Antimicrobial Stewardship - a Priority for Clinical Pharmacists

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Abstract

Inappropriate antimicrobial use is a significant cause of antimicrobial resistance and poor patient outcomes. Antimicrobial stewardship aims to ensure optimal treatment. The aim of the study was to determine whether antimicrobial use is appropriate in a cohort of older patients admitted for rehabilitation and to identify factors to be incorporated in a framework that highlights the clinical pharmacist's intervention in antimicrobial stewardship. The study was carried out at Karin Grech Hospital, a rehabilitation hospital. Data collection was standardised through a data collection sheet which was formulated following a literature search and validated for reliability and comprehensiveness by an expert group. The study included patients over 65 years who were prescribed antibiotics for a suspected lower urinary tract infection. Data was collected retrospectively for 98 patients meeting the inclusion criteria from August to December 2022, and was anonymised by the designated intermediary. Appropriateness was assessed in terms of treatment indication, choice, dose/regimen/route. Appropriateness for treatment indication was evaluated on criteria decided by the expert group, while the evaluation of antibiotic choice, dose, regimen, and route was based on local guidelines. Statistical analysis was carried out using IBM SPSS® v 28. Most patients were in the 80-89 age group (60%, n=59) and female (66%, n=65). The mean score of the Charlson Comorbidity Index was 5, and 47% (n=46) of patients were catheterised. Treatment was evaluated as being appropriate in 32% (n=31) of patients and inappropriate in 28% (n=27). In the remaining 40 (41%) patients, treatment appropriateness was classified as inconclusive due to the possibility of another source of infection or the necessity for further data. Inappropriate prescriptions were mainly

attributed to failure to adjust treatment to culture and sensitivity test results (44%, n=12), and treatment of asymptomatic patients (30%, n=8). A framework incorporating key factors to be considered in treatment decisions may enhance the clinical pharmacists' contribution to optimising antimicrobial treatment.

Keywords: antimicrobial stewardship, antimicrobial resistance, older adults, clinical pharmacists' intervention.

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List of Abbreviations

ADE – Adverse Drug Event

AMR – Antimicrobial Resistance

AMS – Antimicrobial Stewardship

ASB – Asymptomatic Bacteriuria

C&S – Culture and Sensitivity

CAASB – Catheter-Associated Asymptomatic Bacteriuria

CAUTI – Catheter-Associated Urinary Tract Infection

CCI – Charlson Comorbidity Index

CDC – Centers for Disease Control and Prevention

CrCl – Creatinine Clearance

CRP – C Reactive Protein

eGFR – Estimated Glomerular Filtration Rate

EU – European Union

IV – Intravenous

KGH – Karin Grech Hospital

MDH – Mater Dei Hospital

PO – Oral

PPS – Point Prevalence Studies

SAPG – Scottish Antimicrobial Prescribing Group

SmPC – Summary of Product Characteristic

UTI – Urinary Tract Infection

WHO – World Health Organisation

Chapter 1: Introduction

1.1 Introduction

Antibiotics are overused, particularly in hospitals, where half of all patients are expected to receive at least one antibiotic (Magill et al., 2014). In the United States, 30% of antibiotics used are deemed inappropriate due to unnecessary or suboptimal use (Fridkin et al., 2014). Inappropriate antimicrobial use is correlated with antimicrobial resistance (AMR) and adverse events resulting in increased patient morbidity and mortality (Garau & Bassetti, 2017; Suh et al., 2021). AMR has the potential to become one of the leading causes of mortality, with an estimated 10 million annual deaths by the year 2050[1]. In 2019 more than 1.2 million deaths were directly attributed to AMR, with antibacterial-associated death amounting to an estimated 4.95 million deaths (Antimicrobial Resistance Collaborators, 2019). The European Union attributed 33,000 deaths to antimicrobial-resistant bacteria[2]. As an attempt to reduce the occurrence of resistance and improve antibiotic use, policies have been enacted by different countries and organisations, such as the EU One Health Action Plan against AMR [3], which is a holistic approach to ensure the prudent use of antibiotics within all sectors.

[1] World Health Organisation (WHO). New report calls for urgent action to avert antimicrobial resistance crisis [Internet]. New York:WHO; 2019 [Cited 2023 Apr 14]. Available from URL: https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis

[2] European Centre for Disease Prevention and Control. 33000 people die every year due to infections with antibiotic-resistant bacteria [Internet]. ECDC;2018 [Cited 2023 Apr 15]. Available from URL: https://www.ecdc.europa.eu/en/news-events/33000-people-die-every-year-due-infections-antibiotic-resistant-bacteria

[3] European Commission. A European One Health Action Plan against Antimicrobial Resistance (AMR) [Internet]. [Cited 2023 Apr 17]. Available from URL: https://health.ec.europa.eu/system/files/2020-01/amr_2017_action-plan_0.pdf

Malta[4] aims to improve its stewardship approach by, among others, including the use of in vitro diagnostic medical devices to aid in the differentiation between viral and bacterial infections, improving or introducing guidelines, and targeting antibiotics listed on the World Health Organisation (WHO) aWaRE list[5]. The impact of broad-spectrum antibiotics on AMR is debatable, with authors such as Cunha (2018) suggesting that choosing an antibiotic with low resistant potential within the antibiotic class is more important than restricting the use of broad-spectrum antibiotics.

1.2 Inappropriate Antimicrobial Use

Antimicrobial point prevalence studies/ surveys (PPS) such as the WHO PPS are useful, standardised tools which can be used to identify antimicrobial prescribing habits within a single hospital in the same country or between different countries. Point prevalence studies/survey tools can be used to gauge antimicrobial prescribing, identify inappropriate antimicrobial use, and be incorporated in countries with poor resources. The methodology proposed by the WHO retrospectively collects prescription information from patients' records and documentation[6].

Reasons for inappropriate prescriptions can be common across all antibiotics and infection types, such as excessive treatment duration or they can be specific to an

[4] Ministry For Health, Ministry for The Environment, Sustainable Development and Climate Change. A Strategy and Action Plan for the Prevention and Containment of Antimicrobial Resistance in Malta 2018 – 2025 [Internet]. [Cited 2023 Apr 24]. Available from URL: https://meae.gov.mt/en/Public_Consultations/MEH-HEALTH/Documents/AMR%20Strategy_FINAL_EN_%20Public%20Consultation_NOV2018.pdf

[5] World Health Organisation (WHO). 2021 AWaRe classification [internet]. Geneva:WHO; 2021 [cited 2023 APR 29]. Available from URL: https://www.who.int/publications/i/item/2021-aware-classification

[6] World Health Organisation (WHO). WHO Methodology for Point Prevalence Survey on Antibiotic Use in Hospitals [Internet]. Geneva:WHO; 2018 [Cited 2023 Apr 21]. Available from URL: https://www.who.int/publications/i/item/WHO-EMP-IAU-2018.01

antibiotic class or infection type. Examples of a specific inappropriate prescription includes treatment of asymptomatic bacteriuria (ASB) in urinary tract infections (UTI), the use of antimicrobials with medications which would result in a significant drug-drug interaction, and exposure to systemic antibiotic where topical treatment would have sufficed (Baclet et al., 2017). The estimated amount of inappropriate antibiotic prescriptions varies between different settings and countries. Previous studies assessing appropriate antibiotic use between different US hospitals found improper antibiotic use to range between 30% – 50% (Fridkin et al., 2014; Tribble et al., 2020). A recent review by Magill et al. (2021) identified that inappropriate antibiotic use within the different infection types amounted to 55.9%. Infection type can impact the number of inappropriate cases, with the highest reported cases being attributed to respiratory infections (Magill et al., 2021). Antimicrobial misuse can be grouped based on dose, duration, choice, and indication. The latter three were identified as substantial sources of inappropriate use in a study which surveyed antimicrobial prescriptions in a US hospital (Fridkin et al., 2014; Abbas et al., 2022).

Prolonged treatment duration is considered inappropriate since it increases the risk of adverse events and the development of AMR conversely, a non-adequate duration may result in treatment failure (Tansarli et al., 2019). The optimal treatment duration depends on patient factors, infection type, and severity. A shorter duration may be as effective as a longer treatment duration with the same outcomes in certain infections (Sawyer et al., 2015).

The underlying microorganism causing the Infection can affect the optimal treatment duration. In a clinical trial by Chastre et al. (2003) concerning ventilator-associated

pneumonia, while the outcome of the 8-day treatment duration was not inferior to a 15-day duration, the re-occurrence was higher in the cases where the pneumonia was caused by “non-fermenting gram-negative bacilli”. Interestingly, even though the re-occurrence rate was higher in the shorter duration group, the rate of multiple drug-resistant organisms was lower (Chastre et al., 2003). In another trial, staphylococcus aureus-associated infections were linked with an increased rate of treatment failures in shorter duration treatment, as noted in a study comparing 7 days to 14 days of treatment in neonatal bacteraemia (Havey et al., 2011). Patient characteristics and underlying conditions can also warrant a longer duration to ensure efficacy, as noted in the treatment of complicated cystitis and pyelonephritis in cases of urological abnormalities (Hanretty & Gallagher, 2018; Erba et al., 2020).

Source control involves the removal of the source of infection, usually through a surgical procedure and is commonly used in treating intrabdominal infections (Hanretty & Gallagher, 2018) and cholangitis (Haal et al., 2021). The STOP-IT clinical trials (Sawyer et al., 2015) identified that in cases of adequate source control, a 4-day antibiotic duration was not inferior to a longer duration noting no difference in outcomes, even in cases of sepsis (Sawyer et al., 2015; Ho et al., 2020). This contrasts with the traditional duration of up to 14 days in cases of intraabdominal infections (Sawyer et al., 2015). However, these findings do not apply in cases of infections caused by staphylococcus aureus (Ho et al., 2020).

Treatment duration can also be reduced through the personalisation of treatments through laboratory markers, allowing prescribers to identify the individual response to treatment (Von Dach et al., 2020). A recent clinical trial concerning gram-negative

bacteraemia compared three groups following source control and randomisation. The treatment duration of the first group was determined by C reactive protein (CRP) laboratory markers, specifically patients with a 75% reduction in CRP level. The other two groups were fixed at seven and fourteen days, respectively. The CRP-mediated and 7-day groups were not inferior to the 14-day groups. Several studies (Zhang et al., 2017; Wirz et al., 2018; Ho et al., 2020) highlight the potential role of procalcitonin-based stewardship in the reduction of treatment duration and mortality; however, its efficacy in cases of abdominal-associated infections and renal impairment is not known (Wirz et al., 2018).

