Antibiotic Use Practice and Predictors of Hospital Outcome among Patients with Systemic Bacterial Infection at Tikur Anbessa Specialized Hospital: Identifying Targets for Antibiotic and Health Care Resource Stewardship

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This is to certify that the thesis prepared by Getachew Alemkere, entitled: *Antibiotic Use Practice and Predictors of Hospital Outcome among Patients with Systemic Bacterial Infection at Tikur Anbessa Specialized Hospital: Identifying Targets for Antibiotic and Health Care Resource Stewardship,* and submitted in partial fulfillment of the requirements for the degree of Masters of Pharmacy in Pharmacy Practice (M.Pharm), complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

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Addis Ababa University, 2015

Background: Despite massively used in different settings, about half of antimicrobial agents prescribed to hospital in-patients were considered inappropriate. Such malpractice and excess use has been associated with increased mortality, adverse drug reactions, financial cost and the development of resistant bacteria, which have become a threat for the generation. These calls for an integrated intervention that should better are preceded with identification of targets.

Objective: To assess the antibiotic use practice and to identify predictors of hospital outcome among patients with systemic bacterial infection to uncover targets for antibiotic and health care resource stewardship

Methods: A prospective cross-sectional study was performed from 9 April to 7 July in the internal medicine wards of Tikur Anbessa specialized Hospital. Patients who had and/or developed systemic bacterial infections during this period were strictly followed. Data abstraction format was used to collect data on demographic, disease, drug and microbiologic related factors. Pattern of antibiotic use was assessed and predictors for mortality and length of stay (LoS) were identified. Descriptive statistics and Binary logistic regression were used for statistical analysis.

Results: Females accounted for about 52% of the 323 study participants whose mean age was 41.8. Of all, 75.2% of the participants had suspected infection during ward admission. Cephalosporins were the most widely prescribed class of drugs in the internal medicine wards and the medical ICU. Based on changes to microbiologic culture reports the initial antibiotic uses were inappropriate in all of the ICU and 99.3% of the ward patients. About 28% of the wards and 59% of the ICU patients were died during the in-hospital stay. The mean ($\pm$ SD) LoS was 18.5$\pm$12.2 in the wards and 8.9$\pm$4.9 days in the ICU. Whilst presence of HIV, liver-cirrhosis, different signs and symptoms of disease, neoplasm, sepsis, meningitis, renal failure, vancomycin and increased antibiotic courses ($\geq$ 2) were

positive predictors, prolonged antibiotic days (>10) and simultaneous antibiotic uses (≥3) were negative predictors of mortality. On the other hand, age range of 25-44, hospital acquired infection and prolonged agent days (≥21) (positively) and on admission infection (negatively) were independently associated with prolonged LoS.

Conclusion: Generally, these observations call for the establishment and implementation of antimicrobial stewardship that facilitate appropriate use of antimicrobials as a whole in the context of resource limited settings. Any stewardship activity should better start by addressing infections like pulmonary, sepsis and meningitis and drugs like vancomycin.

Key words: Antimicrobial Stewardship, Antibiotic use, Length of Stay, In-hospital Mortality, Tikure Anbesa Specialized Hospital, Ethiopia

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Dedication

This work is dedicated to my father who laid the ground for my current educational careers, but not alive today to see his fruit.

