08 ± 2.08 vs. intervention: 2.42 ± 1.90 days, $p < 0.001$). At the same time, guideline adherence in terms of SAP duration improved significantly (by 59.3%, from 5% to 64.3%, $p < 0.001$). These rates are more pronounced for primary arthroplasties (both THA and TKA), where guideline adherent one-day SAP increased significantly (by 59%, from 2% to 61%, $p < 0.001$).

Antibiotic Exposure and Cost in SAP

Antibiotic exposure in SAP decreased significantly (by 41%, from 6.07 ± 0.05 to 3.58 ± 4.33 DDD/patient, $p < 0.001$). As expected, the decrease of SAP duration led to significantly lower prophylaxis Antibiotics 2021, 10, 1509 4 of 12 costs after intervention (by 54.8%, 9278.79 ± 6094.29 vs. 3598.16 ± 3354.55 HUF/patient, $p < 0.001$). Overall cost was reduced 2.2-fold ($p < 0.001$).

Clinical Outcomes: LOS (Length of Stay) and SSIs

Comparing the pre-intervention and intervention periods, overall LOS decreased significantly for all types of arthroplasties (by 37.2%, from 11.22 ± 6.96 to 7.62 ± 3.02 days, respectively, $p < 0.001$). Hospital readmissions due to SSI were followed for 60 days after discharge in both periods. The mean time of the diagnosis of SSIs was eight days (range 1–23, $p \geq 0.05$). A slight decrease (1.8%, from 3% to 1.2%, $p = 0.21$) in the number of confirmed SSIs was found between the two periods. The number of suspected SSIs was higher (11.6% vs. 2.3%, $p < 0.001$), which is consistent with the fact that empirical or targeted administration of antibiotics was deemed necessary in 19.5% of the pre-intervention cases and 2.7% of the cases in the intervention period ($p < 0.001$).

Results obtained in the empirical antibiotic therapy of the community acquired pneumonia

In the study period, data of 1665 patients were collected, out of which data obtained from 147 patients met the study criteria and could be included in the analysis

Patient Characteristics and Main Outcomes

A total of 64 (43.54%) male patients hospitalized due to CAP were included in the study. Their age at hospital admission ranged from 27 to 95 years; 118 (80.27%) patients were aged ≥ 65 years. Overall, 59.86% of patients had a CCI score above 4. The most common comorbidities included cardiovascular diseases (35.37%) and diabetes mellitus (22.45%). The majority of patients were discharged home (80.95%), and only a small proportion were admitted to ICU (7.48%). The overall 30-day mortality rate was 24 (16.33%), comprising 15 (62.5%) in-hospital deaths and 9 (37.5%) post-discharge deaths.

Guideline Adherence

Amoxicillin–clavulanic acid was the most widely used antibiotic therapy, administered to 29.07% of patients in monotherapy and 54.09% of patients in combination, followed by ceftriaxone (monotherapy: 29.07%, combination: 25.59%) and moxifloxacin (monotherapy: 19.77%, combination: 16.39%). Initial empirical therapies for CAP showed a relatively low rate of guideline adherence: 30.61% for national, 22.45% for BTS/NICE, and 15.65% for ATS/IDSA CAP guidelines.

Dosage appropriateness assessments was in line with the previous section, the highest guideline adherence (agent, dose) rate was found in relation to the national guideline (40/45, 88.89%), followed by ATS/IDSA (18/23, 78.26%) and BTS/NICE (24/33, 72.73%) CAP guidelines.

Antibiotic Therapy for CAP

The majority of treatments (58.50%) were monotherapies; 93 (63.27%) patients received the first antibacterial therapy IV (intravenously), and 14 of them (15.05%) were switched to oral route within 1–5 (median 3.5) days. The average duration of antibiotic therapy for CAP was 7.13 ± 4.37 days (median 6, range 1–27), while the average antibiotic consumption was 11.41 ± 8.59 DDD/patient (range 1–44.5). The majority of patients (81.63%) received short-term (1–6 days) antibiotic therapy. In the majority of cases, there was no change in the first empirical therapy (85/147, 57.8%). However, changes occurred due to sequential antibiotic therapy (9.52%), de-escalation (4.08%), and escalation (28.57%). A significant difference was found in the 30-day mortality rate between these types of antibiotic therapies (no change: 12.94%, sequential antibiotic therapy: 0%, de-escalation: 0%, and escalation: 30.95%, $p = 0.046$.