1.3 Antimicrobial Stewardship

Antimicrobial stewardship (AMS) programmes aim to optimise antibiotic treatment (Borek et al., 2021). Its successful implementation is associated with improved patient outcomes in terms of reducing adverse events, influencing resistant patterns, and reducing costs (Schrier et al., 2018).

AMS is usually managed by a multidisciplinary team of healthcare professionals whose exact composition may vary between different countries and usually, is composed of at least a physician, pharmacist, and microbiologist (Monmaturapoj et al., 2021), ideally with an infectious disease background (Cunha, 2018).

1.3.1 Antimicrobial Stewardship Techniques

Prospective audit and feedback, along with formulary restriction are considered to be the foundations of AMS programmes. A restrictive formulary approach, also known as formulary restriction and pre-authorisation (Kirk et al., 2019), involves restricting the use

of specific antibiotic classes with a high resistance potential or those with an increased risk of adverse events, including certain antibiotics which are members of cephalosporins, fluoroquinolones and carbapenems classes (Chatzopoulou & Reynolds, 2019). The prescription of antibiotics on the restricted formulary would require approval by members of the AMS team (Kirk et al., 2019). When used, the restrictive approach is associated with a rapid decrease in resistance patterns, especially when compared with other stewardship techniques and is useful in urgent cases requiring immediate cessation of antibiotics (Monmaturapoj et al., 2021). The Strategic restriction of fluoroquinolones was associated with decreased incidence of resistant gram-negative bacteria and superinfection (Claeys et al., 2018). Consequently, restricting a specific antibiotic class would result in the increased use of non-restricted classes, which would necessitate using other AMS practices to ensure appropriate use (Claeys et al., 2018).

Audit and feedback are usually carried out by an infectious disease physician or clinical pharmacist (Yamaguchi et al., 2022) and involve checking the appropriateness of the prescribed prescription according to guidelines and local policies. Feedback can be provided prospectively to the prescribing physician during ward rounds (Moghnieh et al., 2020). Compared to the restrictive approach, prospective audits and feedback are associated with decreased antibiotic use (Claeys et al., 2018). They are described by Monmaturapoj et al. (2021) as being more efficacious for improving antibiotic use. Pharmacists can further contribute to the AMS team as drug experts by educating prescribers. The importance of education in improving AMS can be noted in the systemic review by Monmaturapoj *et a*l. (2021), where studies including educational interventions were associated with improved compliance with guidelines and reduced treatment duration. Furthermore, combining education with other AMS techniques was

associated with improved outcomes (Schrier et al., 2018). Monmaturapoj et al. (2021) found that studies combining prospective audit and feedback with educational interventions had better outcomes than those combining educational interventions with other techniques or those using only educational interventions. The benefit of combined interventions can be noted in the five-year prospective study of Alawi et al. (2022), which combined prescriber education with the auditing of appropriateness of treatment. The study was associated with a significant increase in intravenous to oral conversion (IV to PO), decreased use of drugs on the restrictive formulary, and reduced incidence of hospital-acquired resistant infections. Education based intervention utilised in the study included the dissemination of guidelines and meetings with different healthcare professionals.

Intravenous (IV) formulations are useful in treating severe infections such as sepsis and severely immunocompromised patients. IV formulations are also essential in cases where the patient cannot absorb or tolerate the oral dosage formulation. Prolonged IV formulation treatment is not considered appropriate when the oral formulation has a high bioavailability, such as in the case of metronidazole and co-trimoxazole (McCarthy & Avent, 2020). Intravenous antibiotic formulations are generally more expensive than oral formulations and are associated with adverse events such as secondary infection at the IV site and thrombophlebitis (Algargoosh et al., 2022). According to Algargoosh et al, (2022), pharmacists are competent in reviewing and independently switching patients to the oral formulation, allowing for earlier conversion. Diligent conversion to the oral route is associated with lower costs, fewer adverse events related to the route of administration, and shorter hospitalisation duration (Esteve-Palau et al., 2018).

1.3.2 Pharmacist Intervention in Antimicrobial Stewardship

Pharmacists have an essential role in AMS programmes due to their expertise and understanding of pharmacodynamic and pharmacokinetic properties (Stang et al., 2021; Wong et al., 2021). Pharmacy expertise is one of the seven core elements of hospital AMS programme, proposed by the Centers for Disease Control and Prevention (CDC[7]), highlighting the benefit of pharmacists' engagement as leaders or co-leaders in the AMS programmes. The role of pharmacists includes the development of novel guidelines, auditing, and treatment optimisation (Lee & An, 2022), and educating healthcare providers and patients on proper antibiotic use (Garau & Bassetti, 2017; Monmaturapoj et al., 2021).

Numerous studies highlight the impact of pharmacist involvement and leadership in the AMS team (Ohashi et al., 2018; MacMillan et al., 2019; Stang et al., 2021; Turner et al., 2021; Algargoosh et al., 2022; Hashimoto et al., 2022), with improved outcomes in various health settings, including increased appropriateness of the prescribed antibiotic (Mahmood et al., 2021), reduction of inappropriately prescribed antibiotics, and improved adherence to hospital policies and guidelines (Jantarathaneewat et al., 2022).

The impact of the clinical pharmacist on the AMS team is noted by Algargoosh et al. (2022), who highlighted that IV to PO switch interventions were more successful in pharmacist-led cohorts than cohorts which did not include pharmacist intervention.

[7] Centers for Disease Control and Prevention (CDC). Core Elements of Outpatient Antibiotic Stewardship [Internet]. Atlanta:CDC; 2021 [Cited 2023 APR 6]. Available from URL: https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf

1.4 Urinary Tract Infections

UTIs are among the most common indications for antibiotic use within the hospital and community settings (Sadyrbaeva-Dolgova *et al*., 2020; Chuang & Tambyah, 2021), and are commonly associated with inappropriate antibiotic use (Rowe & JuthaniMehta, 2014). UTI are considered to be complicated when the infection is associated with obstruction of urinary flow or is caused by the decrease of host defences (Flores-Mireles et al., 2019). Factors contributing to UTIs in older adults include urinary retention, underlying co-morbidities and previous history of UTI (Cortes-Penfield et al., 2017). Using catheters within the older population further increases the risk of UTIs and is considered one of the most significant risk factors (Chuang & Tambyah, 2021). The risks of UTIs can be reduced in catheterised patients by regularly changing indwelling catheters and attempting trials without catheters (Letica-Kriegel et al., 2019).

1.4.1 Diagnosis

The diagnosis of UTI depends on the patient's characteristics, comorbidities, infection location and the involvement of organs such as the prostate and the kidneys, which can impact the presenting symptoms (Wagenlehner et al., 2022). Inappropriate diagnosis can harm the patient's health since the underlying cause of the observed symptoms, if severe, is not treated. Conversely, if a UTI is not identified and adequately treated, it can result in serious complications (Kaur & Kaur, 2021).

A concern associated with treatment is the correct diagnosis of UTI, especially in older adults who may present with atypical symptoms such as confusion and delirium (Cortes-Penfield et al., 2017; Barman et al., 2021). The latest Infectious Diseases Society of America guidelines advise against treating older patients with bacteriuria and sole

symptoms of delirium/confusion, recommending patient observation and the identification of other possible causes (Nicolle et al., 2019).

Symptoms used to diagnose UTIs, such as increased urgency, frequency, and dysuria can be masked in patients with an indwelling catheter (Woods et al., 2021). Older adults also tend to have an increased risk of co-morbidities such as dementia which could impact the reporting of symptoms associated with UTIs (Rowe & Juthani-Mehta, 2014). Patient falls, confusion, and delirium are common reasons for the suspicion of a UTI in older adults. The latter two, along with behavioural changes, are considered atypical symptoms of UTI in this patient population. However, such symptoms, especially without accompanying specific symptoms, do not necessarily indicate an underlying UTI (Woods et al., 2021) and can result in misdiagnosis and unnecessary treatment (Nicole et al., 2019).

Diagnostic criteria guidelines have been developed to ensure appropriate diagnosis in older adults in long-term settings. One of the first criteria developed was the McGeer criteria in 1991, which required three symptoms from six symptoms for the diagnosis of UTI, the McGeer criteria considered changes in urinary characteristics along with worsening in mental status as eligible criteria to diagnose a UTI (Rowe & Juthani-Mehta, 2014). In 2001 the Loeb criteria were developed, and in contrast to the original McGeer criteria, acute dysuria on its own was considered as being sufficient to diagnose a UTI in patients without a urinary catheter. If acute dysuria was absent, a UTI was diagnosed with fever and 1 urinary symptom (Rowe & Juthani-Mehta, 2014). The Stone guidelines are based on the McGeer criteria (Stone et al., 2012). To diagnose a UTI, two sub-criteria's must be satisfied. The first sub-criteria is associated with symptoms, while the

second criterion is associated with a positive urinary culture. Similarly to the Loeb criteria, the acute onset of dysuria on its own is sufficient to satisfy the first sub-criteria, along with epididymitis and signs of prostate involvement. In the absence of the mentioned symptoms, the Loeb criteria requires a single urinary symptom, in the presence of leucocytosis or fever or two urinary symptoms in the absence of leucocytosis. The second sub-criteria requires a positive urinary culture with a specified colony-forming unit per millilitre (cfu/ml), depending on the number of cultured organisms and the origin of the urinary sample (Rowe & Juthani-Mehta, 2014).

Erroneous use of diagnostic tests and interpretation can result in an inappropriate diagnosis. Urinary culture and sensitivity (C&S) orders should be ideally carried out only in cases where a UTI is suspected with evident underlying symptoms. Aside from specific cases such as septic shock, the use of routine and automatic testing in all patients should be discouraged, as should the ordering of urine C&S based on changes in the urinary characteristics, such as dark, foul-smelling, and sedimentation, which can be attributed to other causes such as dehydration (Cortes-Penfield et al., 2017; Claeys et al., 2022; Werneburg & Rhoads, 2022). C&S tests are also limited to only commonly occurring microorganisms (Peck & Sheperd, 2021).

1.4.2 Asymptomatic Bacteriuria

Diagnosing older adults is more difficult due to the high prevalence of ASB, which is especially prevalent in long-term settings such as nursing homes (Kistler et al., 2022). The high rate of ASB hinders the usefulness of urine analysis in this patient population (Eecen et al., 2022). Patients in this population cohort are at an increased risk of

unnecessary treatment especially those patients with underlying neurological conditions such as dementia and confusion (Anderson et al., 2022).