List of Acronyms and Abbreviations

AMR: …….Antimicrobial Resistance
AOR: …….Adjusted Odds Ratio
ASP: ……..Antimicrobial Stewardship Program
CI: ……..Confidence Interval
COR: …….Crud Odds Ratio
CSA: …….…….Central statistical agency (of Ethiopia)
ESBL: ……...Extended-Spectrum Beta-Lactamases
GFR: …….…….Glomerular filtration rate
HIV: …….……..Human immunodeficiency virus
ICD: ……..…….International classification of disease
ICU: ……Intensive Care Unit
IDSA: …….Infectious Diseases Society of America
IV: ……..Intravenous
LFT: ……Liver function test
LoS: …….Length of Stay
MDR: ……..Multidrug Resistance
MRSA: ……Methicillin-Resistant Staphylococcus Aureus
NDM-1: …….New Delhi Metallo-Betalactamase 1
PO: ……..Per-Oral (oral route of administration)
RCT: …….. Randomized Controlled Trial
RFT: ……Renal function test
SD: ……..Standard deviation
SHEA: …….The Society for Healthcare Epidemiology of America
SPSS: ……..Statistical Package for Social Science
TASH: …….Tikur Anbesa Specialized Hospital
TB: …….Tuberculosis
WHO: …….World Health Organization

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1. INTRODUCTION

1.1. Background

The identification of infected patients at risk of poor hospital outcomes (e.g. longer hospital stay, in-hospital mortality) is important to provide an effective health care service (Maguire *et al*., 1986; Dellit *et al*. 2007; Jenkins *et al*., 2013). Predicting hospital outcomes at admission and during the hospital stay may facilitate the healthcare delivery, as it can allow staff to manage healthcare resources optimally (Roberts *et al*., 2009).

One of the important targets, which should be addressed in the context of the outcome, was the extensive use of antimicrobials with wider ecological effect. As some studies in vancomycin resistance evidenced, it is not the specific drug that contributed for its resistance, instead, agents such as broad-spectrum cephalosporin, clindamycin and floroquinolone appeared to increase the risk for isolation of vancomycin-resistant enterococci, with different agents having different effects on acquisition, amplification, or transmission (Graffunder and Venezia, 2002; Harbarth *et al*., 2002; Rice *et al*., 2004). Consequently, interventions aimed at modulating use of these drugs, as well as the drug itself, have been successful in reducing the rate of development of resistant strains (Hamilton *et al*., 2000; May *et al*., 2000; Cook *et al*., 2011).

Proper use of microbiologic reports during the initiation and modification of empiric therapies was another major area of intervention across the guidelines (IDSA/ATS, 2005; Dellinger *et al*., 2013) and different studies (Erbay *et al.,* 2005; Montravers *et al*., 2011).

Identification of these and other targets should be addressed and carried through appropriate strategies, which best reduce the adverse outcomes of antibiotic resistance like the development of C. *diffcel* infection (Lee CR *et al*., 2013).

Different approaches have been promoted to save these precious drugs from the threat of resistant bacterial selection (WHO, 2001; Powers, 2007; Fonseca *et al*., 2012; Lee *et al*., 2013). Antimicrobial stewardship is currently considered as the promising approach and has been promoted for all, in particular to community, hospitals ultimately to help cope with the challenges of super-infection and emerging resistance to antibiotics (MacDougall and Polk, 2005; Dellit *et al*., 2007; Leung et al., 2011; Karen *et al*., 2012). As per the published studies, it has been proved as an effective proactive intervention (Niwa et al., 2012; Kelly *et al*., 2013). In line to this understanding, the current study was designed to identify targets for future stewardship.

1.2. Statement of the Problem

Based on alarming accumulated facts in the previous few years, antimicrobial resistance is an increasingly important patient safety and public health issue (Gottlieb *et al*., 2011). About half of antimicrobial agents prescribed to hospital in-patients are considered inappropriate (Gottlieb and Nimmo 2011; Duguid and Cruickshank 2011). Moreover, antimicrobials are massively overused in different agricultural settings over the past decades (Cassone *et al*., 2009; Graveland *et al*., 2010; Knapp *et al*., 2010; Overdevest *et al*., 2011).

These malpractices and excess use have been associated with increased mortality, adverse drug reactions, financial cost and the development of resistant bacteria, which hold the threat to the generation (Roberts *et al*., 2009; Arias et al., 2009; Kumarasamy et al., 2010; Gupta *et al*., 2011; De Kracker *et al*., 2011; Carlet *et al*., 2011; Carlet *et al*., 2012).

