A STUDY OF ANTIBIOTIC AGENTS PRESCRIBED, GUIDELINE COMPLIANCE AND ASSOCIATED FACTOR OF ANTIBIOTIC FAILURE AMONG THE HOSPITALISED PAEDIATRIC AND ADULT GENERAL MEDICAL PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA.

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LIST OF ABBREVIATIONS

AMR:Antimicrobial Resistance

AMS: Antimicrobial Stewardship

ATF : Antimicrobial Treatment Failure

AKI : Acute Kidney Injury

BLI : β-Lactamase Inhibitor

CAP: Community Acquired Pneumonia

CDC: Centers for Disease Control and Prevention

CKD: Chronic Kidney Disease

COPD: Chronic Obstructive Pulmonary Disease

CME: Continuing Medical Education

CNS: Central Nervous System

CRP: C- Reactive Protein

ENT: Ear Nose Throat

ESBL: Extended Spectrum β-Lactamases

ESRF: End Stage Renal Failure

GIT: Gastrointestinal Tract

HTAR: Hospital Tengku Ampuan Rahimah

HUSM: Hospital Universiti Sains Malaysia

ICU: Intensive Care Unit

JEPEM: Jawatankuasa Etika Penyelidikan Manusia

MDR: Multidrug-Resistant

MRO: Multi-Resistant Organisms

MRSA: Methicillin-Resistant Staphylococcus Aureus

NAG: National Antibiotic Guidelines

NICU: Neonatal Intensive Care Unit

USM: Universiti Sains Malaysia

ROC: Receiver Operating Characteristic

SARI: Severe Acute Respiratory Infections

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ABSTRAK

Latar belakang : Antibiotik adalah ubat yang paling kerap digunakan di hospital. Penggunaan antibiotik yang salah telah terbukti menyumbang kepada berlakunya organisma rintang pelbagai ubat (MRO). Memahami corak preskripsi antibiotik sangat penting untuk memerangi akses terhad dan penggunaan antibiotik yang berlebihan dan pada masa sama mengawal rintangan antibiotik kepada sesuatu organisma. Oleh itu, tujuan kajian kami adalah untuk menilai penggunaan antibiotik dan faktor kegagalan yang berkaitan di kalangan pesakit yang dirawat di wad perubatan kanak-kanak dan dewasa di hospital USM.

Metodologi: Ini adalah kajian retrospektif mengenai corak penggunaan antibiotik di kalangan wad perubatan kanak- kanak dan dewasa am. Sebanyak 227 pesakit dikenal pasti setelah memenuhi kriteria . Kajian ini menggunakan analisis deskriptif dan inferensi untuk mengetahui objektifnya. Analisis deskriptif merangkumi frekuensi, peratusan, min dan sisihan piawai, yang dilakukan untuk menentukan demografi pesakit, diagnosis pesakit dan komorbid pesakit. Statistik inferensi melibatkan analisis regresi logistik mudah dan analisis regresi logistik berganda pula dilakukan untuk mengenal pasti faktor-faktor yang berkaitan dengan kegagalan rawatan dengan antibiotik**.**

Keputusan : Jangkitan saluran pernafasan ditemui sebagai tempat jangkitan dan dirawat dengan antibiotik tertinggi antara semua kumpulan umur dengan jumlah 163 pesakit. Antaranya, 57.7% (94 pesakit) telah dirawat dengan kumpulan penicilin- β-lactamase inhibitor, diikuti oleh 28.8% (47 pesakit) dengan kumpulan macrolide

dan 13.5% dengan menggunakan antibiotik lain. amoxicillin dan clavulanate dilaporkan paling banyak di gunakan di kalangan kumpulan antibiotik ini iaitu 65.2%. Sebanyak 160 (70.5 %) preskripsi pesakit dicatat menggunakan satu antibiotik sementara 67 pesakit (29.5%) menggunakan 2 kombinasi antibiotik. Kebanyakan rawatan antibiotik diberikan melalui suntikan (75.3%). Sebagai catatan, lebih daripada separuh preskripsi 60.8% (138) dianggap mematuhi garis panduan penggunaan antibiotik yang disebut dalam kajian ini. Kadar kegagalan antibiotik adalah hanya 12.8% (29), iaitu lebih kurang sama dengan beberapa kajian lain.3 faktor kegagalan antibiotic yang ketara dikenalpasti di dalam kajian ini adalah pesakit wanita (OR, 3.459; 95% CI, 1.075,11.130), kegagalan buah pinggang akut (OR, 3.084; 95% CI, 1.021, 9.311) dan kewujudan organisma rintangan ubat (OR, 2.961; 95% CI, 3.813,97.916).