UTIs should be differentiated from ASB, which can be described as the asymptomatic colonisation of the urinary tract and includes at least one species exceeding 10^5 colony-forming units (Nicolle et al., 2019). Except in the cases of pregnancy or surgical intervention involving the urological tract, ASB should not be treated (Drekonja et al., 2019). The treatment of ASB may even be counterproductive in specific patient populations, as recent literature highlights the potential protective role of asymptomatic colonisation of the urinary tract (Owens et al., 2019). Nevertheless, it is estimated that nearly 65% of patients with ASB are treated (Rico et al., 2021). ASB is more prevalent in the older patient population (Rowe & Juthani-Mehta, 2013), and a reason for increased prevalence includes the increased use of indwelling catheters in this patient cohort (Rowe & Juthani-Mehta, 2014; Cortes-Penfield et al., 2017). The overuse of diagnostic testing, including urine analysis and C&S, results in misdiagnosis and increases non-appropriate antibiotic use (Barman et al., 2021). This is significant since colonised patients can present with pyuria and urinary nitrites. Additionally, the presence of pyuria in older adults has limited diagnostic value, as research by Bilsen et al. (2023) has shown that the prevalence of pyuria in older women with ASB exceeds 90%.

A positive urine analysis result is linked to increased C&S testing (Barman et al., 2021), which increases the risk of misdiagnosis. Therefore, using such tests for UTI diagnosis in asymptomatic patients or patients with non-specific symptoms suggesting a UTI is concerning (Barman et al., 2021). AMS efforts to reduce overdiagnosis and overtreatment of UTI included pharmacist auditing of prescribed antibiotics in patients

who previously had positive urine analysis and C&S results, prescriber education, and the use of electronic health records and clinician decision support systems to discourage ordering of diagnostic tests (Keller et al., 2018; Rico et al., 2021).

1.4.3 Catheter-associated Urinary Tract Infections

The use of indwelling catheters provides a means by which bacteria can infiltrate natural defences and colonise the urinary tract resulting in catheter-associated asymptomatic bacteriuria (CAASB) or catheter-associated urinary tract infection (CAUTI). Diagnosis and differentiation between CAASB and CAUTI in patients requiring prolonged use of indwelling catheters is considered more challenging than non-catheter related ASB and UTI (Tambyah et al., 2000; Chuang & Tambyah, 2021). Similarly, in the non-catheterised patient population, asymptomatic colonisation should not be treated, and C&S should be taken only in cases where symptoms suggest an infection (Chuang & Tambyah, 2021). Increases in catheter duration (Flores-Mireles et al., 2019) and length are directly correlated with an increased risk of colonisation and infection, with cases of prolonged use being associated with inevitable colonisation (Flores-Mireles et al., 2019). Catheterisation also allows for a more diverse microbe colonisation, including opportunistic organisms (Flores-Mireles et al., 2019).

For CAUTI to be diagnosed, the CDC[8] requires the catheter dwelling time, to exceed two days with any one of the following symptoms: fever, tenderness, increased frequency/urgency, along with a positive urinary C&S (Letica-Kriegel, 2019). The use of

[8] Centers for Disease Control and Prevention (CDC). Catheter-Associated Urinary Tract Infections (CAUTI) [Internet]. CDC; 2015 [Cited 2023 Apr 23]. Available from URL: https://www.cdc.gov/infectioncontrol/guidelines/cauti/index.html

catheters facilitates the formation of biofilm, which further complicates treatment by limiting antibiotics penetration. In most cases, the biofilm can harbour different bacteria providing the perfect conditions for developing and transferring resistance (Azevedo et al., 2017). To prevent CAUTI, the CDC[8] advises using indwelling catheters when only indicated and for the shortest duration possible (Werneburg & Rhoads, 2022). The guidelines also highlight the importance of proper infection control practices for inserting and maintaining a urinary catheter and discourages unnecessary use in most patients, as this will further increase the risk of resistance (Flores-Mireles et al*.,* 2019).

1.5 Study Rationale

Appropriate treatment is essential to limit adverse events and the development of antibiotic resistance, especially in the older patient population, who are at an increased risk of harm with improper use (Davies & Mahony, 2015). UTIs are common in this patient population, and treatment is complicated with the high prevalence of ASB and non-specific symptoms resulting in unnecessary treatment (Nicolle et al., 2019). Clinical pharmacists are vital members of the AMS team due to their pharmacological expertise. They help ensure appropriate antibiotic use by reviewing usage, improving adherence to guidelines, and implementing stewardship techniques[7]. Establishing a framework for clinical pharmacists through the auditing of antibiotic use in the local setting will help

[7] Centers for Disease Control and Prevention (CDC). Core Elements of Outpatient Antibiotic Stewardship [Internet]. Atlanta:CDC; 2021 [Cited 2023 APR 6]. Available from URL: https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf

[8] Centers for Disease Control and Prevention (CDC). Catheter-Associated Urinary Tract Infections (CAUTI) [Internet]. CDC; 2015 [Cited 2023 Apr 23]. Available from URL: https://www.cdc.gov/infectioncontrol/guidelines/cauti/index.html

identify issues, which can then be tackled by the clinical pharmacist through stewardship interventions.

1.6 Aim and Objectives

The study aimed to assess the appropriateness of antibiotic use and to support an effective clinical pharmacist contribution in AMS.

The objectives of the study were to

- Determine whether antibiotic use for urinary tract infections is appropriate in a cohort of older patients admitted for rehabilitation.
- Identify factors to be incorporated in a framework highlighting the clinical pharmacist's intervention in AMS.

Chapter 2: Methodology

2.1 Design

An overview of the study is detailed in figure 2.1. A literature search to identify the infection of interest was carried out for the patient population in the study setting, resulting in the prioritisation of UTIs. This was followed by a more thorough literature search of UTIs for the development of the data collection sheet. Once developed, the data collection sheet was validated by healthcare professionals with a special interest in the field. Following ethics approval, data was collected retrospectively using the data collection sheet to ensure standardisation. A meeting was held with the expert group to discuss and validate the novel diagnostic criteria for the setting of Karin Grech Hospital (KGH). This was followed by the reviewing and grouping of prescriptions according to the appropriateness of treatment. The observed outcomes of the study were then used to develop a framework to be utilised by clinical pharmacists. The validity of the designed framework was discussed with the clinical pharmacist's team during a focus group session.

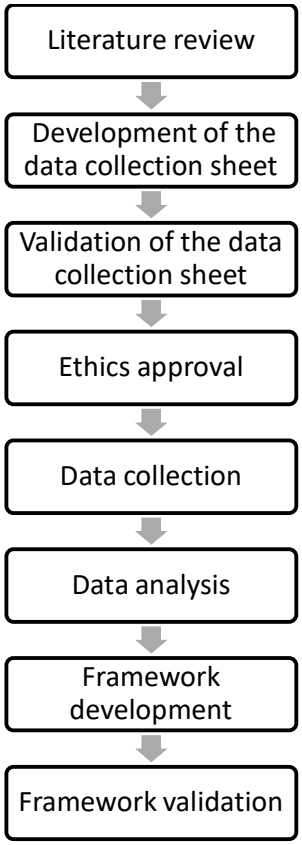

Figure 2.1: Summary of study design

2.2 Setting

The study was carried out at KGH, a nine-ward hospital with approximately 270 beds. The hospital patient population mainly consists of older adults admitted from acute care for rehabilitation. The hospital has a robust clinical pharmacist service where each ward has a designated clinical pharmacist whose role, among others, is to review the prescribed treatment and check for adherence to local guidelines, including those concerning proper antibiotic use.

2.3 Literature Search

The preliminary phase of the study involved the identification of the infection, which would be targeted in the study, and this was carried out through a literature search on the PubMed Medline and Hydi databases. The search focused on the prevalence of infection types in the target patient population and the diagnosis of infection. UTIs were chosen for their high prevalence in the target population, together with the ease and reliability of sampling for C&S when compared to respiratory and wound infections, respectively.

Once the infection of interest was identified, another search was carried out through the PubMed Medline and Hydi databases to formulate a data collection sheet. The search focused on prospective audits and feedback, particularly those in which pharmacists were entrusted with a leadership role.

Boolean operators and MeSH terms were used to enhance both literature searches. The literature search in both instances was restricted to articles released within the last five years to ensure that the obtained data was current.

2.4 Data Collection Sheet

The developed data collection sheet (Appendix 1) was divided into 6 sections; the first five sections involved data collection, while the last section was used to record if the prescription was appropriate in terms of indication, choice, dose/regimen/route.

Section 1 consisted of the collection of the general patient demographic, including the patient's gender and age group and data relating to the patient’s co-morbidities. The antibiotic start date, along with the patient’s weight, was recorded in this section. The

age adjusted Charlson Co-morbidity Index (CCI) score was calculated using the online MDCalc®[9] tool, and the score was based on the patient's age, co-morbidities, and patient history, with an increased score being associated with increasingly more severe co-morbidities/ history, multiple co-morbidities, and a higher age group.

The second section included data collection relating to the patient's catheterisation status and the type of catheter used (indwelling, intermittent, suprapubic, and external). Catheterisation duration was not collected due to incomplete records.

The third section involved information about the antibiotic regimen, including the drug, dose and route, frequency duration, and, and if the treatment was empirically started. Adherence to the local "Antibiotic Stop/Review Policy" was also recorded in this section.

The fourth section of the data collection sheet was used to collect reported patient symptoms. Symptoms were classified into two categories in the data collection, depending on whether they were specific to urinary symptoms or general symptoms.

Laboratory markers, urine analysis and C&S results were recorded in each relevant subsection within the fifth section. Positive blood cultures were also recorded in this section.

The data collection sheet, once developed, was validated by an expert group composed of an infection control nurse, a urology practice nurse, a higher specialist trainee in geriatrics and two clinical pharmacists, one of whom had a special interest in AMS.

[9] MDCALC. Charlson Comorbidity Index (CCI) [Internet]. [Cited 2023 APR 5]. Available from: https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci

2.5 Ethics Approval

Approval was obtained from the KGH Research Committee and the Faculty of Medicine and Surgery Research Ethics Committee with the reference number MED-2022-00056 (Appendix 2).

2.6 Inclusion Criteria

To be included in the study, patients had to be 65 years or older and started on antibiotic treatment at KGH for a suspected UTI. Patients whose treatment was started prior to admission to KGH, those on prophylactic treatment, and confirmed non-UTI were excluded.

2.7 Data Collection

Patients prescribed antibiotics for a suspected UTI between August to December 2022 were identified by the designated intermediaries. The intermediaries filled section 4 of the data collection sheet and laboratory C&S results and provided the investigator with anonymised copies of the respective pharmacy patient profile. The pharmacy patient profile is a document used by clinical pharmacists at KGH to record patient parameters and to note pharmaceutical care issues.