Clinical Outcomes: LOS, 30-Day mortality

In our study, the mean LOS was 8.26 ± 5.64 (range 1–33) days. Adherence to the national guideline led to a slightly lower 30-day mortality rate than guideline non-adherence (15.56% vs. 16.67%, $p > 0.05$), while this difference was more pronounced in the case of international guidelines (BTS/NICE: 21.21% vs. 14.91%, and ATS/IDSA: 21.74 vs. 15.32%, $p > 0.05$). Furthermore, we found that the 30-day mortality rate for the different types of therapies was as follows: 8% for combination of beta-lactam and macrolide, 19.61% for beta-lactam monotherapies, and 21.77% for respiratory fluoroquinolone monotherapies ($p > 0.05$).

Prognostic Factors for Mortality in CAP

We observed a significant difference in the 30-day mortality of CAP between age groups. The 30-day mortality rate increased proportionally with age: it was 6.90% (2/29) among patients aged 20–64 years, 11.11% (8/72) in patients aged 65–84 years, and reached 30.43% (14/46) in the 85+ age group. The CCI score of patients in the 30-day non-survivor group was higher by one point on average (5.71 ± 1.85 vs. 4.67 ± 1.83, $p = 0.012$). In terms of C-reactive protein (CRP) levels at admission, a remarkable difference was found

between the two patient groups (30-day non-survivor: 177.28 ± 118.94 vs. 30-day survivor: 112.88 ± 93.47 mg/L, p = 0.006). Thirty-day mortality was not associated with significantly longer LOS (9.54 ± 8.45 vs. 8.01 ± 4.93 days, p = 0.668), higher antibiotic exposure (8.25 vs. 7.98 DDD/patient, p = 0.21), or longer duration of antibiotic therapy (8.20 ± 7.03 vs. 6.92 ± 3.64 days, p = 0.187). Similarly, we found a median 1-day difference between 30-day survivors and non-survivors in the duration of antibiotic therapies (6 vs. 7 days, respectively), and length of stay (7 vs. 8 days, respectively).

Based on the results of the logistic regression analysis, out of the three factors (increased age, higher CCI score, and higher CRP level) that were associated with higher mortality in the univariate analysis, only the CRP level on admission was found to increase the risk of mortality. Each additional increase of 50 mg/L in the CRP level seen on admission increased the 30-day mortality odds 1.3-fold, indicating that the degree of inflammation affects mortality.

5. Discussion

Antibiotic resistance occurs everywhere in the world. The antimicrobial stewardship program (ASP) aims to slow the emergence of antibiotic resistance. However, currently, there is no official national ASP strategy in Hungary. Different healthcare providers have their own strategies, in which the opportunities and responsibilities of the clinical pharmacists are defined based on the WHO document.

Even though SAP is of major importance in the prevention of SSIs, it is still a hotbed for antibiotic overuse and misuse. The situation is similar for the empirical antibiotic therapy of CAP, one of the most common community acquired acute infection. However, pharmacist intervention can have a significant impact both on SAP compliance in orthopaedic surgical procedures and the empirical therapy of CAP, particularly on the overall guideline adherence that may result in significant decrease in antibiotic exposure, cost, and clinical outcomes. In Hungary, our study is the first that has been conducted regarding the evaluation of antibiotic prescription patterns, associations between guideline adherence and outcomes in SAP applied in orthopaedic procedures, and in patients with CAP who required hospitalization.

Guideline Adherence

Several studies assessing compliance with SAP and CAP guidelines have been published. Overall compliance to SAP guidelines is usually in the range of 20–50%. In the literature, the most important types of non-adherence to guidelines are (i) starting prophylaxis before the day of surgery, (ii) prolongation of prophylaxis in the postoperative period, and (iii) unnecessary use of broad-spectrum agents.