Kesimpulan : Kebanyakan antibiotik yang digunakan dalam kajian ini adalah gabungan penicillin dengan β-lactamase inhibitor. Namun begitu, hanya 12.8% (29) kegagalan antibiotic dilaporkan dan hanya 3 faktor kegagalan yang ketara dikenalpasti. Kajian yang lebih berskala besar dan tempoh lama diperlukan untuk mencari lebih banyak preskripsi antibiotik , tidak terhad kepada wad perubatan tetapi termasuk bahagian lain seperti pembedahan, ortopedik, obstetrik, dan ginekologi untuk merumuskan kadar kegagalan antibiotik yang lebih nyata dan factor-faktor yang berkaitan.

ABSTRACT

Background: Antibiotic is the commonest drugs used in hospitals. Inappropriate use of antibiotics has been shown to contribute to the occurrence of multidrug-resistant organisms (MROs). Understanding antibiotic prescription patterns is essential for combatting limited access and excessive use of antibiotics and controlling resistance. Thus, we evaluated antibiotic agents prescribed and the associated factor of antibiotic failure among hospitalized adult and pediatric patients in Hospital USM.

Methodology: This was a retrospective study of antibiotic patterns among the adult general and pediatric general medical wards. A total of 227 patients were identified after had fulfilled the inclusion and exclusion criteria. This study used descriptive and inferential analysis to find out the objectives. The descriptive analysis includes the frequencies, percentage, mean and standard deviation, carried out to determine the patient's demographic, patient's clinical diagnosis, and patients comorbid. The inferential statistics involving simple logistic and multiple logistic regression are conducted to identify the factors associated with antibiotics failure.

Results: Respiratory tract infections were found to be the highest infection sites and treated with antibiotics among all age groups with a total of 163 patients. Among these, 57.7% (94 patients) have been prescribed with penicillin with β-lactamase inhibitor group, followed by 28.8% (47 patients) with macrolide and a balance of 13.5% with other groups. Amoxicillin and clavulanic acid were reported to be the commonest among the penicillin with β-lactamase inhibitor group prescribed which

was 65.2%. A total of 160 (70.5%) patients' prescription was noted as a single prescription while only 67 (29.5%) were of 2 antibiotics combination prescription. Most of them were given parenterally(75.3%). As of notes, more than half of prescriptions 60.8% (138) were deemed compliance to the guidelines. The rate of antibiotic failure was 12.8% (29) which was quite similar to a few other studies. 3 factors that been identified as the significant associated factor of antibiotic failure in this study were female sex (OR, 3.459; 95% CI, 1.075,11.130), the presence of acute kidney injury (OR, 3.084; 95% CI, 1.021, 9.311) and resistant organisms (OR, 2.961; 95% CI, 3.813,97.916).

Conclusion: Most of the antibiotics prescribed in this study were penicillin with β-lactamase inhibitors. Despite this, there was only 12.8% (29) antibiotic failure and only 3 significant associated factors of failure were reported. Further larger scale and longer study needed to look for more antibiotic prescriptions not limited to the medical ward but including all disciplines such as surgical, orthopaedic, obstetrics, and gynaecology to conclude more realistic rate of antibiotic failure and associated factors.

CHAPTER 1

INTRODUCTION

Antibiotics are medicines that fight infections caused by bacteria. It is one of the most common drugs prescribed by medical practitioners on either outpatient basis or during hospital admission globally. For the optimum goal of therapy, antibiotics are usually prescribed based on clinical indication, dosage, and route. Apart from that, some physicians preferred it based on their experience.

Most of the medical centres in most countries have their own local or national antibiotics guideline that has been made by the expert team that might consist of the infectious disease specialists, pharmacists and other experts based on the local infection susceptibility, antibiotic availability, the availability of local budgets and a few other factors. There is a variety of antibiotics, which are categorized either based on their chemical structures, mode of action, or spectrum of activity (Md Zawawi et al., 2020). Inappropriate use such as overuse and misuse might lead to more harm such as developing antibiotic resistance, increased mortality rate (Cassini et al., 2019), and increased cost of patient care (Dadgostar, 2019).

Antibiotics are important to treat infections and have saved countless lives; however, as effective as they are, they have their own failures, side effects, and even antibiotic resistance, which is one of the most alarming threats to the public health that needs to be looked out for. Extensive mistreatment with antimicrobial drugs (Gross, 2013) have been reported in recent years, and nearly half of all antibiotic drug prescriptions have

been found to be prescribed without proper indication (Ray et al., 2019). Unnecessary antibiotic prescription, broad-spectrum antimicrobial exposure, and cross-infections are important contributing factors to antimicrobial resistance, and subsequently failure to treatment which may contribute to increased morbidity and mortality (Depuydt et al., 2008). Infections caused by antimicrobial-resistant organisms are difficult, and sometimes impossible, to treat and may require extended hospital stays with additional follow-up doctor visits, and costly and toxic alternatives in many cases (Llor and Bjerrum, 2014).