As a result, it is more difficult than ever to challenge infections caused by antibiotic-resistant microbes (Arias *et al*., 2009; Kumarasamy *et al*., 2010; Gupta et al., 2011; Carlet *et al*., 2011). The problem is exacerbated by a decline for a new antimicrobial development, which is particularly

worse for gram-negative infections as no antibiotic is currently being developed against these pathogens (Arias *et al*., 2009).

Although resistance is a worldwide concern, it is primarily a local problem: selection for and amplification of resistant members of a species are occurring in individual hospitals (and communities), which can then spread worldwide (O'Brien, 1997 and 2002). Single and multiple drug resistance to the commonly used antibiotics were high among bacterial isolates in different areas of Ethiopia, warranting rational use of drugs in the local environment (Yismaw *et al*., 2006; Biadglegne *et al*., 2009).

Furthermore, as per the different studies undertaken in Tikur Anbessa Specilaized Hospital (TASH) in the previous year, antimicrobials were the most common drug categories associated with both prescribing (Feyissa *et al*., 2013; Gashaw *et al*., 2013) and administration errors (Gashaw *et al*., 2013). Thus, it will need a widespread effort at the individual institutional level to impact antimicrobial usage and, by extension (hopefully), antimicrobial resistance.

To the best of our knowledge, there was dearth of studies done on the prudent use of antibiotics in TASH as well as in the country. The aim of the present study was therefore to perform a systematic and comprehensive assessment of antibiotic use practice and to identify factors that predict hospital outcomes in hospitalized patients with systemic bacterial infections, in order to identify institutional targets for better antibiotic and health care resource stewardship. In pursuit of this, a multi-component approach was used. Firstly, two hospital outcomes, i.e. prolonged length of stay (LoS) and in-hospital mortality were addressed. Secondly, the appropriateness of antibiotic use was looked at in line with the widely accepted guidelines and recent original articles, using five adopted quality indicators. Finally, the prospectively collected data was analyzed for socio-demographic and

multifaceted clinical and drug related aspects. Ultimately, this study would describe the epidemiology, microbiology and outcome of systemic bacterial infections and the antibiotics used to treat such infections in the internal medicine wards of a referral public hospital. The study would have paramount importance to the hospital therapeutic decision, to the local health and for governmental decisions in the area. It would also be used as an initial insight for hospital based guideline and national restrictive formulary development. The value might not be limited to these, as it could serve as a benchmark for further studies.

1.3. Literature Review

1.3.1. Bacterial Infections

In developing countries, chronic diseases like cardiovascular were the top reasons for hospital admission (Storey *et al*., 2012). In the contrary, infections were more prevalent and well-grounded in the developing countries. Despite this fact, bacterial infections were largely neglected as an important cause of public health concern because of very few and variable population based surveillance studies that evaluate incidence and trends in low-income countries (Kanoksil *et al*., 2013). Based on the inconsistent findings, respiratory tract infections were the most prevalent types of bacterial infections in developing (CSA and ICFI. 2012) as well as developed (Camins *et al*., 2009; Storey *et a*l, 2012) countries. Specifically community-acquired pneumonia was most prevalent (Hall *et al*. 2007, 2010). Based on their deadly nature, sepsis (Kang *et al*., 2004; Gaieski et al., 2013; McPherson *et al*., 2013) and meningitis (Berkley *et al*., 2001; Scarborough *et al*., 2007) were well known across the world. More than one million cases of acute bacterial meningitis amongst adults and children occur annually in sub-Saharan Africa (Sigauque *et al*., 2008), associated with high burden of death and disability (Berkley *et al*., 2001; Scarborough *et al*., 2007).

1.3.2. Challenges of Infection and its Cause

Now a day, what's challenging is the management of these infections, not because of the high prevalence or deadly nature of some of the infections but because of an emerging development of resistant strains that are not amenable to the existing antimicrobials. Studies were evidencing that it is much difficult than ever to eradicate infections caused by resistant genes (Arias *et al*., 2009; Kumarasamy *et al*., 2010; Gupta *et al*., 2011; Carlet *et al*., 2011). There is emergence and dissemination of new mechanisms of resistance through elaboration of novel enzymes such as extended-spectrum beta-lactamases (ESBL) and carbapenemases (Kumarasamy *et al*., 2010; Meir *et al*., 2011; Gupta *et al*., 2011).