In the present study, prophylaxis prior to the day of surgery was considered preoperative empirical antibiotic therapy. Regarding the timing of prophylaxis, although the optimal and recommended timing is 30 min to one hour prior to incision, and antibiotics should consequently be administered in the operation room, the time of their use was generally found to receive low priority among anaesthesiologists as well as surgeons, with both professionals concentrating on their immediate role in the surgical procedure. In addition, surgeons use prolonged SAP (7–10 days) in the belief that it may reduce the incidence of postoperative infections, including SSIs. Non-adherence to guidelines is

frequently motivated by fear of infection, i.e., prescribers perceive prolonged administration of (non-recommended) broader-spectrum drugs as safer. Also, increased antibiotic use is often due to lack of local guidelines.

As for timing, El Hassan et al. found a guideline adherence of 30.4% for the timing of the first dose. Data regarding timing were not collected in this study. We believe that the practice of patients getting the first dose of prophylactic antibiotic on arrival in the operation room.

In this review, guideline adherence in terms of agents was relatively high, 88.6% in the pre-intervention period, and increased to 90.1% in the intervention period. The use of unrecommended antibacterial agents remained almost the same, mostly due to prophylactic use of drug combinations (fluoroquinolones and amikacin, metronidazole, or rifampin) in revision arthroplasties where the risk for PJI is higher. Nevertheless, the use of metronidazole in combinations decreased (by 2.8%, from 5% to 2.2%, $p = 0.122$) in the intervention period. Inappropriate use of metronidazole is not uncommon. A study in Pakistan on different surgical procedures, including orthopaedic surgeries, found that after the pharmacist intervention the use of combination antibiotic therapies with metronidazole decreased significantly (from 26.2% to 16%, $p = 0.011$). However, in the same study the rate of inappropriate antibiotic choice did not change significantly, which is consistent with our findings. Also, an Italian research group failed to show any significant improvement in the choice of antibiotics (78.4% vs. 78.4%, $p = 0.48$)

In our study we found an overall guideline adherence (agent choice, dosage, timing, and duration) of 2% in the pre-intervention period. The adherence to guidelines was relatively high for agent choice (88.6%) and for dosage (86.3%); nevertheless, only 2% of these patients received SAP for an appropriate duration. Due to the shortening of SAP duration, the rate of overall guideline adherence (agent selection, dosage, and duration) improved significantly (increased by 56.2%, $p < 0.001$) in the intervention period, which is in line with above-mentioned international findings.

During the intervention phase of the present study, slight improvement in the dosage of guideline adherent antibiotics (of 2.7%, from 86.3% to 89%, $p > 0.05$) was observed. This adherence rate for SAP dosage after pharmacist intervention is similar to rates of appropriateness of dosage reported in the literature. Zhou et al. reported an increase in appropriateness of dosage for cefuroxime (7.4%, from 77.0% to 84.4%, $p = 0.01$) after

pharmacist intervention in SAP. An Italian study in elective surgical procedures including orthopaedic surgeries reported significant improvement after pharmacist intervention in correct dosage (increased by 14.1%, from 69.7% to 83.8%, $p < 0.001$).

In the present study, SAP duration was observed to decrease significantly in the intervention period; improvement in SAP duration related adherence to the guidelines was recorded in 42.9% of the studied cases. The huge difference in the proportion of one-day prophylaxis in the two periods (59.8% increase, $p < 0.001$), as well as the reduction in the proportion of over five days prophylaxis to one-third of the original rate (11.6% decrease, $p < 0.001$) were particularly favourable changes.

Several studies have focused on the duration of SAP. In Europe, data obtained in a point prevalence survey conducted by the ECDC (European Centre for Disease Prevention and Control) showed that antibiotic use for SAP accounted for 18% of the total antimicrobial use in acute care hospitals in the EU. In surgery, 36% of the administered antibiotics are used for SAP, and more than half (60%) of all these antibiotics were used for more than one day, which implies prolonged use. In Hungary, these rates are above the European average (45% and 56%, respectively).