Resistance of some organisms also differed between the different areas in the hospitals. It was noted that NICU had a lower rate of MRSA, as well as lower resistance to other antibiotics, including gentamicin, rifampicin, and fusidic acid (Ariffin et al., 2012). Examples of antibiotic resistant organisms – methicillin resistant *staphylococcus aureus,* carbapenem resistant *Enterobacter,* vancomycin resistant *Enterobacter,* drug resistant *strep pneumonia,* MDR *pseudomonas aeruginosa,* MDR *TB,* and cephalosporin resistance. These resistant organisms are one of the major concerns that might contribute to the treatment failure of an antibiotic.

Antibiotic prescription should be made after careful consideration of multiple factors such as underlying infective processes, possible aetiologic agents, local susceptibility patterns, known spectrum of a chosen antibiotic, host factors, or even patient comorbidities (Mainz, 2019).

Antibiotic failure is one of the complications of inappropriate antibiotic prescription and antibiotic resistance. However, to date, there is no consensus on the definition of antibiotic failure that has been updated on any guideline (Neill et al., 2022). Antibiotic failure diagnosis has been made based on objective clinical criteria (García, 2009a). This is different from antibiotic resistance which is defined when an organism is not responsive to an antibiotic and proven clinically based on minimum inhibitory concentration (MIC) breakpoints (Martínez et al., 2015). The true incidence of antibiotic failure has never really been established as the true definition of antibiotic failure has never been made and very few prospective studies with the main objective to determine the incidence of antibiotic treatment failures have ever been published (Neill et al., 2022).

Education on antimicrobial stewardship programs (CME, antibiotic awareness program) would improve awareness among physicians at all levels. About 50 healthcare providers, including nurses (33%), pharmacists (29%) and biomedical scientists (23%) were surveyed about the knowledge and awareness of antibiotic use in Ghana Teaching Hospital. Of these, 58% of participants had engaged in continuous professional development antimicrobial stewardship programmes and it was noted that more than 95% demonstrated good knowledge on general use of antibiotics (Kpokiri et al., 2022). Antimicrobial stewardship programs have shown success in reducing antimicrobial use, mitigating antimicrobial resistance, and improving patient outcomes and cost-effectiveness in multiple articles and countries (Hogan et al., 2016).

The main purpose of this research is to study antibiotic agents prescribed in Hospital USM, mainly in adult and paediatric general medical patients and compliance to guidelines. For Hospital USM, the guidelines recommended for adult patients are either National Antimicrobial Guideline 2019, 3rd Edition (NAG 2019), The Antimicrobial Stewardship Program (ASP) Guide To Antimicrobial Therapy 2022 while for paediatric patients are National Antimicrobial Guideline 2019, 3rd Edition (NAG 2019) and Paediatrics Protocol 4th edition. The data or report on antibiotic usage and guideline compliance in Hospital USM may be able to create more awareness and if possible, more classes, CME, or teaching may be done for the purpose of education that may lead to improvement in our healthcare services, reduce the risk of antibiotic resistance prevalence and reduce the risk of antibiotic failure overall.

CHAPTER 2

LITERATURE REVIEW

The emergence of antibiotic resistance has become a challenge to healthcare services not just locally, but globally. Antibiotic stewardship, or improving how antibiotics are prescribed and used, remains critical to optimize the treatment of patients who have infections, protect patients from harm, and combat antibiotic resistance (Frost et al., 2022).

There are various activities that have been introduced by The Centres for Disease Control and Prevention (CDC), including working with partners to expand the use of data by states and payers to engage high prescribers, conducting outreach to partners, and promoting the appropriate use of diagnostic tools to inform of any antibiotic use. They even provided improved access to tools and resources for outpatient providers, including resources focused on prescribing during the transition between inpatient care and outpatient care ("Current Report | Antibiotic Use | CDC," 2022). These mainly reduce the inappropriate antibiotics used in either inpatient or outpatient care ("Current Report | Antibiotic Use | CDC," 2022).

Studies of how antibiotic was prescribed and used are also one method in which it can be directly or indirectly seen how antibiotic practices were conducted in many healthcare settings, either in our country Malaysia or internationally. One of these studies was conducted to determine the prescribing patterns of antibiotics in the

general paediatric wards (Md Zawawi et al., 2020). A total of 544 prescriptions of antibiotics were prescribed for 269 patients in the paediatric wards in a cross-sectional prospective study done in August 2017 in Hospital Tengku Ampuan Rahimah (HTAR), Klang Selangor. Among the patients that were included in this study, the highest number were in the age group between 1 and 5 years old (54.6%) and the lowest number was in the age group between above 5 and 12 years of age (14.5%)(Md Zawawi et al., 2020). The most prescribed antibiotics among the general paediatric population in this study were narrow spectrum antibiotics (71.1%) from the Penicillin class.

