

**ASSESSMENT OF PREVALENCE AND OUTCOMES OF
COMMON INFECTIONS AND PHYSICIANS'
PERCEPTION TOWARDS ANTIMICROBIAL
PRESCRIBING AMONG GERIATRIC PATIENTS IN
PENANG, MALAYSIA**

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UNIVERSITI SAINS MALAYSIA

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PENANG, MALAYSIA**

by

ALI AKHTAR

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TABLE OF CONTENTS

| | |
|---|-------------|
| ACKNOWLEDGEMENT | ii |
| TABLE OF CONTENTS | iii |
| LIST OF TABLES..... | vi |
| LIST OF APPENDICES..... | viii |
| ABSTRAK..... | ix |
| ABSTRACT | xii |
| CHAPTER 1 INTRODUCTION | 1 |
| 1.1 History of Infectious Diseases | 1 |
| 1.2 Aging Demographics | 2 |
| 1.3 Epidemiology of Mortality, Infections and Aging | 3 |
| 1.3.1 Causes of Death | 3 |
| 1.3.2 Common infections in Geriatrics | 4 |
| 1.4 Approach to Antimicrobial Therapy among Geriatric Population | 7 |
| 1.5 Antimicrobial Resistance | 8 |
| 1.6 Problem Statement | 10 |
| 1.7 Study Objectives..... | 13 |
| 1.7.1 General Objective | 13 |
| 1.7.2 Specific Objectives | 13 |
| CHAPTER 2 LITERATURE REVIEW | 14 |
| 2.1 Respiratory tract infections among geriatric population | 14 |
| 2.2 Urinary Tract Infections among geriatrics | 21 |
| 2.3 Skin Infections among older people..... | 30 |
| 2.4 Medication Regimen Complexity / Polypharmacy | 36 |
| 2.5 Health care providers perceptions about antimicrobial usage and resistance..... | 40 |
| CHAPTER 3 METHODOLOGY | 49 |
| 3.1 Introduction | 49 |

| | | |
|-----|--|-----------|
| 3.2 | Study population and inclusion criteria..... | 50 |
| 3.3 | Ethical Approval..... | 50 |
| 3.4 | Quantitative research method..... | 51 |
| | 3.4.1 Quantitative Study Design..... | 51 |
| | 3.4.2 Data Collection..... | 51 |
| | 3.4.3 Medication Regimen Complexity Index..... | 52 |
| | 3.4.4 Data Analysis | 53 |
| 3.5 | Qualitative Research Method | 53 |
| | 3.5.1 Qualitative Study Design..... | 53 |
| | 3.5.2 Sampling method and sample size | 54 |
| | 3.5.3 Interview Guide..... | 54 |
| | 3.5.4 Data Collection..... | 56 |
| | 3.5.5 Data Management and Analysis..... | 57 |
| | CHAPTER 4 RESULTS..... | 59 |
| 4.1 | Quantitative Research Phase | 59 |
| | 4.1.1 Respiratory Tract Infections Among Geriatrics Population | 59 |
| | 4.1.2 Urinary Tract Infections Among Geriatrics Population | 67 |
| | 4.1.3 Skin Infections Among Geriatrics Population..... | 74 |
| 4.2 | Qualitative Research Phase | 82 |
| | 4.2.1 Physicians Perceptions towards Antimicrobials Prescribing and Antimicrobial Resistance..... | 82 |
| | CHAPTER 5 DISCUSSION..... | 93 |
| 5.1 | Quantitative Research Phase | 93 |
| | 5.1.1 Respiratory Tract Infections among Geriatric Patients | 93 |
| | 5.1.2 Urinary Tract Infections among Geriatric Patients..... | 97 |
| | 5.1.3 Skin Infections among Geriatric Patients | 100 |
| 5.2 | Qualitative Research Phase | 104 |
| | 5.2.1 Physicians Perceptions Towards Antimicrobial Prescribing and | |

| | |
|---|------------|
| Antimicrobial Resistance..... | 104 |
| CHAPTER 6 CONCLUSION..... | 108 |
| CHAPTER 7 LIMITATIONS AND RECOMMENDATIONS..... | 111 |
| REFERENCES | 113 |
| APPENDICES | |

LIST OF TABLES

| | | Page |
|------------|--|-------------|
| Table 4.1 | Distribution of the socio-demographic data among the overall study population with respiratory tract infections..... | 60 |
| Table 4.2 | Gender base distribution of data among the study population with respiratory tract infections..... | 61 |
| Table 4.3 | List of Antibiotics and Inhaled Medications among Study Population..... | 62 |
| Table 4.4 | Medication regimen complexity index by Sections..... | 63 |
| Table 4.5 | Association between socio-demographic characteristics and treatment outcomes among study population with respiratory tract infections..... | 64 |
| Table 4.6 | Predictors Affecting the Improved Outcomes of Respiratory Tract Infections among Study Population..... | 66 |
| Table 4.7 | Distribution of the socio-demographic data among the overall study population with urinary tract infections..... | 68 |
| Table 4.8 | Gender base distribution of data among the study population with urinary tract infections..... | 69 |
| Table 4.9 | List of oral medications among study Population..... | 70 |
| Table 4.10 | Medication regimen complexity index by Sections..... | 70 |
| Table 4.11 | Association between socio-demographic characteristics and treatment outcomes among study population with urinary tract infections..... | 71 |
| Table 4.12 | Predictors Affecting the Improved Outcomes of Urinary Tract Infections among Study Population..... | 73 |
| Table 4.13 | Distribution of the socio-demographic data among the overall study population with skin infections..... | 75 |
| Table 4.14 | Gender base distribution of data among the study population with skin infections..... | 76 |

| | | |
|------------|---|----|
| Table 4.15 | List of oral and topical medications among study Population..... | 77 |
| Table 4.16 | Medication regimen complexity index by Sections..... | 78 |
| Table 4.17 | Association between socio-demographic characteristics and treatment outcomes among study population with skin infections..... | 79 |
| Table 4.18 | Predictors Affecting the Improved Outcomes of Skin Infections among Study Population..... | 81 |
| Table 4.19 | Demographics of Physicians..... | 83 |
| Table 4.20 | Themes and sub themes identified from the transcribed Interviews..... | 84 |

LIST OF APPENDICES

APPENDIX A Data Collection Form for Retrospective Study
(Objectives 1,2 and 3)

APPENDIX B Interview Guide (Objective 4)

APPENDIX C Ethical Approvals

**PENILAIAN PREVALEN DAN KESAN JANGKITAN LAZIM DAN
PERSEPSI DOKTOR TERHADAP PRESKRIPSI DAN KERINTANGAN
ANTIMIKROBIAL DALAM KALANGAN PESAKIT GERIATRIK DI
PULAU PINANG, MALAYSIA**