Creatinine clearance (CrCl) and the CCI were calculated and recorded in the data collection sheet by the investigator using the provided anonymised documentations.

2.8 Appropriateness Assessment

Treatment appropriateness was determined by reviewing each prescription in terms of treatment indication, choice, dose/regimen/route.

To ensure that prescriptions were correctly audited in terms of indication, a diagnostic consensus criteria was proposed and discussed in an expert group meeting with, and validated by, the same health care professionals which had validated the data collection sheet. The diagnostic consensus criteria was created by taking into account the factors discussed during the expert group meeting, which included a discussion of the Scottish Antimicrobial Prescribing Group (SAPG[10]) and the local Mater Dei Hospital (MDH) guidelines. The discussion also focused on the limitations of the available guidelines, including obstacles that would result in inaccurate diagnoses and inappropriate antibiotic use. Symptoms that most likely represent an underlying UTI were also discussed, emphasising when patients should be started on empiric treatment or followed up for further diagnostic testing. An inconclusive treatment indication was included in the consensus criteria following discussions with the expert group. This was included because of limitations of the study design and the available guidelines.

Patients who were found to satisfy at least one of the three criteria in which the treatment of a UTI would have been indicated were deemed appropriate in terms of treatment indication. Asymptomatic patients who were treated with antibiotics were deemed as being Inappropriate in terms of indication. While patients whose treatment appropriateness in terms of indication could not have been confirmed or excluded with the available information were categorised as being inconclusive.

[10] Scottish Antimicrobial Prescribing Group (SAPG). Decision aid for diagnosis and management of suspected urinary tract infection (UTI) in people aged 65 years and over [internet]. SAPG; 2021 [Cited 2023 APR 22]. Available from: https://www.sapg.scot/media/5844/decision-aid-for-diagnosis-and-management-of-suspected-uti-in-people-over-65-years.pdf

The local MDH guidelines and C&S results were used to determine the appropriateness of the initial empiric treatment and change of therapy. Appropriateness of dose/regimen was based on local guidelines, British National Formulary® and the respective Summary of Product Characteristics (SmPC). The route of administration was also checked for appropriateness, according to the MDH guidelines.

2.9 Data Analysis

The data was extracted to IBM SPSS® version 28 and Microsoft Excel® for further analysis. The data consisted mostly of categorical variables except for CCI, CrCl and weight.

2.10 Framework Design

A framework for clinical pharmacist interventions in AMS was designed by using the observed study outcomes and feedback from the expert group meeting. The framework interventions were grouped according to the following: indication, choice dose/regimen/route and duration.

Once developed, the validity of the interventions detailed in the framework was discussed with the clinical pharmacist team during a focus group session. The focus group sessions focused on the framework layout and which interventions the clinical pharmacists can undertake independently and those that require interaction with the prescriber. Feedback obtained from the focus group session was then incorporated in the framework.

Chapter 3: Results

3.1 Patient Recruitment

Figure 3.1 depicts patient selection based on the inclusion and exclusion criteria. The majority (n=20) of the excluded patient population included patients with a suspected UTI who were not treated with antibiotics. Following confirmation of a different infection source, 15 prescriptions were excluded from the study, followed by exclusion of patients whose treatment was initiated outside the hospital (n=8) and a single patient who did not meet the age criteria. Ninety-eight patients met the inclusion criteria.

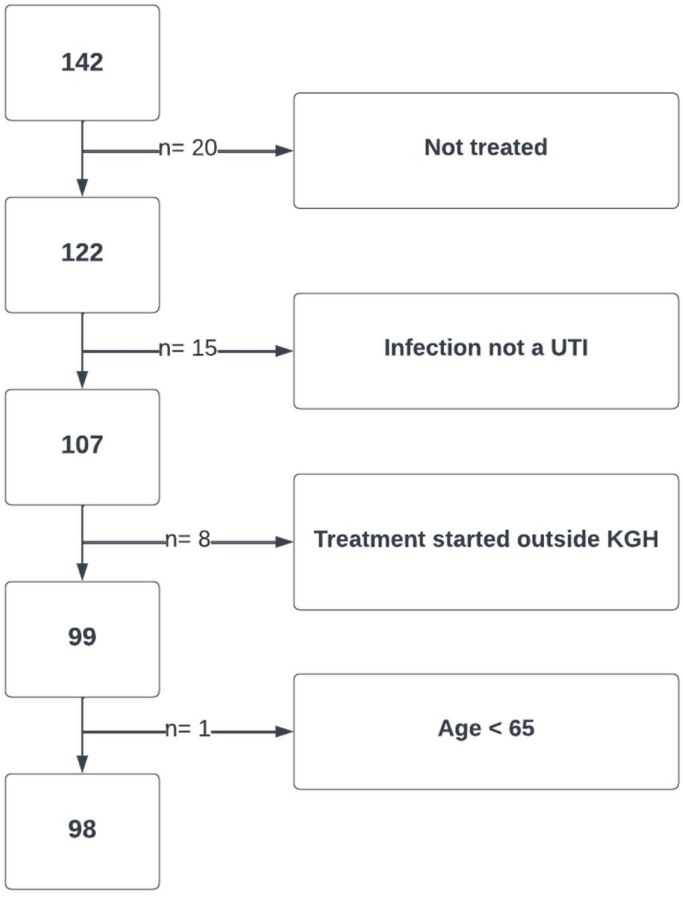

Figure 3.1: Patient selection

3.2 Patient Characteristics

Figure 3.2 depicts the distribution of the study population. The majority of the 98 patients (66%, n=65) with a suspected UTI whose prescription was audited for appropriateness were female. Most of the patients belonged to the 80 – 89 age group, followed by the 70 – 79, 90 – 100 and 65 – 69 age groups, respectively.

As noted by figure 3.3 cardiac-related comorbidities were the most common, amounting to 144, with the majority being hypertension, followed by non- cardiac co-morbidities, including diabetes and renal impairment. The CCI ranged from 2 to 10 with a mean of 5. Almost half of the patient population, 47% (n = 46), had an indwelling catheter. Fifteen percent (n=15) of patients had a reported allergy to antibiotics, with the majority (80%, n=12) being to penicillin.

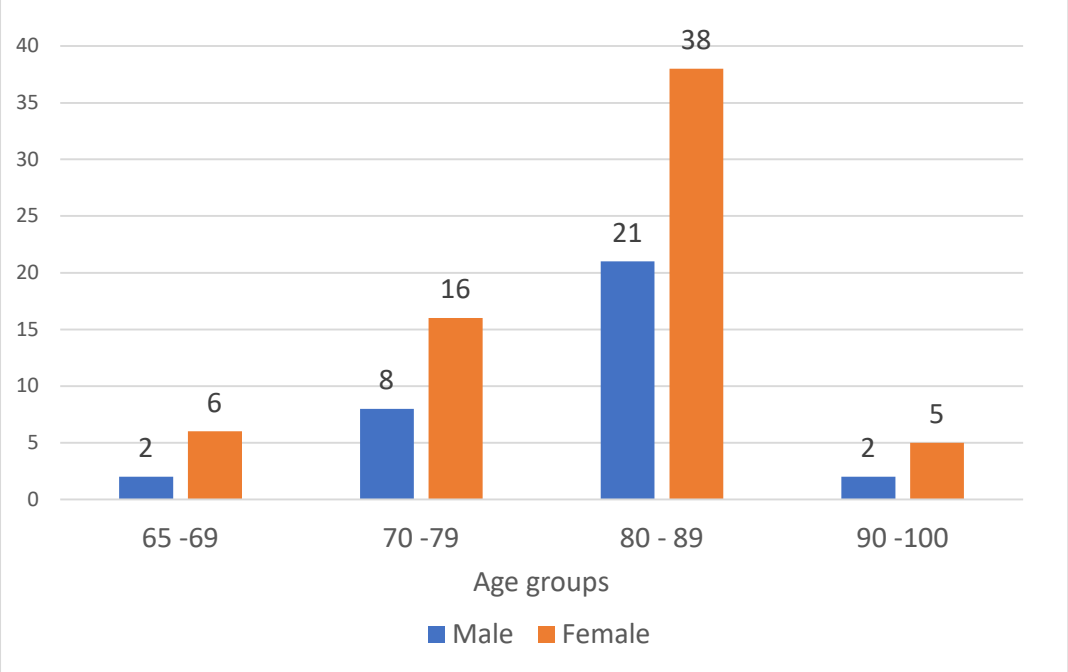

Figure 3.2: Patient distribution according to age group and gender (N=98)

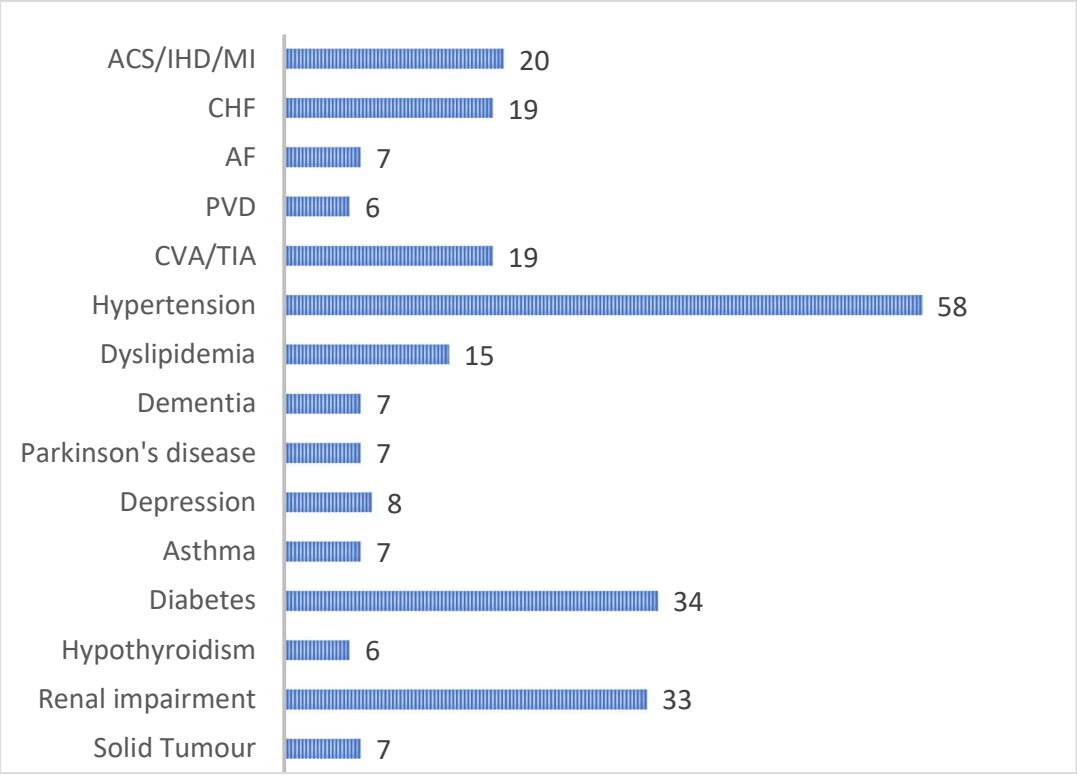

Figure 3.3: Co-morbidities in the patient population

ACS: Acute Coronary Syndrome, IHD: Ischemic Heart Disease, MI: Myocardial Infarction, CHF: Congestive Heart Failure, AF: Atrial Fibrillation, PVD: Peripheral Vascular Disease, CVA: Cerebrovascular Accident, TIA: Transient Ischemic Attack.