Another study that involved a prospective, descriptive, and cross-sectional survey of antibiotic prescriptions, not limited to single centre and in six general hospitals situated in various parts of Malaysia was done (V. Lim, 1994). Out of the 1263 therapeutic prescriptions, only 20% of the prescriptions were based on the microbiological result noted in this survey with only 743 antibiotic prescription (56%) cultures taken before initiating treatment. For both the studies, respiratory tract infections were found to be the most treated, 56.5% and 31%, respectively and ampicillin was the most prescribed antibiotics (V. Lim, 1994; Md Zawawi et al., 2020).

There was also another study conducted in Malaysia in 2021 to see the patterns and compliance of antimicrobial prescriptions with national antibiotic guidelines and local protocols at a Malaysian tertiary teaching hospital (Jamaluddin et al., 2021). A total of 478 patients were identified in 37 adult wards during the survey period, including ICU, burn unit, and a mixed ward and the largest pool (52.1%) of patients receiving

antibiotic was from the medical specialities wards. Empirical therapy (65.5%) was reported with the highest prevalence in the medical, surgical, and orthopaedic units. The most indications for antimicrobial prescriptions were medical prophylaxis (41 prescriptions, 11.5%), followed by empirical therapy for community-acquired pneumonia (36 prescriptions, 10.1%), and the most used antimicrobial agent is amoxicillin with β-lactamase inhibitor (14.8%) (Jamaluddin et al., 2021).

Antibiotics resistance increase and misuse is not just a local issue, it is a global issue that includes both developed and developing countries; therefore, there are many other studies and research that were done and are even ongoing to tackle the issue regarding antibiotic prescriptions. In Saudi Arabia, a study was done to assess the pattern of antibiotic prescription in respiratory tract infections in Hera General Hospital Makkah. Both the hospitalised and emergency department antibiotic uses were included in the study. There were 471 (58.9%) single antibiotic prescription while the rest were combinations of 2 and maximum 3 antibiotics with ciprofloxacin being the commonest antibiotic prescribed for hospitalised patients and amoxicillin in the emergency department (B. et al., 2019). The age of 65 years old and above has been noted to be the most frequent inpatient group to be prescribed with antibiotics in this study, which accounted for 60% prescriptions and being the most attendees (B. et al., 2019).

In Nepal, a study in Kathmandu Medical College Teaching Hospital to identify the prescription pattern of antibiotics in different medical units was done (Dixit and Shrestha, 2018). It was carried out on in-patient prescription data collected at random from patients admitted to different clinical departments in the hospital from December

2016 to July 2017 (Dixit and Shrestha, 2018). In this study, they found that the most prescribed antibiotics were Ceftriaxone, Amoxicillin and Cloxacillin, Azithromycin, Cefixime, and Cloxacillin. Ceftriaxone, the third generation Cephalosporin, was used the most—108 cases accounting for 16.8% of all antibiotics used (Dixit and Shrestha, 2018).

There was also another study in one of the developed countries in Asia, Japan, which was done to evaluate the prevalence and quality of antimicrobial prescriptions using the universally standardized Global-PPS protocol in a non-acute care hospital in Saitama Prefecture. Sulfamethoxazole/trimethoprim was the most prescribed with 20.0% of systemic antibiotic prescribed. The most common diagnosis among patients prescribed with antimicrobials was pneumonia (49.6%, 62 out of 125) (Ishibashi et al., 2022). Meanwhile, for other developed countries such as the European countries, more than 80 % of antibiotic prescriptions were given on an outpatient basis and limited data was available regarding the prescription pattern in the hospitalised patients (Llor and Bjerrum, 2014).

In the few previously mentioned studies of antibiotic prescriptions, there were also some that included the study on antibiotic appropriateness and guideline compliance. The study done in Hospital Tengku Ampuan Rahimah, Klang reported that about 99.8% of the prescriptions with antibiotics were prescribed correctly to the patients in the paediatric ward in terms of indication, dose, and route of administration according to the National Antibiotic Guidelines (NAG), Paediatric Protocols 3rd Edition, Lexicomp and Frank Shann 17th Edition (2017) (Md Zawawi et al., 2020).

Another study by Lim VK also concluded that compliance to guidelines was lower (56%) than most studies from developed countries and even the countries in its region (V. Lim, 1994). While in Japan, they reported a higher percentage of guideline compliance which reached 66.7% (Ishibashi et al., 2022). In addition to antibiotic guideline compliance, Lim VK also studied the overall appropriateness of the antimicrobial prescription, which was determined by an expert panel consisting of infectious disease specialists and pharmacists that found only about 64% of antibiotics were properly prescribed (V. Lim, 1994).

Prevalence Of Antibiotic Failure And The Associated Factors Of Antibiotic Failure.

Based on many studies, many antibiotics were found to be prescribed inappropriately, only 30.8% in a study done in the paediatric ward in Ethiopia (Alekaw et al., 2022a). The reports of misuse and prescriptions without indications are a major concern, as these practises could create more antibiotic resistance and cause antibiotic failure.