ABSTRAK

Geriatric mudah terkena jangkitan, terutamanya jangkitan saluran pernafasan, jangkitan saluran kencing dan jangkitan kulit akibat sistem imun mereka yang terjejas. Selain itu, penggunaan antimikrob yang tidak perlu merupakan masalah yang muncul di seluruh dunia. Objektif utama projek penyelidikan ini adalah untuk menilai kelaziman dan hasil rawatan jangkitan saluran pernafasan, jangkitan saluran kencing dan jangkitan kulit di kalangan pesakit geriatrik, serta persepsi doktor yang bekerja di hospital awam berkenaan penggunaan dan kerintangan antimikrob. Kajian keratan rentas telah dijalankan di tiga jabatan (pernafasan, urologi, dermatologi) Hospital Pulau Pinang, Malaysia. Pesakit berumur ≥ 65 tahun dengan diagnosis jangkitan saluran pernafasan, jangkitan saluran kencing dan jangkitan kulit dengan rekod perubatan lengkap mereka telah dimasukkan dalam kajian. Jangkitan saluran pernafasan yang paling lazim adalah radang paru-paru komuniti (65.6%) diikuti oleh penyakit paru-paru obstruktif kronik (20.7%), bronkitis (8.2%) dan radang paru-paru yang dijangkiti di hospital (5.5%). Merokok (OR = 0.383 [95% CI: 0.186-0.787]; $p = 0.009$), penggunaan alkohol (OR = 0.583 [95% CI: 0.357-0.951]; $p = 0.031$), polifarmasi (OR = 1.858 [95% CI: 1.245-2.774]; $p = 0.002$) dan kehadiran penyakit yang lain (OR = 0.643 [95% CI: 0.429-0.964]; $p = 0.032$) adalah faktor signifikan secara statistik yang dikaitkan dengan hasil rawatan jangkitan saluran pernafasan dalam kalangan geriatrik. Cystitis (37.6%) adalah jangkitan saluran kencing yang paling lazim dalam kalangan pesakit geriatrik diikuti oleh bakteria asimtomatik

(31.9%), pyelonephritis (13.9%), urosepsis (10.2%) dan prostatitis (6.4%). Faktor yang dikaitkan dengan hasil rawatan jangkitan saluran kencing adalah jantina (OR = 1.529 [95% CI: 1.011-2.312]; p = 0.044), polifarmasi (OR = 0.647 [95% CI: 0.426-0.966]; p = 0.033) dan kehadiran komorbiditi lain (OR = 1.872 [95% CI: 1.205-2.907]; p = 0.002). Jangkitan kulit yang paling lazim ialah ekzema (27.6%) diikuti oleh dermatitis (13.8%), xerosis (13.8%), dan pemfigoid bulosa (8.8%). Umur (OR = 1.830 [95% CI: 1.108-3.024]; p = 0.018), penggunaan alkohol (OR = 0.546 [95% CI: 0.322-0.927]; p = 0.025), polifarmasi (OR = 1.917 [95% CI: 1.003-3.663]; p = 0.049), dan kehadiran komorbiditi lain (OR = 1.774 [95% CI: 1.086-2.898]; p = 0.022) adalah faktor terpenting yang mempengaruhi hasil rawatan jangkitan kulit dalam kalangan geriatrik. Fasa kualitatif kajian melibatkan pakar perubatan daripada kepakaran yang berbeza. Temu bual tersebut melibatkan sebanyak 12 temu bual separa berstruktur, bersemuka menggunakan teknik persampelan bertujuan. Semua temu bual dirakam secara audio, kemudian ditranskripsikan ke dalam Bahasa Inggeris dan dianalisis dengan analisis kandungan tematik. Empat tema utama telah dikenal pasti: (1) menetapkan corak doktor mengenai antimikrob; (2) sumber pakar perubatan untuk mengemas kini pengetahuan mereka tentang antimikrobial; (3) rintangan antimikrob; (4) persepsi doctor tentang pengurusan jangkitan mereka. Kesimpulannya, radang paru-paru yang dijangkiti dari komuniti adalah jangkitan saluran pernafasan yang paling lazim diikuti oleh penyakit paru-paru obstruktif kronik, bronkitis, dan radang paru-paru yang dijangkiti di hospital; Cystitis adalah jangkitan saluran kencing yang sangat lazim diikuti oleh bakteria asimptomatik, pielonefritis, urosepsis dan prostatitis; jangkitan kulit yang paling lazim adalah ekzema diikuti oleh dermatitis, xerosis, dan pemfigoid bulosa dalam kalangan populasi kajian. Jantina, umur, merokok, pengambilan alkohol, polifarmasi dan kehadiran komorbiditi lain adalah

faktor penting secara statistik yang dikaitkan dengan hasil rawatan dalam kalangan pesakit geriatrik. Di samping itu, pakar perubatan percaya dengan aktiviti pendidikan yang kerap dan pengetahuan terkini tentang garis panduan antimikrob boleh mengubah tingkah laku preskripsi doktor untuk mengoptimumkan penggunaan antimikrobial.

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ABSTRACT

Geriatrics are susceptible to infections, especially respiratory tract infections, urinary tract infections and skin infections due to their compromised immune system. Moreover, unnecessary antimicrobial use is an emerging problem throughout the world. The main objectives of current research project are to assess the prevalence and outcomes of respiratory tract infections, urinary tract infections and skin infections among the geriatric patients, along with the perceptions of physicians working at public hospital about antimicrobial use and resistance. A cross-sectional study was conducted at three departments (respiratory, urology, dermatology) of Hospital Pulau Pinang, Malaysia. Patients aged ≥ 65 years with confirmed diagnosis of respiratory tract infections, urinary tract infections and skin infections with their complete medical records were included in the study. The most prevalent respiratory tract infection was community acquired pneumonia (65.6%) followed by chronic obstructive pulmonary disease (20.7%), bronchitis (8.2%) and hospital-acquired pneumonia (5.5%). Smoking (OR = 0.383 [95% CI: 0.186-0.787]; $p = 0.009$), alcohol consumption (OR = 0.583 [95% CI: 0.357-0.951]; $p = 0.031$), polypharmacy (OR = 1.858 [95% CI: 1.245-2.774] ; $p = 0.002$) and presence of other co-morbidities (OR = 0.643 [95% CI: 0.429-0.964]; $p = 0.032$) are statistically significant factors associated with treatment outcomes of respiratory tract infections among geriatrics. Cystitis (37.6%) was the most prevalent urinary tract infection among geriatric patients followed by asymptomatic bacteriuria (31.9%), pyelonephritis (13.9%),