3.3 Symptoms and Laboratory Investigations

3.3.1 Symptoms

Figure 3.4 indicates the prevalence of symptoms in the study population, dysuria being the most reported urinary symptom (32%, n=30), followed by fever and new onset delirium.

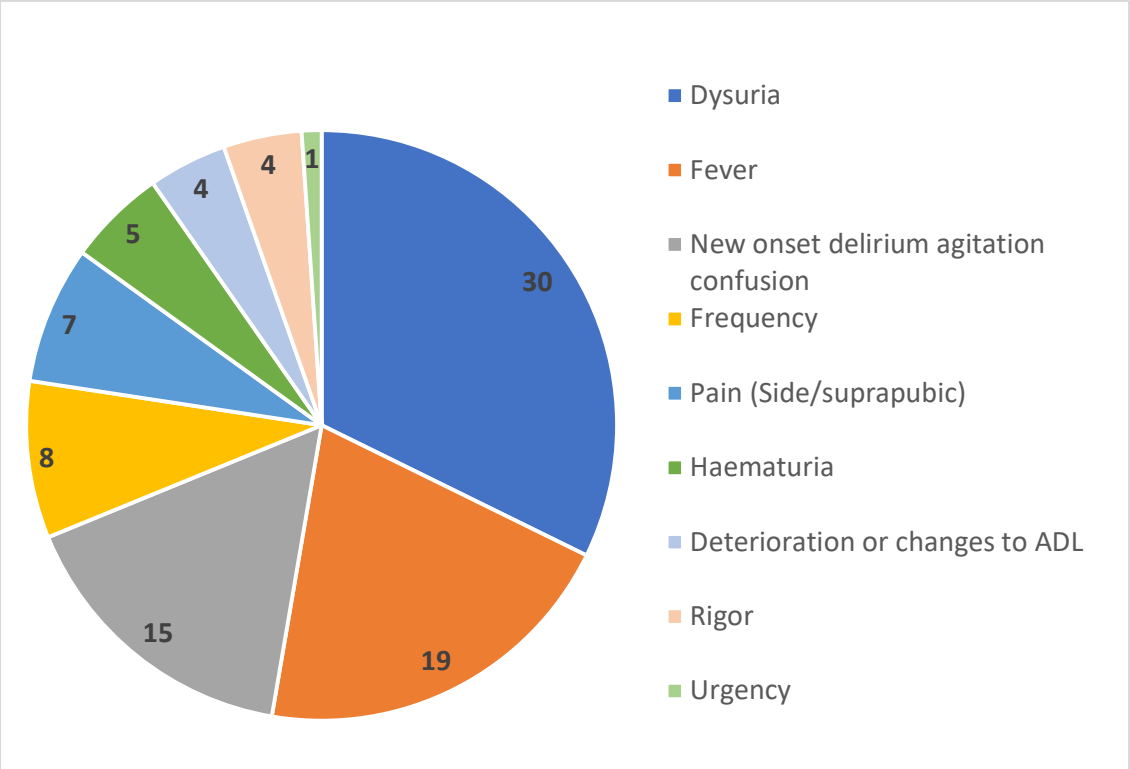

Figure 3.4: Reported specific and general symptoms (n=93)

3.3.2 Laboratory Investigations

Urine analyses were taken in 82 patients (84%) who met the inclusion criteria while C&S were taken in almost all patients (n=96, 98%). The most cultured microorganism was *Escherichia Coli* (n= 28), followed by *Klebsiella pneumonia* (n=18) and *Proteus mirabilis* (n=9).

Serum biomarkers namely WBC (n= 90, 92%) and CRP (n=93, 98%) were measured in most of the study population. When comparing both serum biomarkers, serum CRP was elevated in the majority of the study population (n=73, 82%) while serum WBC was normal (n=57, 63%) in most of the study population.

3.3.3 Renal Function

Table 3.1 depicts the difference in means between the laboratory-provided estimated glomerular filtration rate (eGFR) and the calculated CrCl in patients with a body weight of less than 60kg (n=26). In both instances, the values of the 26 patients had a high variability from the calculated mean, as indicated by the large standard deviation.

Table 3.1: The effect of patient weight on renal dosing (n=26).

	Mean	**Range (minimum – maximum)**	**Standard deviation**
Weight (kg)	50.5	(38 – 59)	6.3
eGFR ($mL/min/1.73m^2$)	78.9	(22 – 148)	31.2
CrCl (mL/min)	41.5	(13 – 77)	15.5

3.4 Antibiotics Prescribed

Figure 3.5 depicts empiric antibiotic use within the study population. Overall, co-amoxiclav (49%, n=48) was the most used empiric antibiotic in the treatment of a suspected UTI, followed by nitrofurantoin (22%, n=22) and piperacillin/tazobactam (7%, n=7). Thirteen (13 %) patients did not receive empiric treatment and were started on targeted treatment following the release of C&S results. Figure 3.5 depicts a greater use of broad-spectrum antibiotics when compared to narrower-spectrum antibiotics.

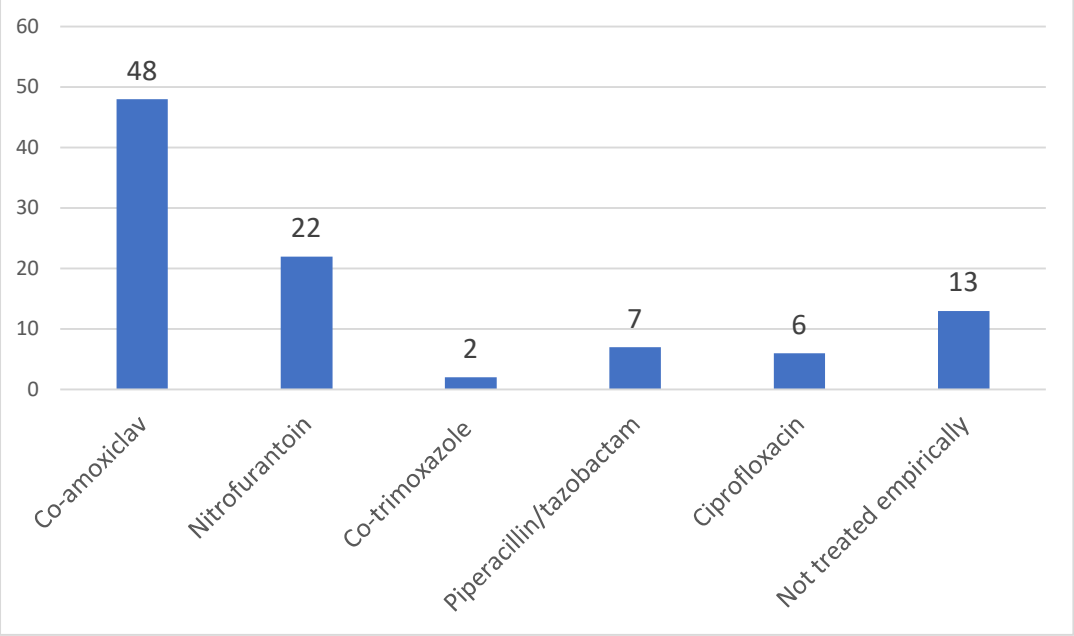

Figure 3.5: Empiric treatment used in study population (N= 98)

Figure 3.6 depicts targeted treatment use within the study population. Forty-three (44%) of the patients in the study received targeted treatment. This refers to patients whose started empiric treatment was switched to a more suitable treatment according to the C&S results. Fifty-five patients were not switched to targeted treatment, including 20 patients whose treatment was not changed according to C&S results, and 35 patients whose treatment susceptibility was omitted by the laboratory. These included mixed isolates and catheterised patients with bacteriuria.

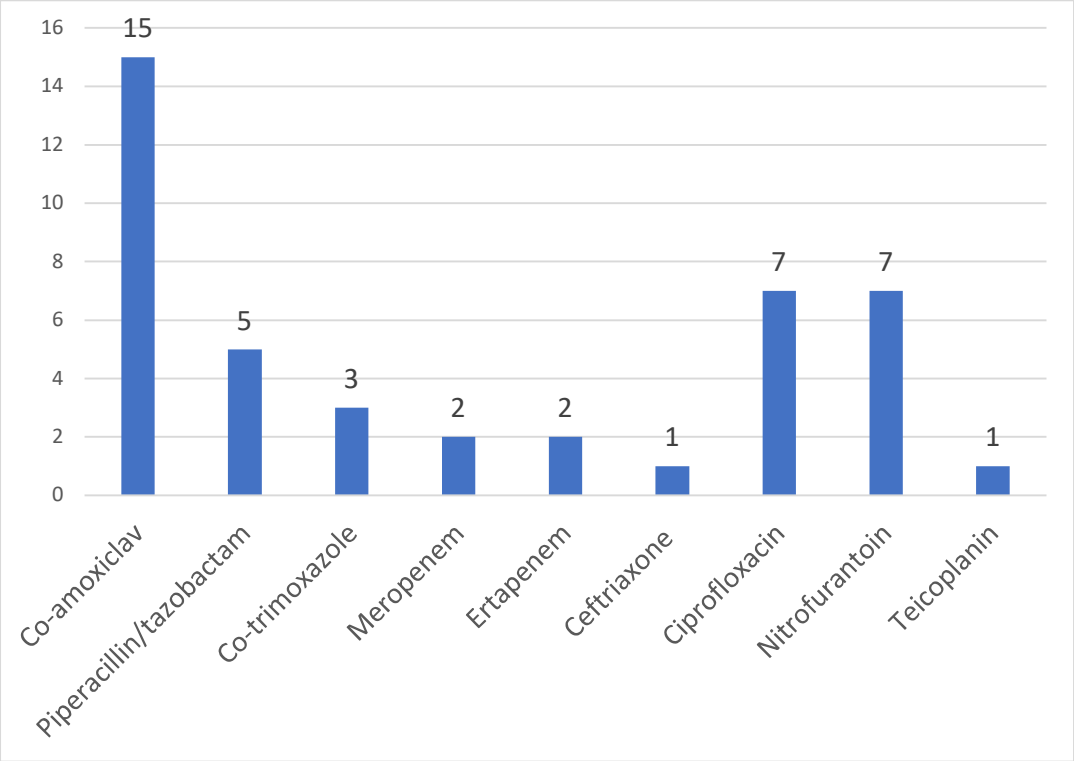

Figure 3.*6*: Targeted treatment in study population (n=43)

3.5 Appropriateness Assessment

Assessment of appropriateness was conducted for treatment indication, choice, dose/regimen/route.