Despite being prescribed for decades since the 1940s where it began with streptomycin for typhoid and penicillin for syphilis, there is still no consensus available that really defines the meaning of failure in antimicrobial treatments (Neill et al., 2022). Most physicians consider antibiotic failure through clinical signs and radiological indications, although some consider microbiological and other biological markers (Rosón and Jordi, 2004). Based on the systematic review and narrative synthesis on variation in antibiotic treatment failure outcome definitions in randomised control trial

and observational studies of antibiotic prescribing strategies, there is substantial variation in the definition used in most studies that extends to studies on the same infection subtype and study design (Neill et al., 2022). There are 3 key components that have been identified for treatment failure definitions which are prescription changes, escalation of care and clinical condition features.

The occurrence of antimicrobial treatment failure in general populations of patients hospitalized with CAP has been as low as 6% and 11%, a considerably higher incidence than intuitively expected, of which 31%, have been published for CAP and other infections (Rosón and Jordi, 2004). A study to deepen the knowledge in regard to the factor associated with antimicrobial treatment failure is important as this may help the physician or any medical practitioner to avoid, recognize and deal with the complication of the failures effectively. There were few studies conducted for this purpose.

One study was conducted at Bellvitge Hospital, a 1000-bed university hospital in Barcelona that serves an area of 1100000 inhabitants. All non-immunosuppressed adult patients with CAP admitted to the hospital between February 13, 1995 and December 31, 2000 were prospectively studied. During the study, 1383 non-immunosuppressed adults with CAP were admitted to Bellvitge University Hospital (Rosón and Jordi, 2004). After 48 hours of hospitalization, 48 patients (3%) died. Of the remaining 1335 patients, 238 (18%) remained febrile, 208 (16%) continued to experience respiratory symptoms, 37 (3%) had worsened respiratory failure, and 21 (2%) had radiologic progression. These abnormalities coexisted in some patients.

After clinical evaluation, 54 (23%) of the 238 patients that remained febrile, 38 (18%) of the 208 that had persistent respiratory symptoms, and all 40 patients (100%) with worsened respiratory failure or radiologic progression were early failures. Overall, 1254 patients were classified as early responders and 81 (6%) were considered to be early failures (Rosón and Jordi, 2004).

This rate of failure was found to be similar in another study by Ortqvist et al. in a Swedish study designed to assess the value of protected brush culture in CAP. They did agree that host-, pathogen-, and drug-related factors should be considered when assessing a patient who fails to respond. High-risk pneumonia (Pneumonia Severity Index score > 90) multilobe infiltrate, *Legionella* pneumonia, gram-negative pneumonia, and discordant antimicrobial therapy were noted to be factors associated with early failures. In this study they defined early failure as the lack of response or worsening of clinical or radiologic status or both at 48 to 72 hours, requiring either changes in antibiotic therapy or performance of invasive procedures for diagnostic and therapeutic purposes or both, including mechanical ventilation and chest tube drainage or else it is considered as early responders.

In France, patients hospitalized in 1 of 16 centres for moderately severe CAP who were clinically stable were recruited, then randomly assigned (1:1) on day 3 of antibiotic treatment to receive β-lactam (amoxicillin-clavulanate [1 g/125 mg] 3 times daily) or placebo for 5 extra days (Dinh et al., 2021). The failure rate was 26.8%. Males (odds ratio [OR], 1.74; 95% CI, 1.01–3.07), age per year (OR, 1.03; 95% CI, 1.01–1.05), Pneumonia Severe Index score (OR, 1.01; 95% CI, 1.00–1.02), the presence of chronic

lung disease (OR, 1.85; 95% CI, 1.03–3.30), and creatinine clearance (OR, 0.99; 95% CI, 0.98–1.00) were significantly associated with failure in the univariate analysis of this study. However, only males and age were associated with higher risk of failure in the multivariable analysis (Dinh et al., 2021).

There was also another study done in Switzerland, which was a prospective, observational, cohort study of 228 adult (> 18 years old) hospitalized patients with CAP admitted to two hospitals in the region (Genné et al., 2006). Antibiotic therapy was administered in the emergency department in accordance with hospital guidelines (in agreement with the study period) and patients were monitored daily during their hospital stay, and their laboratory parameters were analysed every other day or more frequently according to the clinical evolution. Only 62 (28%) were reported to have antibiotic failure with 4 drop outs (Genné et al., 2006). This study showed that aspiration pneumonia, concomitant neoplasia, and neurological disease were all positively associated with treatment failure in the multivariate analysis (Genné et al., 2006).

There were few other studies regarding antibiotic failure; however, most of the studies were done in the primary care or outpatient departments. This study is not limited only to the study of antibiotic prescriptions in HUSM, but also to learn the failure rates of the antibiotics prescribed. This study will also oversee the factor associated with antibiotic failure not just in pneumonia but other infections in the paediatric or adult medical patients.