Emergence and spread of resistance has been attributed to antimicrobial exposure, both at the population and the individual level (Costelloe *et al*., 2010). The most important cause is that there has been a massive overuse of antibiotics worldwide across all ecosystems over the past decades; including humans, animals, aquaculture, and agriculture (Grigoryan *et al*., 2008; Cassone et al.,2009; Graveland et al., 2010; Knapp et al., 2010; Blaser et al., 2011; Overdevest et al., 2011). In Ethiopia, different studies indicate animals as the potential sources of resistant bacteria in the local environment (Bayleyegn*et al*., 2003; Firaol *et al*., 2013).

What's more challenging is that the use of broad spectrum drugs like floroquinolones not only induce resistance for its own but also for the other class of drugs (Graffunder and Venezia, 2002; Harbarth *et al*., 2002; Rice *et al*., 2004). Consequently, interventions aimed at modulating use of these drugs, as well as other broad spectrum agents, were successful at reducing the rate of resistance to them as well as to other class of drugs (Hamilton *et al*., 2000; May *et al*., 2000; Cook *et al*., 2011).

1.3.3. Burden of Antibiotic Resistance and its Solutions

The spread of the new resistance gene, the New Delhi metallo-betalactamase 1 (NDM-1), or other carbapenemases in Enterobacteriacae is alarming because these "superbugs" are resistant to most available antibiotics and can disseminate worldwide very rapidly, in particular as a consequence of medical tourism (Kumarasamy *et al*., 2010).

High morbidity, mortality, and serious financial cost were attributable to multiresistant bacteria in critically ill patients in different countries. In the USA, the annual cost of antimicrobial resistance (AMR) in hospitals is estimated at more than US$ 20 billion with an even wider clinical impact than human immunodeficiency virus (HIV)-related disease (Roberts *et al*., 2009).

Therefore, the best way to tackle the consequence of these infections will rely on the preservation of the existing antimicrobials. These needs designing an appropriate antimicrobial use strategies (Chang-Ro *et al*., 2013).

Increasingly, an active protection of antibiotics (part of the so-called "antibiotic stewardship (AS)") is gaining much emphasis (MacDougall and Polk 2005; Dellit *et al*., 2007; Roberts *et al*., 2009). "AS" is an ongoing effort by a health care institution to optimize antimicrobial use among hospitalized patients in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequel of antimicrobial use (including antimicrobial resistance)" (MacDougall and Polk 2005). The ultimate goal is the preservation of current and future antibiotics against the threat of antimicrobial resistance, although improving patient safety and reducing healthcare costs are important concurrent aims (MacDougall and Polk 2005; Dellit et al., 2007).

As identified by IDSA/SHEA guidelines, the proactive strategies for promoting antimicrobial stewardship include: (i) formulary restriction and pre-authorization, and (ii) prospective audit with intervention and feedback. These strategies are not mutually exclusive. Other supplemental strategies involve education, guidelines and clinical pathways, antimicrobial order forms, de-escalation of therapy, intravenous-to-oral (IV-to-PO) switch therapy, and dose optimization (Dellit et al., 2007) (Figure 1).