Table 3.2: Consensus criteria on appropriateness of indication for treatment

Treatment indication	Criteria
Indicated	One or more urinary signs/symptoms indicative of a UTI (acute dysuria, acute increase in urinary urgency and or frequency, acute or worsening incontinence, acute suprapubic/costovertebral pain, or gross haematuria) with elevated serum laboratory markers* in non-catheterised patients Two or more urinary signs/symptoms indicative of a UTI in non-catheterised patients One or more of the following symptoms (fever, rigors, acute suprapubic/costovertebral pain, new onset delirium) in catheterised patients, if there is no other infectious focus
Not indicated	Presence of signs/symptoms not indicative of a UTI (foul-smelling urine, urinary sediment, dark colour)
Inconclusive	One or more of the following non-urinary symptoms (fever, functional deterioration, confusion) in non-catheterised patients with elevated serum laboratory markers* One urinary symptom without elevated serum laboratory markers* in non-catheterised patients

*C Reactive Protein (CRP) or White Blood Cells (WBC), UTI: Urinary Tract Infection

Table 3.2 depicts the consensus criteria agreed upon by the expert group to ensure the appropriateness of indication for treatment. In the consensus criteria, treatment is

considered to be indicated, not indicated or inconclusive. The inconclusive criteria include patients in which diagnosis for a UTI could not be confirmed or excluded considering the reported symptoms and laboratory markers.

Figure 3.7 depicts categorisation according to appropriateness of treatment prescribed. Prescriptions which were appropriate in all the following: indication, choice, dose/regimen/route were categorised as being appropriate (32%, n=31). Prescriptions which were inappropriate in at least one of treatment indication, choice, dose/regimen/route were classified as being inappropriate. Treatment indication was inconclusive in a substantial portion of the reviewed treatment (41%, n= 40) based on the inconclusive criteria outlined in Table 3.2. The most common reason for inconclusive classification was non-urinary symptoms with elevated serum markers (n=32). Additionally, the inconclusive category included 8 patients who presented with one urinary symptom but no other signs of an underlying infection.

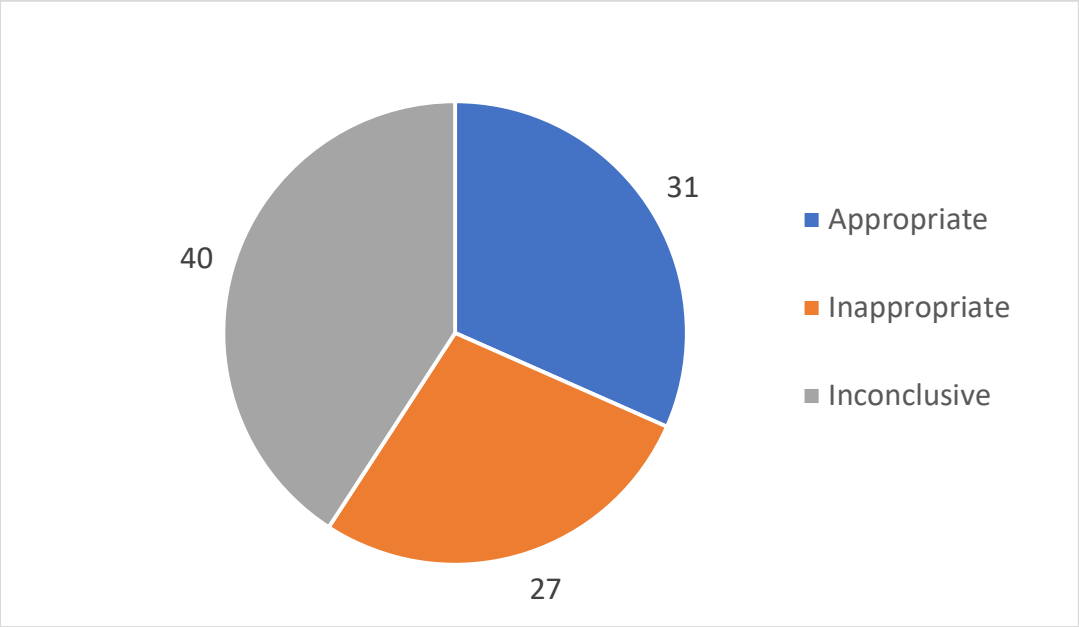

Figure 3.7: Prescription categorisation according to appropriateness (N= 98)

Figure 3.8: gives an overview of the 29 instances of inappropriate treatment according to indication, choice, and dose/regimen/route. The reason why instances of inappropriate treatments (n=29) exceed the number of inappropriate prescription (n=27) is because 2 patients had more than 1 reason for inappropriate treatment, in a single prescription.

Eight (28%) prescribed treatments were inappropriate in terms of indication. These included the treatment of ASB in which treatment was not indicated according to the consensus criteria. Most inappropriate treatments were associated with treatment choice (69%, n=20). Twelve (60%) of these were not changed according to urinary C&S to a more optimal antibiotic.

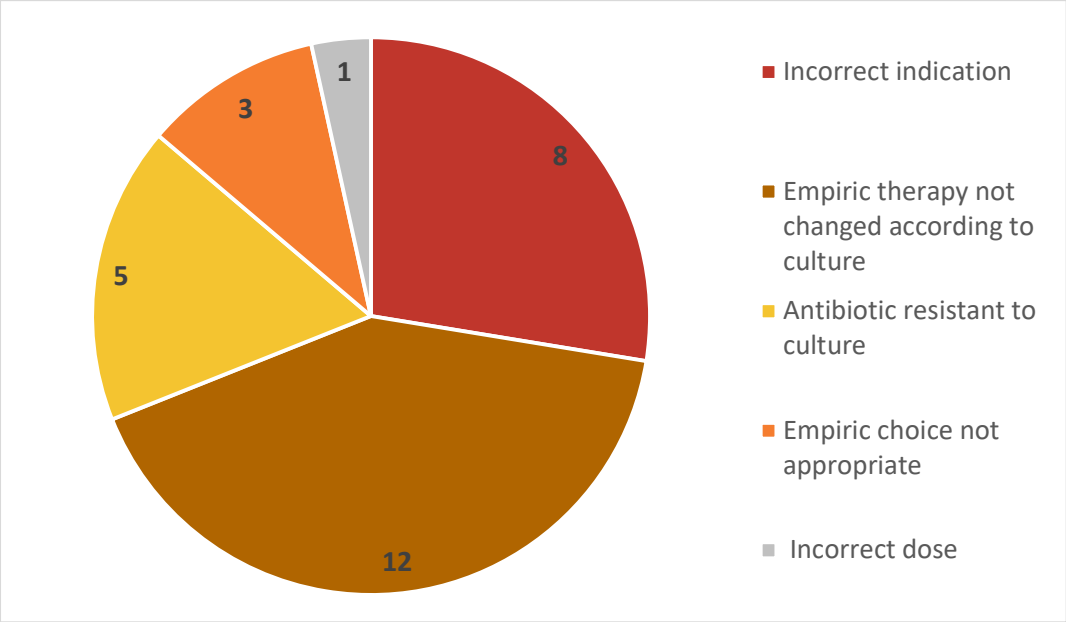

Figure 3.8: Inappropriate treatment according to indication, choice, and dose/regimen/route (n=29)

3.6 Framework

Figure 3.9 highlights areas where clinical pharmacists can intervene to ensure appropriate antibiotic use in UTIs. The framework is separated into 4 sections according to the proposed interventions for treatment indication, choice, dose/regimen/route, and duration. Interventions which can be carried out solely by the clinical pharmacists are depicted in white. The framework also emphasises the importance of collaborative interventions with other healthcare professionals to ensure appropriate antibiotic use, which are depicted in grey. The framework is designed in a way to support effective clinical pharmacists' intervention by integrating in routine practice already undertaken by the clinical pharmacist's team.