2.1Rationale of study

For the past years, the production of new antibiotics has been slowed down, besides, there is a rapid process of antimicrobial resistance (AMR) against almost all available antibiotics. Antibiotic stewardship is the practice of prescribing antibiotics only when antibiotics are considered necessary. The use of the appropriate agent(s), dose, duration, and route of therapy to optimize clinical outcomes while minimizing the unintended consequences of antibiotic use such as the occurrence of multidrug resistant organisms (MROs).

Most of the physicians explained that their prescribing patterns among them depend on the guidelines given by the hospital, their preferences, and their experience in their respective fields (Akhtar et al., 2020). However, we do not know if the prescribing pattern in HUSM is based on available guidelines or individual preference, the data or studies about the antibiotic prescribing pattern at Hospital USM among pediatric and adult patients is limited.

Conducting drug utilization research can provide useful information to healthcare providers and policymakers and might help in avoiding or minimizing antibiotic resistance. At the same time, we also might be able to determine what are the factors associated with the treatment failure in our hospital USM.

CHAPTER 3

OBJECTIVES

3.1 GENERAL OBJECTIVES

To study on the antibiotic agents prescribed, compliance with guidelines and associated factors of antibiotic failure among hospitalized general medical and pediatric patients in Hospital USM.

3.2 SPECIFIC OBJECTIVES

1. To describe the antibiotic agents prescribed and compliance with guidelines among hospitalized general medical and pediatric patients in Hospital USM.

2. To determine the proportion of antibiotic failure in the hospitalized general medical and pediatric patients prescribed with antibiotic in Hospital USM.

3. To identify the factors associated with antibiotics failure among patients in general medical and pediatric ward at Hospital USM.

3.3 RESEARCH QUESTIONS

1) What are the antibiotics agents prescribed and guideline compliance among the hospitalized general adult and pediatric patient in Hospital USM?

2) What is the prevalence of antibiotic failure among the hospitalized general adult and pediatric patient in Hospital USM?

3) What are the factors associated with antibiotic failure in Hospital USM?

3.4 RESEARCH HYPOTHESIS

3) Treatment failure among hospitalised general adult and paediatric patients in Hospital USM is associated with multiple factors.

3.5 NULL HYPOTHESIS

3) Antibiotic failure among the hospitalized general adult and pediatric patient in Hospital USM is not related to any associated factor.

CHAPTER 4

METHODOLOGY

4.1 STUDY DESIGN

Retrospective cohort study

4.2 STUDY LOCATION AND DURATION

General medical wards (ward 7S, 7U) and general paediatric ward at Hospital Universiti Sains Malaysia (ward 6S)