urosepsis (10.2%) and prostatitis (6.4%). Factors associated with treatment outcomes of urinary tract infections were gender (OR = 1.529 [95% CI: 1.011-2.312]; $p = 0.044$), polypharmacy (OR = 0.647 [95% CI: 0.426-0.966]; $p = 0.033$) and presence of other comorbidities (OR = 1.872 [95% CI: 1.205-2.907]; $p = 0.002$). The most prevalent skin infections were eczema (27.6%) followed by dermatitis (13.8%), xerosis (13.8%), and bullous pemphigoid (8.8%). Age (OR = 1.830 [95% CI: 1.108-3.024]; $p = 0.018$), alcohol consumption (OR = 0.546 [95% CI: 0.322-0.927]; $p = 0.025$), polypharmacy (OR = 1.917 [95% CI: 1.003-3.663]; $p = 0.049$), and presence of other co-morbidities (OR = 1.774 [95% CI: 1.086-2.898]; $p = 0.022$) are the most important factors that affected the treatment outcomes of skin infections among geriatrics. Qualitative phase of the study involved physicians from different specialties. The interview included a total of 12 semi-structured, face-to-face interviews using purposive sampling technique. All interviews were audio recorded, then transcribed into English language and analysed by thematic content analysis. Four major themes were identified: (1) prescribing patterns of physicians regarding antimicrobials; (2) Physician's sources for updating their knowledge about antimicrobials; (3) antimicrobial resistance; (4) Physician's perceptions about their management of infections. In conclusion, community acquired pneumonia was the most prevalent respiratory tract infection followed by chronic obstructive pulmonary disease, bronchitis, and hospital-acquired pneumonia; Cystitis was the highly prevalent urinary tract infection followed by asymptomatic bacteriuria, pyelonephritis, urosepsis and prostatitis; the most prevalent skin infections were eczema followed by dermatitis, xerosis, and bullous pemphigoid among the study population. Gender, age, smoking, alcohol consumption, polypharmacy and presence of other co-morbidities are statistically significant factors associated with treatment

outcomes among geriatric patients. In addition, physicians believed in regular educational activities and updates about the latest antimicrobial guidelines may change the prescribing behavior of physicians to optimize the use of antimicrobials.

CHAPTER 1

INTRODUCTION

1.1 History of Infectious Diseases

From many decades, mankind faced various kinds of infectious diseases throughout the world. Prior to modern world of antimicrobials, infections were the major cause of mortality among human beings and even today one-third deaths all around the world are due to infections (Lyons & Petrucelli, 1978). Millions of people died in mid-twentieth century due to outbreaks of different diseases like plague, typhus, cholera, typhoid, smallpox, tuberculosis and diphtheria globally. In addition, scarlet fever, rheumatic fever, pertussis, measles, mumps, syphilis and poliomyelitis were resulted in mortality as well as cause deformities, disabilities, social rejection and functional capacity limitation (Lyons & Petrucelli, 1978). In World War II, infections accounted for more mortalities than with battle injuries (Murphy, 1998). Poor hygiene and sanitation, inadequate immunity against different diseases, close contact and higher stress levels among the military individuals made them vulnerable against typhoid, dysentery, malaria, smallpox, measles and tuberculosis (Murphy, 1998). Individuals aged 65 years or more are more susceptible towards infections than younger individuals because of decline in immune function particularly in cell-mediated immunity (Ben-Yehuda & Weksler, 1992).

After the origin of germ theory of diseases, field of medical advances in sanitation, antisepsis, public health measures, immunization and antibiotics which reduces the impact of infectious diseases on morbidities and mortalities among human population in middle of twentieth century (Murphy, 1998). In the last half of 20th century, vaccination and antimicrobial therapy successfully conquer the lethal effects of

poliomyelitis, smallpox and other different infections (Murphy, 1998). Nevertheless, Center for Disease Control and Prevention (CDC) reported the first case of Acquired Immunodeficiency Syndrome (AIDS) in 1981 and in 1984, they reported that AIDS could be caused by human immunodeficiency virus (HIV) (Murphy, 1998). AIDS has become a global health care problem, striking the young, old, rich, poor, men, women and people of all ethnic and racial backgrounds. In past two decades, many new pathogens were emerged like Ebola virus, Hanta virus together with antibiotic-resistant organisms that includes penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, vancomycin resistant enterococci, multiple drug-resistant gram-negative bacilli and *Clostridium difficile* (Boyce, 2008; Gerding, Muto, & Owens Jr, 2008; Kauffman, 2003; Yoshikawa & Thomas, 1998). These new and changing infectious diseases have a great impact on the health of human beings in the future and infectious diseases clinicians and specialists should focus on developing different strategies to overcome the burden of infectious diseases for the better care of general public (Yoshikawa & Thomas, 2002).

1.2 Aging Demographics

The average life expectancy was recorded in 1900 was estimated to be 47 years (48 years for females and 46 years for males) in the United States (U.S.) (National Center for Health Statistics, 1986). The population of individuals having age 65 years or more were only 4% of total U.S. population (Yoshikawa & Norman, 2009). The life expectancy increases drastically in later half of 20th century due to reduction in childhood mortality rate because of advancements in medical field to overcome the

impact of infectious diseases. In the modern era, the average life expectancy of U.S. population is estimated to be 75 years (80 years for females and 73 years for males) (National Center for Health Statistics, 1986). Moreover, elderly population (individuals aged 65 years or more) is now become the 13% of total population of U.S. It is expected that in next thirty years, the percentage of elderly population reaches up to 21% of the total population (Yoshikawa & Norman, 2009).

Asia's population aged 60 and above is projected to increase from 507 million in 2015 to 1293 million by 2050 (Tey et al., 2016). The speed of aging in Asia is unprecedented and poses great challenges to existing models of caregiving and social support (McCutcheon & Pruchno, 2011). The policies and systems in some countries are lacking for this dramatic demographic shift (Arun, 2013; Sasat & Bowers, 2013; Zhang, Guo, & Zheng). In 2020, it was estimated that Malaysian population aged 65 years and above stood at 7% (Statista, 2020a). Malaysia is currently facing the prospect of an aging population, and the latest statistical data predicted this to be happening as soon as in 2030. According to a statement by Malaysia's Chief Statistician in July 2019, the 15% threshold would be crossed in 2030 (Statista, 2020a).

1.3 Epidemiology of Mortality, Infections and Aging

1.3.1 Causes of Death

From the beginning of 20th century, infections were responsible for the half of the top ten causes of death in U.S. Unfortunately, children were the most affected group due to infectious diseases. With the discovery of antibiotics and immunization, many of the life-threatening infections were prevented or mitigated. With the increase in life expectancy of U.S. population, there was decrease in the rate of mortality due to infections. In modern times, cancer, heart disease and stroke are the major causes of death in U.S. population. Moreover, in elderly population, influenza and pneumonia are

the 4th, diabetes mellitus and infections are at number six and bacteremia is at number 9th most common cause of death (National Center for Health Statistics, 1995).