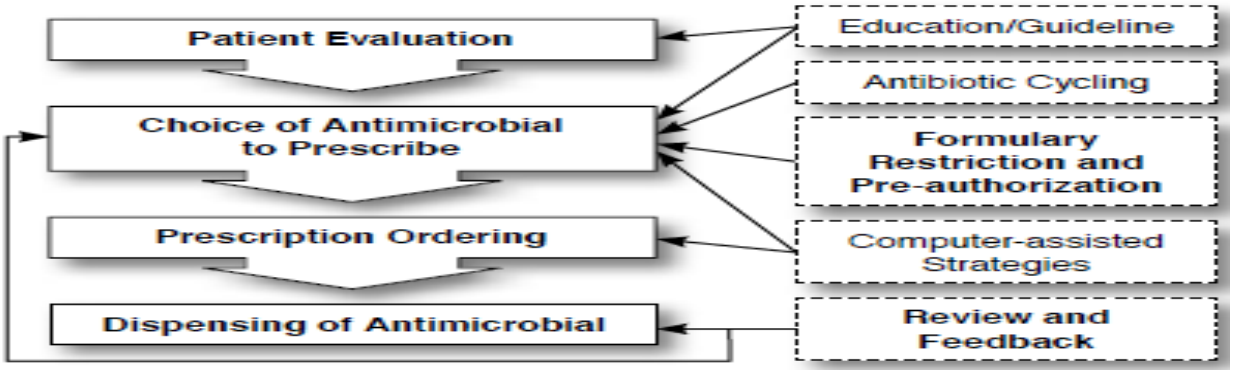

Fig 1: Antimicrobial prescribing process and antimicrobial stewardship strategies *(Source: MacDougall and Polk, 2005)*

Since the aim is to preserve the existing antibiotics, these policies/strategies should better be explained by their benefit in improving hospital outcome in the short-term and reversion of resistance development in the long-term, which should be measured objectively in terms of appropriate antibiotic use.

1.3.4. Appropriate Antibiotic Use

One of the important requirements for an effective stewardship program in order to set priorities and focus improvement is the ability to measure the appropriateness of hospital antibiotic use (van den Bosch *et al*., 2014).

Antibiotic resistance can be reduced by using antibiotics prudently based on guidelines of antimicrobial stewardship programs (ASPs) and various data such as pharmacokinetic and pharmacodynamic properties of antibiotics, diagnostic testing, antimicrobial susceptibility testing, clinical response, and effects on the microbiota as well as by new antibiotic developments (Chang-Ro et al., 2013). As one of the appropriateness measure, adherence to guidelines that improve clinical outcome is profoundly correlated with less development of resistance to antibiotics and lower costs (Larson *et al*., 2007; Asadi *et al*., 2009; Lee *et al*., 2011, Menendez *et al*., 2012).

A study performed in 41 French ICUs used correct changes to culture-sensitivity report as appropriateness measure and identified 22% of the new antibiotic initiations as inappropriate (Montravers et al., 2011). Currently, different scholars have been developing different quality indicators for measuring appropriate antibiotic use (van den Bosch *et al*., 2014a and 2014b).

Measurement of consumption (some refer prescribing) is an important component of AS (Dellit *et al*., 2007; Berrington A., 2010). Berrington. (2010) reported volume-related (agent days, antibiotic days and defined daily dose) and an exposure-related measurement of consumption (courses, treatment periods). Exposure related measures like antibiotic days could tell us the number of days of drug exposure. Studies showed that prolonged antibiotic exposure was associated with multiple costs like the emergence of antibiotic resistance (Dennesen *et al*., 2001).

1.3.5. Hospital Outcome Indicators and their Predictors

Predictors of hospital outcome could be classified as modifiable and non-modifiable (Battleman *et al*., 2002). Those that used for appropriate antibiotic use measure were largely modifiable but those like demographic and disease related factors might not. In a good stewardship, the non-modifiable

ones will be prioritized and targeted and those of the modifiable ones will be routinely evaluated for improvement (Jenkins *et al*., 2013).