Duration of study: October 2022 until February 2023

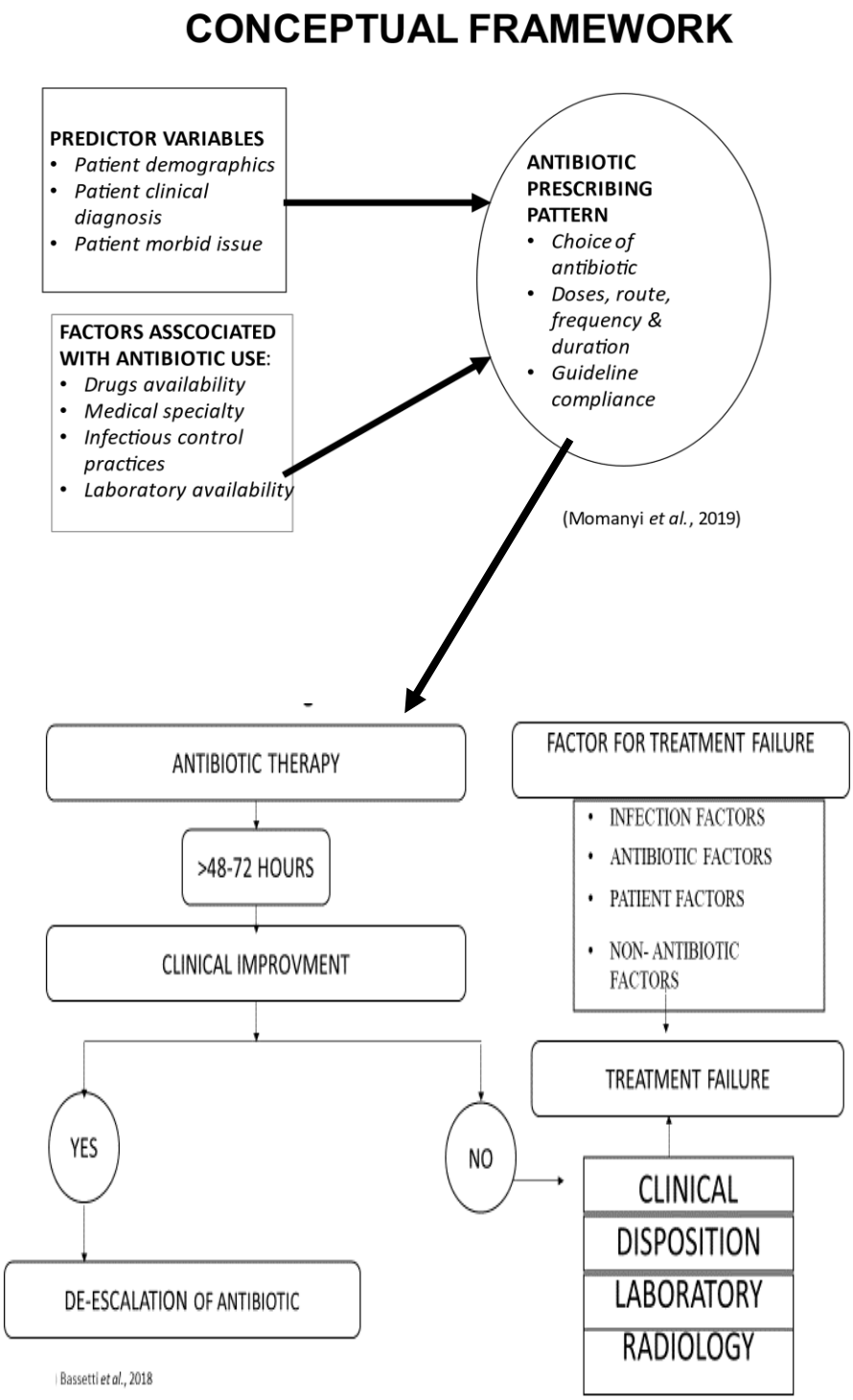
4.3 STUDY POPULATION

Reference population: All patients who were admitted to pediatric and adult general medical wards at Hospital USM

Source population: All inpatient patients from the pediatric general ward and adult general medical wards who were commenced on antibiotics during the ward admissions from 1st September 2022 till 31st October 2022

Sampling frame: All inpatient patients from the paediatric general ward and adult general medical ward who were commenced on antibiotics during admission from 1st September 2022 till 31st October 2022 and had fulfilled the inclusion criteria and exclusion criteria

4.4 Conceptual framework



4.5 OPERATIONAL DEFINITION

Antibiotics are referred to as medicines used to prevent and treat bacterial infections and are further classified into the group such as penicillin, penicillin with β-lactamase inhibitor, macrolide, and others. Sepsis defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. While organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10% (Singer et al., 2016).

Table 1: Sequential [Sepsis-related] Organ Failure Assessment (SOFA) Score.

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2, mmHg (kPa)	⩾400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3$ μL^{-1}	⩾150	<150	<100	<50	<20
Liver					
Bilirubin, mg dL^{-1} ($\mu mol\ L^{-1}$)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ⩾ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ⩽ 0.1 or norepinephrine ⩽ 0.1[a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[a]
Central Nervous System (CNS)					
Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg dL^{-1} ($\mu mol\ L^{-1}$)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL per day				<500	<200

FIO_2: fraction of inspired oxygen; MAP: mean arterial pressure; PaO_2: partial pressure of oxygen.
[a]Catecholamine doses are given as $\mu g\,kg^{-1}\,min^{-1}$ for at least 1 h.
[b]Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.

(Singer et al., 2016)

The empirical antibiotic therapy was defined as the initial antibiotic regimen started within 24 hours of admission without any positive culture to direct the therapy (Mettler et al., 2007). Targeted antibiotic is defined when antibiotic was prescribed based on causative organisms which proven by presence positive culture and the susceptibility to an antibiotic (Avis et al., 2021). Prophylaxis antibiotics is defined as the administration of antibiotics before contamination by surgical incision has occurred and is given with the intention of preventing infection (Smith, 2015).

Antibiotic resistance is defined when an organisms become non responsive to an antibiotic and proven clinically based on minimum inhibitory concentration (MIC) breakpoints(Martínez et al., 2015). Resistant organism defined any bacteria that developed antibiotic resistance and proven clinically based on minimum inhibitory concentration (MIC) breakpoints(Martínez et al., 2015) .Example of these are drug-resistant *Campylobacter*, drug-resistant *Candida*, extended-spectrum *β*-lactamase (ESBL)-producing *Enterobacteriaceae*, vancomycin-resistant *Enterococci (VRE)*, multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*, drug-resistant *nontyphoidal Salmonella*, drug-resistant *Salmonella serotype Typhi*, drug-resistant *Shigella*, methicillin-resistant *Staphylococcus aureus (MRSA)*, drug-resistant *Streptococcus pneumoniae (S. pneumoniae)* and drug-resistant *Tuberculosis (TB)* (Frieden T, 2013).