According to a clinical pharmacist's study, in 60.5% of all orthopaedic surgeries SAP was administered for a longer duration than 24 h. After the pharmacist intervention in SAP (56.6% orthopaedic surgeries), significant reductions were observed in the mean duration of antibiotic prophylaxis (17%, from 66.01 ± 41.015 to 55.20 ± 36.214 h, $p = 0.003$). This is very important because the fear of infection motivated prolonged prophylaxis was not found to be associated to any benefit regarding to clinical outcomes.

In the case of the CAP we also found shortcomings in the guideline-adherence. Among the patients hospitalized with CAP investigated in the present study, the rate of national guideline adherence for antibiotic selection was 30.61% ($N = 45$).

Based on ATS/IDSA and BTS/NICE CAP guidelines, combinations of beta-lactams and macrolides, or respiratory fluoroquinolones (RFQs) are recommended as first choice agents to treat empirically moderate-severe (hospitalized in non-ICU ward) CAP.

The Hungarian guideline for patients hospitalized with CAP is similar to international guidelines in terms of agent selection. This guideline recommends the use of respiratory fluoroquinolones (moxifloxacin or levofloxacin) as monotherapy or the combination of beta-lactam (amoxicillin clavulanic acid or ceftriaxone) and clarithromycin to cover both

typical (e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus*, Group A streptococci, *Moraxella catarrhalis*) and atypical pathogens (e.g., *Legionella, Mycoplasma pneumoniae, Chlamydia pneumoniae*) responsible for CAP.

The most common guideline adherent empirical treatment for CAP was amoxicillin-clavulanic acid combined with clarithromycin, or moxifloxacin or levofloxacin as monotherapy (23, 47.92% in both cases), followed by ceftriaxone combined with clarithromycin (2, 4.16%).

Guideline adherent empirical antibiotic use in CAP is quite varied in the related literature. Three studies evaluating patients hospitalized with CAP found guideline adherent antibiotic therapy in 57%, 57%, and 65% of the cases; these rates were higher compared to our results. At the same time, an Italian multicenter before-and-after guideline implementation survey found that guideline adherent antibiotic prescribing increased significantly (33 vs. 44 %; $p < 0.001$) compared to a poor initial guideline adherence, similar to our results. The low guideline adherence found in our study may be explained by the fact that although there was a Hungarian guideline, its dissemination and accessibility were not adequate; consequently, it had not been integrated in daily practice.

Even though we found high adherence to the national guideline in terms of dosing (88.89%), over- and underdosing still affected relatively high proportions of patients (8.89% and 2.22%, respectively). Overdosing occurred most commonly in renal impairment, when dose adjustment would have been required for amoxicillin-clavulanic acid, clarithromycin, and moxifloxacin. The other common error occurred mostly due to routine underdosing of levofloxacin and clarithromycin, or not taking into account patients' extreme body weights.

Considering the route of administration, the majority of patients (63.27%) received IV initial antibacterial therapy for CAP. At the same time, switching from an IV to oral regimen (in 9.52% of the cases) was performed within 1–5 (median 3.5) days. These results are mostly supported by the national and international guidelines, according to which the empirical antibiotic treatment in patients hospitalized with CAP can be initiated via any route, but using antibiotics exclusively intravenously is only recommended when the oral route is compromised. The review of intravenous antibiotics after 48 h of use and switching

to oral antibiotics are recommended, if possible, when either the same agent or the same drug class should be used.

In addition, more antibiotic therapy needed further escalation (28.57%), while changes in the first empirical therapy due to de-escalation (4.08%) occurred at relatively low rates. The guidelines for CAP stress the importance of de-escalation of empirical antibiotic therapy, recommending the stricter use of broad-spectrum antibiotics. Although appropriate dosage and de-escalation are important in optimizing antibiotic use and reducing antibiotic resistance, studies dealing with antibiotic dosing in CAP treatments are rare. A cross-sectional study in Australian patients hospitalized with CAP found that the most common errors in high-risk CAP were inappropriate dose, route, and duration, which affected 69% (N = 27) of patients. Routine underdosing of ceftriaxone was the most frequent (N = 17, 44%), while 54% of patients were prescribed antibiotics to administer via a route not recommended on the basis of CAP severity. According to a multicentre study in the Netherlands, where de-escalation occurred in 16.7% of the patients hospitalized with CAP, physicians seem to be more inclined to continue the regimen when it appears to be effective.