According to Malaysian Census, 7.9% of the total population is above 60 years with 5.1% aged more than 65 years of age. This increment is in line with the transition towards an aging population of Malaysia (NoorAni et al., 2018). Aging population has a great impact on health care system in developed as well as in developing countries. Around 71% of deaths around the world were recorded due to non-communicable diseases. In Addition, more than 15 million people die from non-communicable diseases every year, in which 85% deaths were recorded in low and middle-income countries (WHO, 2021). Higher rates of mortality and morbidity, increased risk of hospitalization, particularly more specialized care are the major factors contributed with the increase in age which ultimately increased the expenditure of health care system (Mafauzy, 2000; Parker & Thorslund, 2007). To overcome this situation, studies should be conducted on the pattern of different types of infections and their current management among the aging community and helps the stakeholders for better planning for geriatrics.

1.3.2 Common infections in Geriatrics

Even though older people are more susceptible for acquiring different types of infections, however, there is a little data available that reports that age is directly associated with the greater risk of infections. Whether aging alone vs age-related diseases, that have negative impact on the host resistance to infections makes older people more vulnerable to different infections remains controversial and debatable (Castle, Uyemura, & Makinodan, 2006). Moreover, many studies reported that there are certain types of infections that occur more frequently in older people and their mortality and morbidity rates are also high as compared in young individuals

(Yoshikawa, 1981, 1983, 1997, 1999). Respiratory tract infections, urinary tract infections, skin and soft tissue infections, infective endocarditis, herpes zoster and tuberculosis appear to have a special predilection for geriatrics. In addition, mortality rate due to these infections is appeared to be three times higher in older people as compared with young adults with the same infection (Yoshikawa, 1994, 1997, 2009). Several possible risk factors contributed in this higher rate of mortality and morbidity which include; chronic underlying diseases, decreased host resistance, age-related reduced physiologic reserve capacity, delayed or poor response to antimicrobial therapy, increased risk of adverse effects and high chance of nosocomial infections (Yoshikawa, 1994).

The risk for developing an infection, and to some extent its severity, is directly proportional to the inoculum and virulence of the pathogen(s) and inversely proportional to the integrity of the host defences. Aging and comorbidities associated with aging affect all three of these factors. It is the interplay of these three variables that account for the increased susceptibility to and severity of infections in the geriatric population. Impaired immunity is much more associated with disease burden than the chronological age (Castle, Uyemura, Fulop, & Makinodan, 2007).

Older adults with chronic diseases (e.g., diabetes mellitus, chronic obstructive pulmonary disease (COPD) or heart failure) are more susceptible to common infections and exhibit weaker vaccine response than those without underlying health problems (Castle et al., 2007). Age-related organ-specific physiologic changes also increase the risk of infection and affect the clinical presentation of infectious syndromes.

The rate of RTIs increases rapidly with age. Bacteria are responsible for most of the RTI in older adults. Although 1 out of every 1,000 cases needs to be hospitalized,

this rate is 12 in 1,000 for patients over 75 years and 33 in 1,000 for nursing home patients. As in many diseases, the clinical manifestation of pneumonia may be atypical and subtle in older patients. Sore throat, headache following nose run, weakness, fever, chills, shortness of breath, chest pain, and productive cough are typical clinical symptoms for pneumonia. However, these symptoms may not be seen especially in the frail aged or in patients with cognitive impairment and multi-morbidity. Complaints may include fatigue, loss of appetite, anorexia, confusion, delirium, falls, or sometimes urinary incontinence. Older adults may not have fever even in severe infections (Yoshikawa & Norman, 2017). Around 50% of all CAP occurs in adults older than 65 years of age (Blasi et al., 2017). Severe sepsis may be present in approximately one-third of all patients with community acquired pneumonia at the time of admission to the emergency room (Cillóniz, Rodríguez-Hurtado, & Torres, 2018).

Bacteriuria is rarely seen in young men, its prevalence reaches $\geq 5\%$ in those ≥ 65 years in the community setting. On the other hand, bacteriuria occurs in 5–10% of women aged >65 years as compared to 2–5% of young women (Yoshikawa & Norman, 2017). In the absence of typical clinical symptoms of an infection, it is important to differentiate asymptomatic bacteriuria from symptomatic bacteriuria. In an elderly critically ill patient with an indwelling urinary catheter, a persistently sterile urine culture should not be attempted since repetitive courses of antibiotic therapy simply select more resistant bacteria. On the other hand, in a critically ill patient, it proves extremely difficult to differentiate between asymptomatic bacteriuria and real UTI (Cortes-Penfield, Trautner, & Jump, 2017). Clinical instability usually would require a course of antimicrobial therapy depending on the susceptibility of the bacteria isolated from urine (Pappas et al., 2016).

1.4 Approach to Antimicrobial Therapy among Geriatric Population

Approaches used for the treatment of infections in elderly population could be different from younger individuals, however, basic guidelines for the treatment of infections with antimicrobials generally apply on both. These basic guidelines include rapid and early diagnosis, initiation of broad-spectrum empirical therapy for the suspected cause of infection followed by specific antimicrobial agent based on the laboratory results (Yoshikawa & Thomas, 1990). In elderly population, the main cause of delay in initiation of antimicrobial empirical therapy is the delays in diagnosis of infection because in older people many hallmarks signs of infection may be absent or blunted (Yoshikawa & Thomas, 1990).

The appropriate selection of antimicrobial agent is based on number of factors that include proper identification of pathogen, site of infection, antimicrobial resistance pattern, pharmacodynamics and pharmacokinetics properties of the specific agent along with its possible harmful effects to the patient (Yoshikawa & Norman, 2009).

Previous studies reported in a literature review suggested that selection and timing of administration of antimicrobial agents are the main factors of death in critical ill patients with serious infections (Paul, Benuri-Silbiger, Soares-Weiser, & Leibovici, 2004). Moreover, the selection of antimicrobial agent used for empirical therapy should be based on condition of the patient's illness, presence of other co-morbidities, previous exposure to antimicrobials and history of any drug allergy (Paul et al., 2004).