In-hospital mortality and length of stay (LoS) were mostly evaluated outcome measures. Comparing the two, a study by Lagu *et al*. (2011) did not find a significant association between hospital spending and mortality. Prolonged hospital stay was enormously associated with higher hospital costs (Mauldin et al., 2010). Hospital system or policy gaps like waiting for diagnostic or therapeutic procedures and delay in discharge may result in extended length of in-hospital stay (Ghods et al., 2014). Most studies signify the benefits of adequate (Tumbarello *et al*., 2007) and immediate (Kang *et al*., 2003; Gao *et al*., 2006; Kumar *et al*., 2006) initiation of empiric antibiotic therapies, particularly for critically ill patients, as this was associated with decreased mortality and/or shorter hospital stay. Guidelines recommend de-escalation of these empiric therapies based on microbiologic reports and/or the clinical response of the patient (IDSA/ATS, 2005; Dellinger *et al*., 2013). Studies that based on these guidelines had found fascinating changes (Larson *et al*., 2007; Asadi *et al*., 2009; Lee *et al*., 2011, Menendez *et al*., 2012).

In addition to the appropriate antibiotic use, demographic, disease and drug related factors were also important predictors of hospital outcome, though not easily amenable for improvement. Different studies reported that older age was significantly associated with mortality (Yu *et al*., 2003; Nakamura *et al*., 2006; Robenshtok *et al*., 2006) and prolonged hospital stay (LoS) (Maguire *et al*., 1986 and Gordon 2003; Suter-Widmer *et al*., 2012). A study by De Buyser *et al*. (2014) performed in geriatric and internal medicine acute care wards of Italian hospitals reported metastasized cancer, renal failure or dialysis and infection as independent predictors of LoS. A study conducted by Tumbarello et al (2007) reported that a significantly higher number of non-survivors had liver diseases. Another study conducted in the medical wards of Queen Elisabeth Central Hospital in

Malawi identified hypotension and level of consciousness as important predictors of mortality in patients with pneumococcal meningitis or bacteremia (Gordon, 2003). Other studies reported independent association between mortality and HIV (McCabe *et al*., 2009 or cefepime use (Chopra *et al*., 2012).

Several studies have also found that origin of infections, risk of multidrug resistant (MDR) bacterial exposure and the immune status of patients to be important factors that determine the infection risk status of patients and the associated variation in the hospital outcome. Diekema *et al*. (2003) reported an independent association of nosocomial bloodstream infections with mortality and cost. Another study by Zilberberg *et al.* (2009) also reported a statistically significant increased mortality and Prolonged LoS, compared with community-acquired counterparts. The study performed by Lye *et al*. (2012) reported an independent association of MDR risk with Prolonged LoS in survivors. A similar study reported the association of MDR with 30-day mortality despite the absence of such evidence in the multivariate analysis (Lye *et al*., 2012).

A study conducted in bacterial infected patients admitted to ICUs in countries considered to have high levels of antibiotic resistance compared to those with low levels (Hanberger et al., 2014) reported that high antibiotic resistant ICUs had longer median ICU (12 days vs 5 days for low) and hospital (24 days vs 16 days for low) LoS. A similar study (Hanberger et al., 2014) reported higher crude ICU (20.0% for high vs 15.4% for low) mortality rates. It is known that immunosuppressive diseases like human immunodeficiency virus (HIV), disseminated tuberculosis, presence of cancer, major organ transplant and the use of immunosuppressive drugs could potentially put patients at higher risk for infection and its associated complication (O'Grady *et al*., 1998). Though expected, one study analyzing the presence of immunosuppressive disease did not found association with mortality in the multivariate logistic regression (Montravers *et al*., 2011).

2. OBJECTIVE

2.1. General Objective

To assess antibiotic use practice and to identify predictors of hospital outcome among patients with systemic bacterial infection in the internal medicine wards of TASH.