Regarding to the duration of antibiotic therapy, our results are in line with the requirements of international guidelines: most of our patients (81.63%) receive short antibiotic therapy (1–6 days), while the median duration of antibiotic therapies for CAP was 6 days (range 1–27). The optimal duration of antimicrobial therapy in CAP is not well-established. Although the national CAP guideline for in-patients does not cover the duration of antibiotic treatment, according to the ATS/IDSA guideline, patients hospitalized with CAP should be treated for a minimum of 5 days.

Clinical Outcomes

As the findings reported earlier reveal, neither prolonged prophylaxis, nor choosing agents with a broader spectrum than recommended, nor combinations provided any benefit in terms of length of stay. At the same time, an experimental pre-post prospective study on orthopaedic surgeries found that overall guideline adherent SAP (agent selection, dosage, and duration) was associated with a one-day decrease in LOS.

Some studies found direct association between pharmacist intervention and decrease of LOS; a study on different surgical procedures including orthopaedic surgeries found that pharmacist intervention resulted in favourable outcomes with significantly decreased LOS (by 16.6%, from 5.4 ± 4.814 to 4.50 ± 3.398 days, $p = 0.023$). Xi et al. found that pharmacist intervention in SAP reduced significantly the average LOS (31.78%, from 17.64 ± 4.92 to 13.34 ± 2.05 days, $p < 0.001$) in patients undergoing hip arthroplasty. Likewise, Zhou et al. observed that pharmacist intervention in SAP significantly reduced the average LOS (7.45%, from 23.3 ± 8.9 to 20.9 ± 8.9, $p < 0.001$). Our results support these findings by showing similar improvement in the intervention period, when LOS decreased significantly for all types of arthroplasties (by 37.2%, from 11.22 ± 6.96 to 7.62 ± 3.02 days, $p < 0.001$).

Although there was no pharmacist intervention in our second study, regarding clinical outcomes, we found that guideline adherence to national recommendations was associated with slightly lower 30-day mortality than guideline non-adherence (15.56% vs. 16.67%, $p > 0.05$).

Similar to SAP, several studies in the empirical therapy of CAP have focused on the relation between mono- or combination therapies and clinical outcomes. The results of a multicentre study in patients admitted to non-ICU wards with CAP have shown clinical outcomes, recovery rate and mortality to be unaffected by the choice of a beta-lactam, beta-lactam and macrolide, or respiratory fluoroquinolone antibiotic regimen. According to a systematic review on antibiotic therapy for non-ICU hospitalized patients with CAP, fluoroquinolone monotherapy had similar efficacy and favourable safety compared to beta-lactam with or without macrolide.

In the present study, we found a slightly better mortality rate in CAP hospitalized patients with the combination of beta-lactam and macrolide, compared with beta-lactam or respiratory fluoroquinolone monotherapies (8% vs. 19.61% and 21.77%, respectively, $p > 0.05$).

Further, changes in the first empirical therapy due to de-escalation (4.08%) and switching from intravenous to oral regimen (9.52%) occurred relatively infrequently, and were not associated with increased 30-day mortality rates (0% for both).

Regarding the duration of CAP empiric antibiotic therapy, we found no difference in mortality rates between short- and long-term therapies (16.67% vs. 14.81%, $p>0.05$),

which may suggest that short antibiotic therapy can be as effective as long antibiotic therapy. A previous meta-analysis of five randomized trials (which included patients of all ages, excluded neonates, and any severity of CAP) found no differences in clinical outcome and mortality rates comparing short (1–6 days) versus long (≥7 days) antibacterial therapies. Our results support these finding by showing similar mortality rates for both short and long antibiotic durations.