1.5 Antimicrobial Resistance

In the developed and developing countries of the world, the prevalence of antimicrobial resistance is an emerging problem. The emergence of *Staphylococcus aureus* with decreased sensitivity to vancomycin (CDC, 2015), worldwide presence of *Streptococcus pneumoniae* highly resistant to high-dose penicillin (Carratala, Marron, Fernandez-Sevilla, Liñares, & Gudiol, 1997), and unabated progression of multi-resistant *Mycobacterium tuberculosis* present unprecedented challenges for clinicians. Antibiotic-resistant pathogens were accounted for over half of the nosocomial infections in United States (Yoshikawa & Norman, 2009). Antimicrobial resistance develops when exposure to the agent fails to completely eradicate the infection. Factors associated with the emergence of antimicrobial resistance includes enzymatic modification or inactivation, altered target sites, bypass pathways and decreased uptake. Multiple-drug resistance is generally due to conjugal transfer of plasmids containing multiple resistant genes. Genetic mutations may increase resistance by altering drug targets, destroying antimicrobials and enhancing drug efflux (Hawkey, 1998). Centre for disease control and prevention (CDC) developed many evidence-based guidelines for the prevention of antimicrobial resistance but adherence to these guidelines by the health care professionals is not optimal (CDC, 2002). Four areas were emphasized by CDC to improve the prescribing behaviors of physicians to enhance the rational use of antimicrobials that includes; preventing infections, diagnosing and treating infection effectively, using antimicrobials wisely and preventing transmission (CDC, 2002). The importance of considering antibiotic resistance when treating at-risk populations such as elderly is highlighted by their greater vulnerability to the adverse consequences of antibiotic resistance.

According to National Surveillance on Antibiotic Utilization coordinated by Pharmacy Practice and Development Division, Ministry of Health, Malaysia, university hospitals showed the highest total antibiotic utilization overall and in ICU wards with median (interquartile range, IQR) of total DDD/1000 patient days of 324.14 (267.96-327.80) and 938.72 (727.13-1067.64), respectively, between 2008 and 2017 (MOH Malaysia, 2020). The most common antibiotic used in “All Wards” and ICU over the period of 10 years is reported to be Cephalosporin with median percentage of utilization of 68.39 (IQR: 63.79-68.72) and 43.21 (IQR: 43.18-45.30), respectively, from total antibiotic utilization (MOH Malaysia, 2020).

Antibiotic utilization had increased from 2008 to 2017 in Malaysia. Significant relationships existed between the utilisation of broad-spectrum antibiotics such as glycopeptides, carbapenems and penicillin-beta lactamase inhibitors (MOH Malaysia, 2020). Rational use of these agents must be evaluated to prevent unnecessary usage that could lead to the rise of resistant pathogens.

1.6 Problem Statement

Infections are leading causes of morbidity and mortality in the geriatric patients. Various factors including presence of co-morbidities, polypharmacy, decline in immune system may modify the frequency and severity of infections in elderly patients. Normal body reactions to ensuing infection, such as increased body temperature, may be blunted in those patients' causing difficulties in differential diagnosis between infection and other diseases (Esme et al., 2019). Impaired immunity is much more associated with disease burden than the chronological age. Older adults with chronic diseases (e.g., diabetes mellitus, chronic obstructive pulmonary disease (COPD) or heart failure) are more susceptible to common infections and exhibit weaker vaccine response than those without underlying health problems (Castle et al., 2007, Esme et al., 2019).

The irrational or unnecessary use of medications cause serious implications on the health of geriatric patients around the globe. Malaysia has similar concerns regarding the irrational usage of medications (Azmi, Fahad, et al., 2016; Bahri, Othman, Hassali, Shafie, & Ibrahim, 2009). The irrational use of medicines led to different types of adverse events, the risks of adverse drug reactions (ADRs) is increased, especially in geriatric patients or in co-morbid individuals who may have compromised physiologic functions (Margo et al., 2021). The irrational use of medicines is a global problem that reported in both developed and developing countries. In developing countries, this problem is vast and not well documented. Usually, communities of developing countries have limited knowledge and awareness on the safety of drugs commonly found in home and proper storage of medicines (Kheir, El Hajj, Wilbur, Kaissi, & Yousif, 2011).

Rational prescribing has significant importance for the elderly. However, the prescribing practice for this population is challenging for several reasons. Multiple comorbidities and complex treatment regimens render the elderly particularly vulnerable to drug-related adverse effects. In addition, prescribing in the elderly is often more problematic due to alterations in physiological functions, which can lead to compromised pharmacokinetics (Mallet, Spinewine, & Huang, 2007; Milton, Hill-Smith, & Jackson, 2008). Several instruments have been developed to assess the quality of prescribing (O'Mahony et al., 2015; Panel et al., 2015; Renom-Guiteras, Meyer, & Thürmann, 2015). WHO developed a set of prescribing indicators to evaluate the appropriateness of medication, including the number of drugs prescribed per medical appointment; the percentage of drugs prescribed by generic name; and the percentage of medical appointment with antibiotics, injections, and drugs prescribed from the essential drug list (WHO, 2002).

Several factors are involved to increase the susceptibility of infections among geriatric population. Due to increase in age, there is a burden of other comorbidities among geriatric adults such as renal insufficiency, diabetes, arthritis etc. Due to different comorbid conditions, these individuals become more prone to infections. Immunosenescence in geriatrics population due to increase in age make them infected with different types of infections as compared to young adults.

Previous studies reported that respiratory tract infection is the most common infection among the geriatric population followed by urinary tract infections and skin infections (Cristina et al., 2021, Jump et al., 2018 & Cairns et al., 2011). Therefore, present study focusses on the management of respiratory tract infections, urinary tract infections and skin infections among the geriatric population. Moreover, current study also explores physician's perceptions antimicrobial prescribing and antimicrobial

resistance. Therefore, this study is very important, to evaluate the prevalence of RTIs, UTIs, and SIs among geriatric patients, medication regimen complexity and factors associated with the treatment outcomes for the better management of above said infections among older people. In addition, this study provides in depth thoughts of physicians regarding their antimicrobial prescribing patterns and antimicrobial resistance in their daily practice.

1.7 Study Objectives

1.7.1 General Objective

To assess the management of common infections among geriatric patients and physicians' perception towards antimicrobial prescribing and resistance in a tertiary care hospital, Malaysia.

1.7.2 Specific Objectives

1. To determine the prevalence of different respiratory tract infections, medication regimen complexity and different factors involved in the treatment outcomes of respiratory tract infections (RTIs) among geriatrics in the tertiary care hospital in Northern region of Malaysia.

2. To evaluate the prevalence of different urinary tract infections, medication regimen complexity and identify different risk factors involved in the treatment outcomes of urinary tract infections (UTIs) among geriatrics in the tertiary care hospital in Northern region of Malaysia.

3. To determine the prevalence of skin infections and factors affecting the treatment outcomes of skin infections among among geriatrics in the tertiary care hospital in Northern region of Malaysia.

4. To explore and compare physicians' perspective on prescribing patterns and knowledge on antimicrobial use and resistance in relation to the management of common infections at a tertiary care hospital in Northern region of Malaysia.