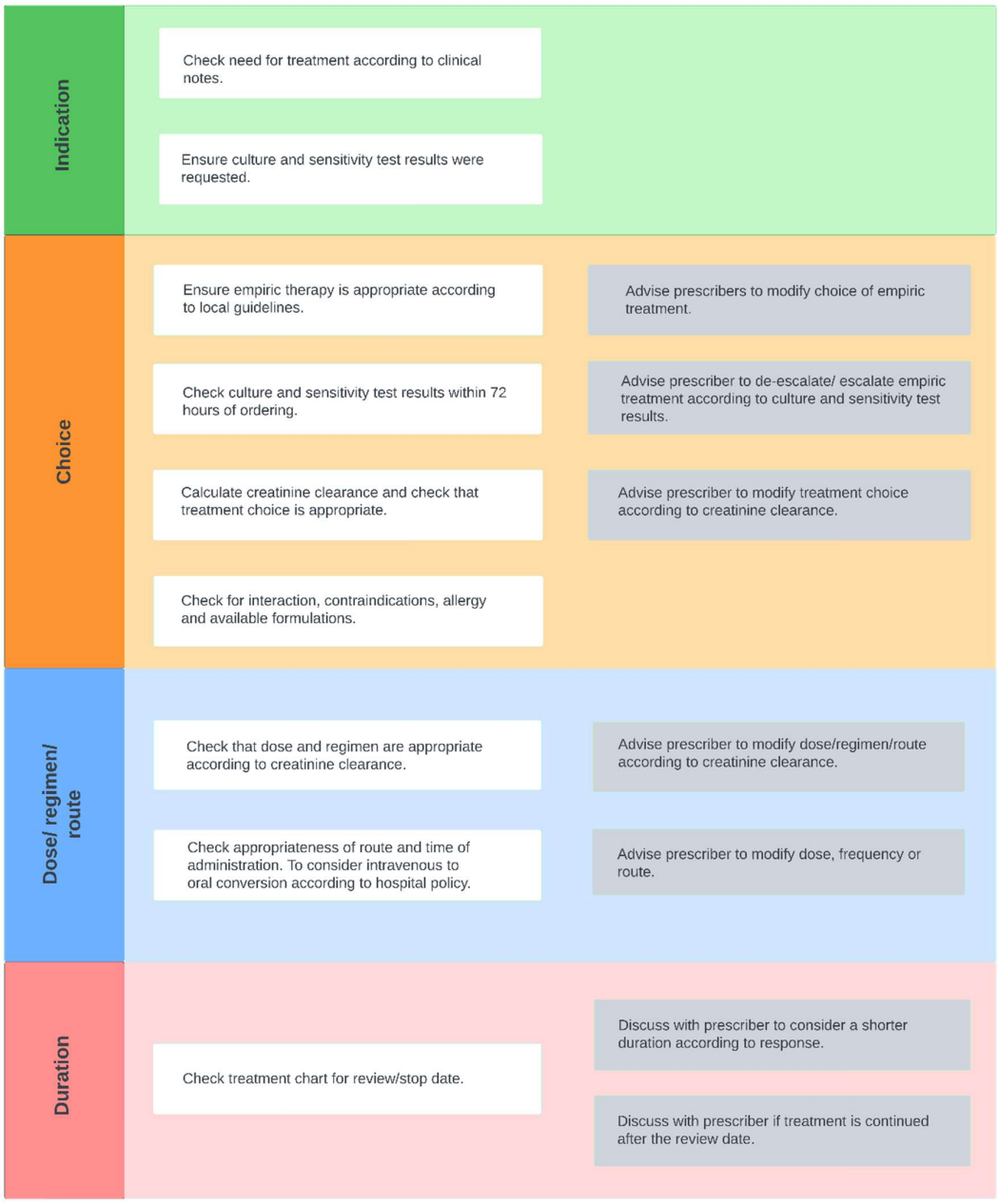

Figure 3.9: Validated framework to be implemented by clinical pharmacists at KGH to increase pharmacists' intervention in AMS

Chapter 4: Discussion

4.1 Assessing Appropriateness of Antibiotic Use

AMS attempts to maximise the therapeutic benefits of antibiotic treatment while limiting as much as possible the harms associated with treatment use and maintaining treatment cost-effectiveness[7]. Appropriateness needs to be assessed in terms of different factors, including treatment indication, choice of treatment, dosage regimen/route and treatment duration.

The determination of appropriateness of indication was a significant challenge in this study because of the patient population, which constituted of older adults, the majority of which belonged to the 80 – 89 age group. Patients in these age groups have a higher incidence of atypical symptoms and co-morbidities, which can contribute to the difficulty in obtaining an accurate diagnosis (Rowe & JuthaniMehta, 2014; Cortes-Penfield et al., 2017). The patient population also had a high indwelling catheterisation rate, which is associated with an increased risk of asymptomatic colonisation of the urinary tract (Flores-Mireles et al., 2019). To prevent colonisation and CAUTI, the hospital attempts to limit catheter duration by challenging catheterisation need and conducting a trial without a catheter. ASB in this patient population is expected to be significant and can lead to inappropriate antibiotic use. In colonised asymptomatic patients, misusing diagnosis tests result in false positive results and unnecessary antibiotic use (Biggel et al., 2019; Rousham et al., 2019).

The determination of appropriateness of indication is further complicated by the lack of consensus about diagnostic criteria in the available guidelines. While the available

[7] Centers for Disease Control and Prevention (CDC). Core Elements of Outpatient Antibiotic Stewardship [Internet]. Atlanta:CDC; 2021 [Cited 2023 APR 6]. Available from URL: https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf

guidelines are clear regarding treatment choice and dose/regimen/route, indication criteria are limited for the study setting of KGH, due to differences in patient populations targeted by the guidelines. For this reason, a consensus for diagnostic criteria specific to the setting of KGH was developed following discussions with the expert group. The first criteria for appropriateness consisted of the requirement of one urinary symptom and elevated serum biomarkers. The diagnostic role of dysuria differs between the developed consensus criteria and the revised McGeer Criteria (Stone et al., 2012), which was designed for long-term settings. According to the revised McGeer criteria, the presence of acute dysuria in the absence of elevated biomarkers is sufficient to indicate a UTI. This differs also from the SAPG[10] guidelines designed for the primary care setting, namely community and nursing homes, which require an additional urinary symptom in addition to dysuria for the diagnosis of a UTI.

In this study, the largest group was the inconclusive category, accounting for 40% of patients. It included individuals with non-urinary symptoms and abnormal serum biomarkers or a single urinary symptom in the absence of elevated serum biomarkers. These patients would have required additional investigations and monitoring to identify, confirm or rule out an underlying UTI. In the developed criteria for appropriateness of indication, emphasis was made on identifying asymptomatic patients with changes in urinary characteristics. Changes in the urine do not necessarily indicate a UTI, especially if they are not present with symptoms indicative of an underlying UTI. Monitoring and identifying the source of the change in urinary characteristics, such as dehydration, is

[10] Scottish Antimicrobial Prescribing Group (SAPG). Decision aid for diagnosis and management of suspected urinary tract infection (UTI) in people aged 65 years and over [internet]. SAPG; 2021 [Cited 2023 APR 22]. Available from: https://www.sapg.scot/media/5844/decision-aid-for-diagnosis-and-management-of-suspected-uti-in-people-over-65-years.pdf

recommended in these patients (Cortes-Penfield et al., 2017; Nicolle et al., 2019). The treatment of ASB was the second most common cause of inappropriate treatment in the study setting.

C&S tests are useful to guide and optimise antibiotic treatment in patients with suspected UTIs rather than to diagnose or confirm a UTI. In this study most of the inappropriate treatments in terms of choice were associated with not using the available C&S results to guide and optimise the empiric antibiotic treatment, including failing to de-escalate treatment according to the available C&S result and the continued use of antibiotics that were resistant to the culture organism. Appropriate treatment de-escalation, according to the C&S result, reduces broad-spectrum antibiotic use and the associated adverse outcomes (Alshareef et al., 2020). The use of antibiotics resistant to the cultured organism would result in treatment failure, unnecessary antibiotic exposure, and the requirement for additional treatment with an alternative antibiotic course.

The use of laboratory-issued eGFR can result in over-estimation of renal function in underweight patients, resulting in the incorrect use of dose/regimen. To correct this overestimation of renal function, the dose/regimen of underweight patients should be based on the calculated CrCl using the patient's actual body weight (wood et al., 2018). The study population is more susceptible to incorrect renal dosing due to the higher occurrence of underweight patients in this age group, which can be attributed to malnutrition or co-morbidities. In this study, even though the calculated CrCl was lower than the eGFR, the prescriptions which required a change in dose/regimen were low.

The low number of inappropriate prescriptions associated to dosing reflects the attention given to CrCl for dose adjustments at KGH.

Intravenous dosage forms are essential for patients with severe infections and those who cannot tolerate oral dosage forms. Intravenous dosage form should be used diligently and de-escalated to the oral formulation when appropriate to avoid the risks associated with continued use. The risks of continued use of intravenous antibiotics are detailed by McCarthy & Avent (2020) and include an increased risk of secondary infection at the venous catheter site and are associated with increased direct and indirect costs.

Optimisation of treatment duration is essential to limit antibiotic exposure. Ideally, the duration is adequate to ensure treatment efficacy while being long enough to prevent treatment failure. The SAPG[10] guidelines recommend a shorter duration of first-line antibiotics in uncomplicated cases of UTI. In cases of more severe infections such as pyelonephritis, there is evidence that in the absence of complicating factors, a treatment duration of fewer than 7 days would be comparable in effectiveness to a longer duration (Erba et al., 2020). Treatment duration can be shortened by using other techniques, such as source control (Sawyer et al., 2015) and individualisation according to patient characteristics and serum biomarkers e.g. WBC and CRP. The monitoring of the biomarker trend over time can be used as a guide to individualise treatment in symptomatic patients. Specifically, a sudden decrease in CRP following antibiotic use can be attributed to antibiotic efficacy (Aulin et al., 2021). However, this can be challenging

[10] Scottish Antimicrobial Prescribing Group (SAPG). Decision aid for diagnosis and management of suspected urinary tract infection (UTI) in people aged 65 years and over [internet]. SAPG; 2021 [Cited 2023 APR 22]. Available from: https://www.sapg.scot/media/5844/decision-aid-for-diagnosis-and-management-of-suspected-uti-in-people-over-65-years.pdf

to implement since CRP is not specific to infections, and underlying conditions may impact the rate of decrease of the biomarker. Regular monitoring of CRP also requires personnel for regular blood samples (Von Dach et al., 2020).

At KGH, treatment duration is regulated according to a Start/Review Date policy. When treatment commences, the prescriber determines a stop or review date, which is recorded on the treatment chart. The review date allows for the determination of the continued need for treatment, while the stop date designates the maximum treatment duration. In this study, the appropriateness of treatment duration was not assessed for two reasons. Firstly, there were inconsistencies in the treatment duration recommendations between MDH guideline, BNF®, and the respective SmPC. Secondly, due to the study's retrospective nature, it was difficult to determine if the patient required prolonged treatment.

Determination of the treatment appropriateness is especially important in the older adult patient population, which is at an increased risk of adverse drug events (ADE) and interactions because of increased co-morbidities and polypharmacy (Cortes-penfield et al., 2017; Giarratano et al., 2018). The prevalence of such ADE is linked to pharmacological changes associated with increased fragility and changes in body composition (Davies & Mahony, 2015).

The study patient population is especially at risk of *C. difficile* superinfection as a complication of broad-spectrum antibiotics (Asempa & Nicolau, 2017) and ADE specific to antibiotic classes. Notable ADE associated with specific classes includes tendonitis,

neuropathy, and abnormal blood glucose with fluoroquinolone use[11], while older adults taking trimethoprim and co-trimoxazole have a greater risk of developing hyperkalaemia (AdAwi et al., 2021), acute kidney injury (Rajput et al., 2020), and hyponatremia (Lei et al., 2022).