In terms of clinical outcomes, in the SAP study, another parameter examined was the rate of SSIs. Based on previous findings, SSIs are most likely to develop in the first 60 days; thus, most probably only a small proportion could have remained unreported in the present study. We found a relatively low rate of confirmed SSIs for both periods (3% vs. 1.2%, $p = 0.21$). Beside this, median time to diagnosis of SSI in this study was eight days (ranging from 1 to 23 days). At the same time, we believe that these SSI rates are also confirmed by the fact that the number of cases requiring postoperative antibiotic treatment due to infections related to the surgery also decreased significantly (by 16.8%).

According to a literature review, significant variability in the incidence of orthopaedic SSIs (due to perioperative circumstances, patients' medical conditions) was noted between different studies (from 1.9% to 22.7%). However, according to the literature pharmacists' interventions on SAP resulted in significantly decreased rates of SSIs (from 3.5% to 1.2%, $p = 0.02$). These SSI rates published by Zhou et al. before and after the intervention are almost identical to our findings.

Prognostic Factors for Mortality Due to CAP

Previous research found that increased age, male gender, increased CRP, and comorbid conditions (mainly malignancy, congestive heart failure, diabetes mellitus, and renal disease) act as predictive factors for mortality in patients hospitalized with CAP.

As for age, our results show that 30-day mortality in patients aged ≥ 85 years was 3-fold compared with those aged 65–84 years (30.43% vs. 11.11%). Studies found that age ≥ 85 years was an independent predictive factor for mortality in CAP, increasing the risk of death significantly. According to Torner et al., age ≥ 85 years was markedly associated with mortality in CAP, since the 30-day mortality rate was 2.6 times higher in this age group compared with patients aged between 65 and 84 years. Moreover, Luna et al.

concluded that an age of 80 years or more should already be considered a risk factor for poor outcome in CAP.

Furthermore, a temporal analysis of pneumonia (excluding influenza-related pneumonia, aspirational pneumonia, and congenital pneumonia) mortality rates in European countries between 2001 and 2014 revealed gender discrepancy: mortality was higher in males than in females. Regarding Hungary, a mortality rate of 7.46% in males and 3.72% in females was reported. Surprisingly, the mortality rate in the present study was higher among females than males (18.07 vs. 14.06%). However, this difference is not clinically significant. Even though in the study population there were more females (56.46%) than males, we cannot give an obvious explanation for these mortality rates, since CCI and CRP did not differ across genders.

The other commonly studied prognostic factor for CAP mortality is CRP level. The CRP test is the most widely used serum biomarker in the differential diagnosis (viral or bacterial aetiology) of lower respiratory tract infections. Due to bacterial infection, CRP levels rise within the first 6 to 8 h in response to several inflammatory stimuli.

Several studies evaluated the relationship between C-reactive protein serum level and outcomes of CAP concluding that CRP values increase in line with the severity of CAP, and can be used as an independent prognostic predictor of the severity of CAP, for the follow-up of patients' condition, for response to antibiotic therapy, and CAP clinical outcome. Moreover, CRP level may guide CAP empirical treatment decisions and help avoid unnecessary antibiotic use in hospitalized patients. A recent study conducted in a Scottish hospital demonstrated that a CRP level below 100 mg/L on admission was significantly associated with reduced 30-day mortality (OR 0.18, $p = 0.03$). In a Danish teaching hospital, the highest mortality risk was found in patients with CRP > 75 mg/L on admission. Results of the present study are consistent with these previous findings, as we recorded significantly higher average CRP values on admission in the group of patients who died within 30 days compared to 30-day survivors (177.28 ± 118.94 vs. 112.88 ± 93.47 mg/L, $p = 0.006$).