CHAPTER 2

LITERATURE REVIEW

2.1 Respiratory tract infections among geriatric population

Respiratory tract infections (RTIs) are very common in all ages but most particularly, it effects elderly individuals due to their weak immune system along with the presence of other co-morbidities (Lieberman & Lieberman, 2003). The burden of RTIs among the elderly population significantly contributes increased risk of mortality, morbidity and costs throughout the world (Prina, Ranzani, & Torres, 2015). Around 85% of deaths among elderly population were recorded in United States due to RTIs, moreover, over 16.1 billion dollars were spent on RTIs in 2013 (Aronen et al., 2019). One-fifth of the total population in Europe is more than 65 years of age and they may increase up to 25% in 2030 (van Heijl et al., 2018). The incidence of RTIs is more in elderly individuals as compared to young ones (Meyer, 2010; Yoshikawa & Thomas, 2000), as the susceptibility to infections increases with the increase in age (Janssens & Krause, 2004; Millett, Quint, Smeeth, Daniel, & Thomas, 2013; Welte, Torres, & Nathwani, 2012). The mortality rate in individuals over 65 years of age increases approximately 6-7% with the presence of RTIs (van Asten et al., 2012) and the possible contributing factors are co-morbidities, weak immune system and poor response towards respiratory vaccines (Jartti et al., 2011b; Yu et al., 2011).

In developed countries, pneumonia is one of the major causes of death among elderly population. Furthermore, approximately 200 million cases of community acquired pneumonia (CAP) were reported every year with equal distribution among young children and adults, however, elderly individuals were the most affected group among the adult population (Ruuskanen, Lahti, Jennings, & Murdoch, 2011). With

presence of other co-morbidities and/or polypharmacy, occurrence of adverse drug reactions and drug-drug interactions also reduces the treatment outcomes of RTIs among elderly individuals (van Heijl et al., 2018).

As the occurrence of chronic diseases increases with the increase in age, therefore, the number of medications also increases accordingly (Kim et al., 2014; Sera & McPherson, 2012). A serious problem arises in pharmacotherapy of elderly population is the consumption of several medications simultaneously which leads to polypharmacy. Polypharmacy is defined as concurrent consumption of five or more medications regardless of duration of consumption and dosage form (Blozik, Rapold, von Overbeck, & Reich, 2013; Dovjak, 2012; Wickop & Langebrake, 2014). In older individuals, polypharmacy leads to many significant problems which includes: drug-drug interactions, adverse effects, decreased quality of life and other medical problems (Carvalho et al., 2012; Hofer-Dückelmann, 2013). In addition, polypharmacy also increases the rate of hospital admissions, length of stay, repeated hospitalizations and even death among the elderly population (Chiang-Hanisko, Tan, & Chiang, 2014). Therefore, proper medications should be prescribed to the older people according to their disease history, mental and physical health, drug resistance, memory, physical ability and support of their family members (Banerjee, Mbamalu, Ebrahimi, Khan, & Chan, 2011).

In elderly population, rate of mortality caused by RTIs increases up to 6 – 7% with the increase in age (van Asten et al., 2012). Other risk factors among older people with RTIs were underlying co-morbidities and poor response towards their treatment (Jartti et al., 2011a). The etiology of RTIs among older individuals could be different as compared with young population, which may require adjusted empirical therapy of antimicrobials. Moreover, the diagnosis of RTIs might be more challenging in elderly

population which could lower the threshold for prescribing the antimicrobials. In addition, with increase in age, changes in the human body might alter the pharmacodynamics and pharmacokinetics of antimicrobials (George et al., 2004). In Malaysia, pneumonia was the second highest cause of death across all ages in 2020 (Statista, 2020b). Community acquired pneumonia is associated with a 4.2% fatality rate (Azmi, Aljunid, et al., 2016) which is lower than other Western countries reports (7.7-12%) (Garcia-Vidal et al., 2008; Limper, 2012).

An observational prospective follow up study was conducted in Leiden, Netherlands to assess the preventive measures of respiratory tract infections among geriatrics. A total of 587 individuals were selected from the general population aged 85 years or above. Baseline data was collected from physicians practising in nursing homes as well as general physicians to predict the development of respiratory tract infections among geriatrics. Results showed that incidence of respiratory tract infections among included 85 years plus individuals were 94 per 1000 person years. Smoking, chronic obstructive pulmonary disease, glucocorticosteroid usage, stroke history, cognitive impairment and decline in functional capabilities were associated with the increased incidence of respiratory tract infections (Sliedrecht, den Elzen, Verheij, Westendorp, & Gussekloo, 2008).

A population based cross-sectional study conducted by Can-You Zhang *et al.* (2019) in China evaluated the prevalence and explored the risk factors of tuberculosis among geriatrics. Sputum samples were collected from the patients for bacteriological examination by microscopy. Multiple logistic regression was used to identify different risk factors of tuberculosis among the elderly study population. Estimated prevalence of active pulmonary tuberculosis and bacteriologically confirmed tuberculosis in elderly study population was 563.19 per 100,000 (95% CI 483.73 – 642.65) and

180.92 per 100,000 (95% CI 135.89 – 225.96) respectively. Increasing age, male gender, underweight individuals, rural areas residents, diabetes, previous tuberculosis history, close contact with tuberculosis patients were the potential risk factors identified for tuberculosis. In conclusion, active case finding could be implemented among geriatrics with diabetes, underweight individuals, previous history of tuberculosis and close contact with tuberculosis patients as a priority which will get significant yields and could be cost-effective.

A study conducted in Lisbon, Portugal evaluated causative agents and outcomes of respiratory tract infections among eighteen aged care homes with a total of 1022 elderly individuals. Nasopharyngeal swabs were taken from the residents with symptoms of respiratory tract infections. RT-PCR and PCR were carried out for respiratory syncytial virus, human Bocavirus, enterovirus, human coronavirus, enterovirus, human metapneumovirus, adenovirus, parainfluenza virus and influenza A/B. A total of 188 individuals had episodes of respiratory tract infections in which rhinovirus (n = 53) is the most common virus detected among the study population followed by influenza A (n = 19) and human Bocavirus (n = 14). Nineteen patients were suffering from severe infections in which 11 were fatal, *Legionella pneumophila*, human metapneumovirus, respiratory syncytial virus and rhinovirus were related with these fatalities. Severe infections were associated with age, respiratory disease and human metapneumovirus among the residents of aged care homes. This study concludes that causative agents were found in 60% of the respiratory tract infection episodes. Moreover, information regarding different respiratory viruses circulating in aged care homes increases the importance of screening different viruses and bacteria in severe cases of respiratory tract infections (Chasqueira et al., 2018).