4.2 Clinical Pharmacist Intervention

AMS techniques can be broadly classified into two types, those which are collaborative and those which are restrictive in nature. During the study, the restrictive approach was mostly noted in the issued C&S results. The microbiology laboratory limits the released C&S based on the patient's catheterisation status to guide antibiotic use. In patients without a catheter, reported susceptibilities are determined by the resistance profile of the cultured microorganism. The laboratory also omits the susceptibility results in catheterised patients with underlying bacteriuria to reduce the treatment of ASB, directing the prescriber to contact the laboratory for the results. The undertaken approach of limiting antibiotic susceptibility results had limited efficacy in the study population, as noted by the large proportion of patients whose treatment was not de-escalated according to the issued sensitivities. While it is true that restrictive approaches are useful in cases where a rapid response is required, collaborative approaches are described as being more efficacious than their restrictive counterparts (Tamma et al., 2017). As indicated by a recent study by Monmaturapoj et al. (2021), the most effective stewardship techniques involved those which combined collaborative methods with

[11] Food Drug Administration (FDA). FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions [Internet]. Maryland:FDA; 2018 [Cited 2023 APR 1]. Available from URL: https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics-risks-mental-health-and-low-blood-sugar-adverse

education-based interventions. These techniques can help improve and change future prescribing patterns in the hospital setting.

The clinical pharmacists at KGH regularly participate in clinical practice, making them well-equipped to adopt collaborative stewardship practices. Interventions which clinical pharmacists can undertake are detailed in the designed framework, which was discussed and validated by the hospital clinical pharmacist team. The framework focuses on factors in which clinical pharmacists can intervene in the appropriateness of indication, choice, dose/regimen/route, and duration. The clinical pharmacists in daily clinical practice can discuss the need for initiating antibiotics treatment with the prescriber, especially in asymptomatic patients, reducing the unnecessary start of empiric antibiotics. The appropriateness of treatment can be reviewed through prospective audits and by reviewing clinical notes and treatment charts. Following the initiation of empiric treatment, pharmacists can ensure that the urinary C&S was ordered within 72 hours and can check the C&S results. This AMS technique is known as antibiotic time out. Paulson et al. (2022) investigated pharmacist-initiated antibiotic timeout and found that such intervention increased and improved treatment de-escalation, evaluation, and documentation. According to the findings of this study, the majority of inappropriate prescriptions were associated with a failure to de-escalate empiric treatment based on C&S results and the use of antibiotics that were not susceptible to the cultured microorganism. Failure of treatment de-escalation can be mitigated by implementing a system in which pharmacists check the appropriateness of all initiated empiric antibiotics up to three days after starting empiric treatment. The proposed system contrasts with the current review date policy, which varies by patient and is prescriber dependent. During the first 72 hours of treatment, patients who have been started on intravenous

antibiotics can be monitored, and the continued need for further intravenous treatment can be discussed with the treatment team. While not included in the determination of appropriateness in this study, treatment duration can be reduced by setting up new guidelines and enforcing current policies on stop dates. When starting a new treatment, pharmacists can ensure that a review/stop date is scheduled.

The benefits of pharmacist intervention in AMS interventions are well known (Ohashi et al., 2018; MacMillan et al., 2019; Campbell et al., 2020; Cantudo-Cuenca et al., 2022). Clinical pharmacists are described by the CDC[7] as important members of stewardship teams and can contribute to AMS through leadership roles because of their expertise in antibiotic pharmacology. To increase the effectiveness of the AMS intervention, the CDC recommends further training and experience. The importance of continued training and development is noted by Curran et al. (2022) who, along with a lack of time, identified a lack of expertise as a hindrance to effective AMS offered by ward pharmacists. Expertise in AMS techniques can be improved through educational intervention using case reviews, as detailed by Khumra et al. (2022). The introduction of AMS services and clinical pharmacist integration requires both time and financial investment, but the benefits of a successful implementation outweigh the initial cost (Nathwani et al., 2019).

[7] Centers for Disease Control and Prevention (CDC). Core Elements of Outpatient Antibiotic Stewardship [Internet]. Atlanta:CDC; 2021 [Cited 2023 APR 6]. Available from URL: https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf

4.3 Strengths and Limitations

The study's main strength is that the hospital already has a robust clinical pharmacist service in each ward, with the clinical pharmacist intervening to ensure medicines optimisation. Since the necessary mechanisms are already in place, it would be simple to integrate the developed framework into their regular practice and support an effective AMS within all wards.

The study's main limitation was its retrospective nature, which relied on secondary data that may not have been complete. Incomplete data could have had an impact on assessment of treatment appropriateness. This contrasts with a prospective-based scenario where the completeness and validity of the collected data would have been confirmed with the prescribers. Another limitation was that the indication for treatment was inconclusive in a substantial proportion of the study population and consequentially decreased the number of patients to be assessed for appropriateness of treatment.

4.4 Recommendations for Further Studies

The study identified a lack of available guideline criteria for the appropriate diagnosis of UTIs in the study setting. A future study can compare outcomes before and after the implementation of the consensus criteria. Future research could focus on the impact of the applied framework on treatment appropriateness in terms of treatment indication, choice, dose/regimen/route.

The study was limited to a specific setting. Future studies can focus on antibiotic appropriateness and clinical pharmacist intervention in different care settings.

4.5 Conclusion

The study highlighted instances of inappropriate antibiotic use in the study population. Clinical pharmacists are in a position to intervene in AMS to ensure treatment appropriateness. The designed framework can support AMS practices by clinical pharmacists and be adapted to different care settings.

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Appendix 1: Data Collection Sheet

Patient Code _____ _____ _____

Date of review:

1.Demographic and general information

Gender	Male ☐	Female ☐		Not declared ☐
Age range	60 - 69 ☐	70 – 79 ☐	80 - 89 ☐	90-100 ☐

Antibiotic allergy	
Patient co-morbidities or patient history	
CCI	
Date of start of antibiotic (day 0)	

2. Catheterization

Is the patient catheterized?	Yes ☐ No ☐
Urinary catheterization type	Indwelling ☐ Intermittent ☐ suprapubic ☐ External ☐
Duration of catheterization	More than 4 weeks ☐ Less than 4 weeks ☐

Was a TWOC attempted?	Successful ☐	Not successful ☐	Not attempted ☐

3. Antibiotic regimen
Antibiotic:
Dose & route:
Duration and frequency:

Prophylaxis ☐

Empiric treatment ☐

According to C&S testing ☐

First line according to MDH guidelines:

Yes ☐
No ☐

Stop/Review Date	Yes ☐ No ☐
Action following antibiotic review stop/review date	Treatment was stopped ☐ Antibiotic regimen was changed ☐ Escalation ☐ De-escalation ☐ Treatment was continued ☐ IV to PO Switch ☐

Antibiotic route	
Is IV to PO switch recommended according to local hospital polices (48 – 72 hours)	Yes (patient meets inclusion and exclusion criteria detailed in the local hospital policy and IV antibiotics are not needed) ☐ No ☐ Not applicable ☐ Cannot be determined ☐
Reason:	

Changes to antibiotic regimen

Reason for antibiotic regimen change

Not responding to treatment ☐

Side effect ☐

C&S result ☐

Other

Antibiotic	
Dose/dosage form	
Frequency	
Date started	
New stop date	Yes ☐ No ☐

First line: Yes ☐ No ☐

Narrow spectrum/ changed according to C & S result ☐

4. Infection characteristics	
Patient diagnosis	Lower UTI ☐ Upper UTI e.g., pyelonephritis☐ Urosepsis ☐ CAUTI ☐ Other:
	Non- recurrent ☐ Recurrent (three UTI in a 12-month period/ two UTI in a 6-month period)☐
General symptoms suggesting infection	Fever ☐ Hypothermia ☐ Sudden worsening of diabetes control ☐ Rigor☐ Lower central back pain/ tenderness☐ Deterioration in activities of daily living ☐
Specific symptoms suggesting urinary tract infection	Sudden new onset of confusion/agitation ☐ Increased urinary urgency ☐ Increased urinary frequency ☐ Pain (flank/ suprapubic pain) ☐ Dysuria ☐ Hematuria (macroscopic) ☐

Other symptoms:

5. laboratory investigations			
Investigational tests	Urine analysis ☐ Urine C&S testing ☐		
Identified microorganism	*Escherichia coli* ☐ *Klebsiella pneumoniae* ☐ *Enterococcus faecalis* ☐ *Pseudomonas aeruginosa* ☐ *Staphylococcus aureus* ☐		
Other:			
C & S testing result			
	Susceptible	Intermediate	Resistant
Amikacin	☐	☐	☐
Amoxicillin	☐	☐	☐
Cefotaxime	☐	☐	☐
Ciprofloxacin	☐	☐	☐
Co-amoxiclav	☐	☐	☐
Co-trimoxazole	☐	☐	☐

	Susceptible	Intermediate	Resistant
Ertapenem	☐	☐	☐
Fosfomycin	☐	☐	☐
Gentamicin	☐	☐	☐
Meropenem	☐	☐	☐
Nitrofurantoin	☐	☐	☐
Piperacillin-tazobactam	☐	☐	☐
Other			
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

Resistance type

ESBL ☐
CRE ☐
VRE ☐
Other:

Urinary analysis	
WBC	
Nitrite	
pH	
Other	

5b. Laboratory investigations		
	Date	Value
WBC (4.3 – 11.4 x10^9L)	Day 0	
CRP (0-5 mg/L)	Day 0	

	Date	Value
eGFR (mL/min/1.73m^2)	Day 0	
CrCl (mL/min)	Day 0	
Other	Day 0	

HbA1c (if available within the past three months)	< 6.5% ☐	6.5% – 6.9% ☐	7.0% – 7.5% ☐	> 7.6% ☐

Blood culture Positive blood culture ☐

Cultured microorganism

6. Evaluation

Antibiotic appropriateness	First regimen	New regimen
Is the antibiotic indication appropriate?	Yes ☐ No ☐	Yes ☐ No ☐
Is the antibiotic choice appropriate?	Yes ☐ No ☐	Yes ☐ No ☐
Is the antibiotic dose appropriate?	Yes ☐ No ☐	Yes ☐ No ☐
Is the antibiotic regimen appropriate?	Yes ☐ No ☐	Yes ☐ No ☐
Is the dosing duration appropriate?	Yes ☐ No ☐	Yes ☐ No ☐
Comments		

Appendix 2: Ethics Approval

L-Università ta' Malta

Faculty of Medicine & Surgery

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Ref No: MED-2022-00056

3 October 2022

With reference to your application submitted to the Faculty Research Ethics Committee inconnection with your research entitled:

Antimicrobial Stewardship - A Priority for Clinical Pharmacists

The Faculty Research Ethics Committee is granting ethical approval for the above-mentioned application.

Professor Anthony Serracino Inglott
Chair
Faculty Research Ethics Committee