Regarding comorbid conditions, we found that CCI scores differed significantly between the 30-day non-surviving and 30-day surviving patients (5.71 ± 1.85 and 4.67 ± 1.83, $p = 0.012$). A higher CCI score due to the presence of comorbidities was associated

with higher mortality rates (CCI score 0–4: 11.86%, CCI score 5–10: 19.32%) in CAP, similar to other literature data. A secondary analysis of CAP performed by Luna et al. found that the presence of comorbidities was associated with poorer outcomes

Antibiotic Cost

As our results show, pharmacist intervention can have a significant impact on SAP compliance resulting in a significant reduction in the amount of antibiotics used for SAP (by 41%, from 6.07 ± 0.05 to 3.58 ± 4.33 DDD/patient, $p < 0.001$) as well as in prophylactic cost (by 54.8%, $p < 0.001$), not only in primary arthroplasties, where the adherence to guidelines improved very much (56.2%, $p < 0.001$), but also in revision hip arthroplasties (by 50.5%, $p > 0.05$).

To our knowledge, there are no published data in the literature on the amount of antibiotic exposure in SAP in orthopaedic wards. However, a study conducted at a surgical ICU with the aim to reduce SAP showed a significant reduction of cefuroxime use in SAP (14.4%, from an estimated mean of 1036 DDD/1000 to 887 DDD/1000 patient-days) after intervention. According to another study, pharmacist intervention in SAP reduced irrational use of antibiotics, leading to a decrease in the average total cost of antibiotic use (by 71.06% in USD).

Pharmacist Intervention

Our study points out that guideline adherence in both orthopaedic SAP and empiric therapy of CAP was relatively poor, and the optimization of these antibiotic therapies may be an important part of AAP in the surgical and internal medicine departments.

In the present study, we found that in the pre-intervention period irrational antibiotic use was quite frequent for SAP in orthopaedic surgery. Redundant antibiotic combinations of beta-lactams or quinolones with metronidazole, and prolonged SAP duration contributed to the high total antibiotic consumption and costs of SAP. In the intervention period we implemented daily pharmacist intervention, which resulted in remarkable changes in several parameters of SAP and clinical outcomes. There are several studies where pharmacist intervention was shown to be particularly effective in increasing the guideline adherence rates of SAP in terms of agent selection, dosing, timing, and duration.

Based on the available evidence, it was found that clinical pharmacists play an important role in all aspects of rational antibiotic use.

In the intervention period, the activity of the clinical pharmacist was not only welcome, but actively sought for. Studies also show that adherence to guidelines may be facilitated by consultation, and even more by regular audits of the prophylaxis practice.

There was no pharmacist intervention in the empirical therapy of CAP. At the same time, the poor guideline adherence highlights the need for this more than anything, as guideline adherent therapy in both of our studies has resulted in a more favourable clinical outcome and more rational use of antibiotics.

Limitations and Strengths

One of the important limitations of our study is that it was a single-centre study conducted in a university-affiliated hospital; therefore, findings may not be directly extrapolated to other settings. At the same time, this study provides detailed, first-hand observations of everyday work processes on SAP at an orthopaedic ward and on empirical treatment of CAP in internal medicine ward. However, retrospective data collection from medical records might contain inaccuracies and potential biases.

One of the most important limitations of the study made on the internal medicine ward was that no clinical case definition of CAP was given or standardized at hospital level. However, the diagnosis of pneumonia was confirmed in every case by chest radiography. Furthermore, there was a lack of knowledge of pneumonia severity score (PSI score), since not all elements of the score were retrievable from medical records. Moreover, there were no set hospital standard guidelines for the empirical antibiotic treatment of CAP. Therefore, national and international guidelines were used for assessing antibiotic use. Third, we also consider it likely that de-escalation (prescribing an oral antibiotic) occurred after discharge. However, no data were collected on de-escalation after discharge.

In conclusion, there are few studies in Hungary that explore those important healthcare practices at the individual patient level that may lead to the development of antimicrobial resistance. We believe that our results may contribute to the optimization of antibiotic therapy for both SAP and CAP, highlighting the important role of the pharmacist in inpatient care.

6. Summary

The development of antibiotic resistance cannot be prevented, but the extent of its impact on modern medicine can be decreased by properly used affordable antibiotics.

It is the responsibility of all prescribers to become an antibiotic supervisor, prescribing antibiotic only for bacterial infections requiring treatment, optimizing the use of antibiotics already at the patient level. The ASP (Antibiotic Stewardship Program) should be developed as part of a national plan, together with enhanced surveillance, reporting and infection prevention initiatives. If we want to change the course of history and to save 10 million lives annually from death due to antibiotic-resistant infections by 2050, both prescribing physicians and pharmacists must be active ASP participants in order to preserve this valuable resource.