Aronen and colleagues conducted a prospective follow up study in Turku, Finland to test whether inflammatory makers and nasopharyngeal swab test in older people associated with radiographically confirmed pneumonia. A total of 382 individuals aged 65 years or above were recruited in this study with respiratory tract infection symptoms. Nasopharyngeal swabs tests were conducted for 14 types of respiratory tract viruses along with white blood cell count and C-reactive protein. Radiologist analysed the chest radiographs. Clinical endpoints were the hospital revisits, length of hospital stay and death of the individual in the hospital ward. Median age of the included patients was 83 years. 29% of the patients were diagnosed with pneumonia, patients with more than one respiratory virus were 37%. Patients with over $15 \times 10^9/L$ white blood cell count and over 80mg/L of C-reactive protein value were associated with presence of pneumonia. Less visits to hospital ($p < 0.05$) was associated with the presence of respiratory virus, however, C-reactive protein ($p < 0.05$) value more than 100mg/L was associated with the death of the patient. Presence of other respiratory virus in confirmed diagnosed pneumonia patients was not significant ($p = 0.09$) in this study. Thus, current study concludes that white blood cell count and C-reactive protein values does not associated with the presence of respiratory viruses in pneumonia diagnosed geriatrics patients (Aronen et al., 2019).

Abdullah and his colleagues conducted a prospective study in India to evaluate the radiological, clinical and bacteriological profile of elderly patients suffering from community acquired pneumonia. Fifty elderly patients were included in study with age range from 66 years to 88 years with confirmed diagnosis of community acquired pneumonia. Patients varies from mild symptoms to very serious condition. The most common risk factors involved in study population was presence of chronic obstructive

pulmonary disease and smoking status of the patients. *Klebsiella pneumonia*, *Streptococcus pneumonia*, *H. influenza*, *Pseudomonas* and *Staphylococcus aureus* were the most common organisms found in current study. Difficulty in collecting the test sample (sputum) from the elderly population leads to delay in diagnosis and difficult to identify the main causative agent. Therefore, empirical therapy should be initiated that covers both atypical and typical organisms that helps to start the treatment of elderly patients which may improve the overall health of the patients (Abdullah, Zoheb, Ashraf, Ali, & Nausheen, 2012).

A retrospective study was conducted by Wei Li *et al.* in China to adjudicate the association between different risk factors in elderly patients suffering from severe pneumonia. Electrolyte imbalance, chronic kidney disease, low levels of phosphorous and many more were the independent risk factors which showed statistically significant association with severe pneumonia by using univariate analysis. In logistic multivariate regression, levels of serum prealbumin and pro-BNP were found to be the independent risk factors. Gram-negative bacteria *Acinetobacter baumannii* and gram- positive bacteria *staphylococcus aureus* were found in majority of the sputum culture results. They concluded that if the risk factors of elderly patients suffering from pneumonia were analysed then the pharmacotherapy of these patients could be improved significantly (W. Li, Ding, & Yin, 2015).

A cross-sectional study was conducted in Felege Hiwot Referral Hospital situated in Northwest of Ethiopia to determine the different types of bacterial isolates and their antimicrobial resistance patterns among the patients suffering from community acquired pneumonia. Culture and biochemical tests were performed on the

collected sputum samples of the included participants and demographic data were obtained by using a comprehensive questionnaire. For antimicrobial resistance testing, Kirby Bauer disk diffusion method was used. SPSS was used for descriptive and multivariable analysis of the data. A total of four hundred and fourteen patients were included in the study, in which 40.3% of the patients were identified with bacterial pathogens. Among these patients 76% patients were having multidrug resistance isolates. *Streptococcus pneumoniae* (35.9%) and *Klebsella pneumoniae* (18%) were the most prominent isolates among the study population. Alcohol consumption [OR = 4.043 (95% CI 2.537 – 6.443)] and overcrowded living conditions [OR = 1.579 (95% CI 1.015 – 2.456)] were found to be significantly associated with culture positive sputum. In conclusion, as study population showed high prevalence of multi and mono drug resistance isolates, therefore, regular monitoring of different types of isolates along with their drug resistance patterns should be considered. For prevention of community acquired pneumonia, interventions should be integrated particularly, for the consumption of alcohol and modifications in life styles for the general public (Temesgen, Bereded, Derbie, & Biadlegne, 2019).

Loeb *et al.* conducted a multicentre cohort study to evaluate the risk factors and outcomes of pneumonia and other respiratory tract infections on residents of five residential aged care homes. Around 272 episodes of pneumonia and other respiratory tract infections were observed in 170 residents of included aged care homes. Male sex ($p = 0.3$), increase in age ($p = 0.01$), difficulty to take oral drugs ($p = 0.02$) and swallowing ($p = 0.01$) inability were the statistically significant risk factors for pneumonia by using multivariable analysis. Age ($p = 0.05$) and decrease in physical activities ($p = 0.01$) were the potential risk factors for other respiratory tract infections

were reported in current study. In conclusion, difficulty in swallowing and paucity of influenza vaccination among the residents of aged care homes were the modifiable risk factors for pneumonia and other respiratory tract infections (Loeb, McGeer, McArthur, Walter, & Simor, 1999).

To evaluate the prescribing patterns of different types of medications in respiratory tract infections, a retrospective study was conducted by the department of pharmacology at Shri Guru Ram Rai Institute of Medical and Health Sciences in India. By using WHO guidelines for drug indications, 585 prescriptions of respiratory tract infections were randomly collected from the hospital to assess the prescribing trends. Approximately 50% of the medications were prescribed from the National Medication List while 88% of the drugs were prescribed using their brand names. Polypharmacy and irrational prescribing were observed in the study. Regular training and updated knowledge should be given to the physicians to improve their prescribing behaviours to increase the rational use of medications and improves the quality of life of the patients (Beg et al., 2017).

2.2 Urinary Tract Infections among geriatrics

Urinary tract infections (UTIs) are the most common type of infection among elderly population around the world and the most common cause of hospitalization due to bacterial infections (Genao & Buhr, 2012). Generally, UTI is defined as an infection in urinary tract system which may include both upper urinary and lower urinary tracts (Rowe & Juthani-Mehta, 2013). Around 7 million hospital visits, 1 million emergency visits and 100,000 hospitalizations are due to UTIs which is around 25% of all infections among older people every year (Ruben et al., 1995). Approximately, overall incidence

of UTIs among older men and women range in 1 infection per 14 to 20 persons-years (S. L. Jackson et al., 2004). Treatment and diagnosis of UTIs is more difficult among elderly population as compared to young individuals because of many underlying risk factors such as older age, spinal cord injuries, diabetes mellitus, impaired immune conditions and most importantly catheterization (S. L. Jackson et al., 2004).