Persistent culture defined as finding of an organism in more than one separate cultures for longer than a 2-day period in a single infection episode (Kang et al., 2013).

Antibiotic failure referred to termination or new prescription of a different antibiotic drug(s) or the presence of any parameter of antibiotic failure either clinical, disposition , laboratory or radiological (based on tables 1) within 48- 72 hours of initiation of antibiotics (Neill et al., 2022).

PARAMETER OF TREATMENT FAILURE	**PARAMETERS ASSESSED AFTER 48-72 HOURS**
Clinical	Death, or Persistent symptoms (unresolved symptoms that the patient presented that contributed to the infection that are currently been treated with antibiotics)
Disposition	Admission to ICU (A new decision due to clinical deterioration after 72 hours on the antibiotics)
Laboratory	Persistent culture from either urine, blood or sputum from the admission, or Abnormal FBC count :leucocytosis or thrombocytopenia (based on age) after 72 hours of antibiotic prescribed, or High CRP (no 50 % reduction of CRP).
Radiological	Progressive worsening radiological imaging compared to the initial upon presentation.

Table 2: Parameter Of Antibiotic Failure

Site of infection defined as source of infection and categorised according to the system due to wide variation of data.

Infection Site	**Definitions**
Blood	This is defined by any bacteraemia infection without source of infection
CNS	Infections involving the brain (cerebrum and cerebellum), spinal cord, optic nerves, and their covering membranes—example meningitis, encephalitis, and abscesses (Archibald and Quisling, 2013).
ENT	Infection that involved the ear , nose and throat or any structure in between them such as otitis media, otitis externa, pharyngitis , tonsillitis
GIT	Defined by any infection of gastrointestinal tract that consists of the oral cavity, pharynx, oesophagus, stomach, small intestine, and large intestine, liver such as candida oesophagitis , *helicobacter pylori* infection ,acute gastroenteritis , hepatitis and lining covering including peritonitis (Atmar and Estes, 2016).

Respiratory	Defined as any infectious disease of the lower respiratory tract infections (LRTIs) include acute bronchitis, bronchiolitis, pneumonia , bronchopneumonia and tracheitis (B. et al., 2019).
Genitourinary	Infections of the genitourinary tract include uncomplicated and complicated lower urinary tract infections (UTIs); prostatitis; pyelonephritis; renal abscesses; epididymitis and orchitis; and vaginitis, metritis, and pyometra (Sykes and Westropp, 2013).
Skin	The skin infection could be either primary infection which have a characteristic clinical picture and disease course, caused by a single pathogen, and usually affect normal skin. Impetigo, folliculitis, and boils are common types. While Secondary infections occur in skin that is already diseased such as Intertrigo and toe web infection. ("Microbial Infections of Skin and Nails - Medical Microbiology - NCBI Bookshelf," 1996).
Eye	Referred to infection involving the eye such conjunctivitis, endophthalmitis , keratitis or any structure in between.
Cardio	Defined by infection involving the cardiac structure includes pericardium, valves such endocarditis , cardiac wall myocarditis or abscess , of any cardiac devices infection (Edwards et al., 2018)
Others	Any infection that are not defined in other categories such as leptospirosis , scrub typhus.

Table 3 : Operational Definition Of Site Of Infection

Definition of factors associated with antibiotic failure.

Factors associated with antibiotic failure	**Variables**
INFECTION FACTORS Secondary bacteraemia -Blood culture (Invasive disease)	Bacteraemia was defined as secondary when laboratory examination showed infection by the same microorganism at a distant site in the same time or up to three days earlier (Kwiecińska-Piróg et al., 2018).
Resistance organisms	Any organism with resistance to an antibiotic and proven clinically based on minimum inhibitory concentration (MIC) breakpoints (Martínez et al., 2015).

Presence of any collection pus /Large abscess more than 5 cm	Drainage is necessary for large abscesses, equal to or larger than 5 cm in size as patients with large abscesses have a high likelihood of failure with only medical therapy (Tan et al., 2006).
Multilobes infiltrates - extensive disease	Multilobes pneumonia was defined as chest-radiograph infiltrates involving ≥2 lobes (Liapikou et al., 2016).
ANTIBIOTIC FACTORS Antibiotic type (spectrum)	This is defined by type of antibiotic prescription either empirical , targeted or prophylaxis as this may contribute to the failure of an antibiotic prescription.
Guideline Compliances	Guideline compliance is defined as prescription the recommended first-line or preferred agent, route, dose, and frequency, according to the below guidelines and adult patients, National Antimicrobial Guideline 2019 , 3rd Edition (NAG 2019), the Antimicrobial Stewardship Program (ASP) Guide To Antimicrobial Therapy 2022 or paediatrics patient, National Antimicrobial Guideline 2019 , 3rd Edition (NAG 2019) and Pediatric protocol 4th edition.