The aim of this study was to highlight the need for the active participation of the clinical pharmacist at the ward. The clinical pharmacist needs several years of clinical experience to become expert, and their participation in continuous training is essential. The adequate treatment of patients with bacterial infections is a difficult and complex task, in which the pharmacist also plays an extremely important role. Their active participation in the multidisciplinary therapeutic team can be a major contribution to optimizing antibiotic use and reducing health care costs.

The continuous presence of the clinical pharmacist at the orthopaedic surgery ward led to a significant improvement in SAP (Surgical Antibiotic Prophylaxis) guideline adherence and decreased antibiotic consumption. These resulted in a reduction of the direct antibiotic cost, number of surgical site infections, and length of hospital stay. Our results suggest that the clinical pharmacists as an active member of the antibiotic stewardship team (through providing antibiotic related advices, monitoring the administered antibiotics, and concomitant consultation with prescribing physicians) may play an important role in the rational use of SAP avoiding unnecessary SAP costs.

Assessing the empirical antibiotic therapy for CAP (Community-acquired Pneumonia) we found a poor adherence to national and international CAP guidelines in terms of drug selection and dosing. In addition, the CRP value on admission was markedly associated with mortality in CAP. We believe that our results may help to avoid unnecessary antibiotic

use in future inpatient-care by influencing or even directing decisions made in the CAP empirical antibiotic therapy.

The dissertation's studies highlight that a significant improvement in antibiotic use can be achieved with the continuous presence of the clinical pharmacist at the ward.

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Subject: PhD Publication List

Candidate: Adina Fésüs
Doctoral School: Doctoral School of Pharmacy

List of publications related to the dissertation

1. **Fésüs, A.**, Benkő, R., Matuz, M., Engi, Z., Ruzsa, R., Hambalek, H., Illés, Á., Kardos, G.: Impact of Guideline Adherence on Outcomes in Patients Hospitalized with Community-Acquired Pneumonia (CAP) in Hungary: a Retrospective Observational Study.
Antibiotics-Basel. 11 (4), 1-17, 2022.
DOI: http://dx.doi.org/10.3390/antibiotics11040468
IF: 4.639 (2020)

2. **Fésüs, A.**, Benkő, R., Matuz, M., Kungler-Gorácz, O., Fésüs, M. Á., Bazsó, T., Csernátony, Z., Kardos, G.: The Effect of Pharmacist-Led Intervention on Surgical Antibacterial Prophylaxis (SAP) at an Orthopedic Unit.
Antibiotics-Basel. 10 (12), 1-12, 2021.
DOI: http://dx.doi.org/10.3390/antibiotics10121509
IF: 4.639 (2020)

List of other publications

3. Tóth, H., Buchholcz, G., **Fésüs, A.**, Balázs, B., Nagy József, B., Majoros, L., Szarka, K., Kardos, G.: Evolution of the Gram-Negative Antibiotic Resistance Spiral over Time: a Time-Series Analysis.
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DOI: http://dx.doi.org/10.3390/antibiotics10060734
IF: 4.639 (2020)

4. López-Lozano, J. M., Lawes, T., Nebot, C., Beyaert, A., Bertrand, X., Hocquet, D., Aldeyab, M., Scott, M., Conlon-Bingham, G., Farren, D., Kardos, G., **Fésüs, A.**, Rodríguez-Baño, J., Retamar, P., Gonzalo-Jiménez, N., Gould, I. M., THRESHOLDS study group: A nonlinear time-series analysis approach to identify thresholds in associations between population antibiotic use and rates of resistance.
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5. Tóth, H., **Fésüs, A.**, Kungler-Gorácz, O., Balázs, B., Majoros, L., Szarka, K., Kardos, G.: Utilization of vector autoregressive and linear transfer models to follow up the antibiotic resistance spiral in Gram-negative bacteria from cephalosporin consumption to colistin resistance.
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