Geriatrics are more prone to UTIs as compared to young individuals due to high rates of urinary retention, urinary incontinence, long-term hospitalizations, presence of comorbidities, accompanying urinary catheterizations and declining immune responses (Drekonja, Rector, Cutting, & Johnson, 2013; D. Li et al., 2017). Modifiable risk factors of UTIs among older people include urinary tract abnormalities particularly in those with urinary retention or incontinence (e.g. prostatic hyperplasia), diabetes mellitus, urinary catheterization and sexual intercourse, which is the major risk factor for both men and women in older age (Rahn et al., 2014).

The prevalence of UTI is higher in females as compared to males in all age groups. In sexually active young females, the incidence of UTI ranging from 0.5 to 0.7 per person-year (Hooton et al., 1996), however, in young males it is 0.01 per person-year . In middle age the incidence of UTI decreases but it increases with the increase in age (Rowe & Juthani-Mehta, 2013). Around 10% of women aged more than 65 years reported UTI in last 12 months (Foxman, Barlow, D'Arcy, Gillespie, & Sobel, 2000), whereas, this number increase up to 30% in females aged more than 85 years (Eriksson, Gustafson, Fagerström, & Olofsson, 2010). A study on post-menopausal women, the incidence of UTI has been reported as 0.07 per person-year and 0.12 per person-year in women with uncontrolled diabetes mellitus. The incidence of UTI significantly increases in both males and females aged more than 85 years (S. L. Jackson et al., 2004).

Polypharmacy is the major risk factor for overactive bladder syndrome in geriatrics (Schneidinger et al., 2016). ‘Overactive bladder syndrome’ is the complex of symptoms which include sudden need to urinate with the fear of involuntary leakage, nocturia, leakage of urine prior to urine intention and pollakiuria. Some drugs stimulate incontinence as their adverse effect and some of the drugs have interactions between them which increases the chances of overactive bladder syndrome (Schneidinger et al., 2016).

The pathophysiology of UTI is that bacteria multiplying in the bladder trigger an inflammatory response, and many leucocytes enter the bladder (Struthers, Weinbren, Taggart, & Wiberg, 2019). Thus pyuria (presence of leukocytes in the urine) makes the diagnosis of UTI much more likely (Struthers et al., 2019). Nitrites result from bacteria breaking down nitrates in the urine, which require contact time. Nitrites are specific for bacteria, but not very sensitive, as they may be flushed out if urine is passed frequently (Jackson et al., 2019). Thus, the finding of nitrite negative but leucocyte positive may occur in UTI. If only nitrites are positive, not leucocytes, bacteria are confirmed in the urine, but they may be commensals or contaminants (Mody & Juthani-Mehta, 2014; Struthers et al., 2019). Clinical presentation of UTIs among geriatrics leads to complexity in the diagnosis due to localized urinary symptoms and typical clinical history as compared to young individuals. Increased prevalence of asymptomatic bacteriuria (ASB) among elderly population may lead to more difficulty in the diagnosis of UTIs (Myriam et al., 2019). In primary and secondary care, empirical antibiotics are prescribed for suspected UTI in which more than 50% of the prescribed antibiotics are considered unnecessary among elderly patients (Nace, Drinka, & Crnich, 2014). In Malaysia, a morbidity survey in primary care reported that only 43.3% of the prescriptions for UTI were antibiotics

recommended by guidelines (5). Adherence to prescribing advice can be improved by using audit reports and reminders integrated into patient management software (6). To reduce the threat of antibiotic resistance to public health, antibiotic stewardship programs and national guidelines for the rational use of antibiotics have been adapted to control this situation (Myriam et al., 2019).

A retrospective cohort study was conducted in Taiwan by Wei-Yi *et al.* to evaluate the risk factors involved in urinary tract infections among the residents of home care patients. Five hundred ninety-eight patients were included in the study with a mean age of 81.9 years. Around 47% of the included patients had at least one episode of urinary tract infection. Urinary catheter indwelling (OR = 3.21) was found to be the most important risk factor for urinary tract infections among the elderly population. Chronic kidney disease, coronary artery disease, diabetes mellitus were the comorbidities related to urinary tract infection. Polypharmacy (OR = 1.84) is also found to be significant risk factor related to urinary tract infections. Haemoglobin (OR = 0.91) and high levels of albumin (OR = 0.68) were inversely related to urinary tract infection among included patients. In conclusion, excepting the factors that are unmodifiable, unnecessary medications, avoid urinary catheter for longer period and giving good nutritional support may prevent from urinary tract infection in residents of home care patients (Wei-Yi et al., 2019).

Yesim and his colleagues conducted a study among geriatric patients with confirmed diagnosis of urinary tract infections in Yunus Emre State Hospital, Turkey to evaluate the etiology, antimicrobial therapy, prognosis, diagnostic procedures, contributing risk factors and clinical findings of urinary tract infections. One hundred and forty hospitalized patients were included in the study in which 41% had urinary

tract diseases followed by diabetes mellitus (21%) and neurological disorders (19%). Vomiting, fever, pyuria, dysuria, haematuria were the common sign and symptoms of the patients. 56 mm/s, 84 mg/dL and 11.9 ($10^3\mu\text{L}$) were the mean values of ESR, CRP and leucocyte blood count respectively. A 17% of the patients had urinary catheter with 28% had a history of urinary tract infections and 29% were hospitalized previously. The most common organisms involved in the urinary tract infections among included patients were *Klebsiella pneumoniae* and *Escherichia coli*. The mortality rate was 5% and 7.6 days was the mean duration of hospital stay. Due to serious complications and high mortality rate among the elderly patients suffering from urinary tract infections, empirical therapy should be initiated immediately and re-examined after the culture results received (Yesim, Aykin, Korkmaz, Gulduren, & Caglan, 2018).

To assess the association between antibiotic therapy and adverse effects in elderly patients suffering from urinary tract infections in England, a retrospective population-based cohort study was conducted from 2007 to 2015 by Myriam *et al.* Patients aged 65 years or more with at least one episode of urinary tract infections, a total of 1,57,264 patients were included in the study. 7% of the included patients had no record of antibiotic prescription while 6% appeared to have delayed prescription of antibiotics. After 60 days of initial urinary tract infection, only 0.5% patients recorded bloodstream infections. Patients that have not prescribed with antibiotics (2.9%) had higher rate of bloodstream infections as compared to those that were prescribed with antibiotics (2.2% v 0.2%; $p < 0.001$). Patients prescribed with no (27%) or delayed (26.8%) antibiotics had the double rate of hospitalization as compared to the patients received antibiotics immediately (14.8%). The mortality rate was also higher in patients with no or delayed antibiotic as compared to those that received antibiotics