2.2. Specific Objectives

- ☞ To determine the rate of infection in the internal medicine wards
- ☞ To describe different types of infections and drugs used to treat such infections
- ☞ To quantify the changes/adjustments made to the initial therapy
- ☞ To determine appropriateness of antibiotic use, using standardized quality indicators
- ☞ To identify independent predictors of in-hospital outcome (prolonged hospital stay and in-hospital mortality)

3. METHODS

3.1. Study Setting and Period

TASH is a teaching hospital with medicine, surgery and other multiunit services. It is a full-service 600-bed governmental University affiliated tertiary care hospital of the country, Ethiopia. Through its different ambulatory clinics and wards, it provides ambulatory and in-hospital care for patients coming from different corners of the country. Large number of patients have been seen each year at both outpatient and inpatient level. For instance, 266,975 patients were seen in 2010. Physicians and other professionals' have a well-established role in the hospital with the ultimate patient care but full-time pharmacists in different wards resumed providing service since September 2013. The laboratory performs microbiology services supposedly including preparation of an annual facility antibiogram. Almost all the recording systems of the hospital are carried manually.

The in-hospital care is diversified, majorly involving the 120 bed internal medicine wards including a 6 bed medical intensive care unit (ICU). The study was conducted in all these internal medicine wards including medical ICU, since most adult cases were supposed to be admitted to this unit. The study was conducted from 9 April to 7 July 2014 for 3 consecutive months.

3.2. Study Design

The design was a prospective cross sectional study employed to identify targets for Antibiotic and Health Care Resource Stewardship.

3.3. Source and Study Population

All patients attending the internal medicine wards including medical ICU of TASH during the study period were considered as the source population. On the other hand, the study populations were all

infected patients who had been admitted to the internal medicine wards including medical ICU of TASH during the study period.

3.4. Sample Size & Sampling Methods

All patients attending the adult internal medicine wards including the medical ICU of TASH during the study period and who had and/or developed systemic bacterial (non-mycobacterial) infection were included.

Inclusion:

- ☞ All those admitted to the adult internal medicine wards, prescribed and dispensed with systemic antibacterial agents during the study period.

Exclusion:

- ☞ Wards other than the adult internal medicine ward
- ☞ Clients not prescribed and/or dispensed with antibacterial agents
- ☞ Clients aged <18 years
- ☞ Clients taking antibacterial for $\leq$ 72 hours
- ☞ Clients lost to be followed or
- ☞ Clients discharged against the medical advice
- ☞ Clients taking anti-mycobacterial agents
- ☞ Clients taking non-systemic antibacterial agents
- ☞ Clients taking prophylactic antibacterial agents
- ☞ Clients with other drugs

3.5. Study Variables

Dependent Variables

- ☞ In hospital mortality
- ☞ Prolonged LoS (taking the median value)

Independent Variables

- ☞ Socio-demographic factors like sex, age, etc.
- ☞ Disease related factors like primary/admission diagnosis, infection diagnosis, etc.
- ☞ Drug related factors like different antibiotics, changes from initial therapy & antibiotic metrics.
- ☞ Antibiotic use quality indicators for appropriateness of therapy

3.6. Data Collection Process

3.6.1 Data Collection Instruments

Data abstraction format was adopted from different studies involving antimicrobial stewardship. After the pilot test, the corrected, validated and clinically reliable version was used (see Annex I).

In addition, another sheet was used to record the number of weekly admissions from the nursing admission and discharge registration book. The sheet has list of all the wards and bed numbers as well as weekly monitoring form to acknowledge the works of data collectors (see Annex II).

3.6.2 Recruitment and Training of Data Collectors

The data collectors were four newly appointed clinical pharmacy staff members at the hospital and they were trained for two days. They were assigned for the collection of data under strict supervision of the principal investigator with a weekly monitoring sheet.

3.6.3. Data Quality Control

To maximize quality of the data, training of the data collectors on how to fill the data collection instruments and extract the necessary information was conducted. Besides, the investigator did adequate supervision and monitoring. In addition, pre-test was conducted using 5% of the initially assumed antibiotic user patients, outside of the study period. In each ward, the principal investigator was the supervisor leading the team of data collectors and fully responsible for the whole quality of data. He assured that all the facilities were measured in the same way in all the months considered.

3.7. Decision Making Processes in Data Interpretation

All adult patients admitted to the internal medicine wards including the medical ICU during the study period were eligible for enrollment. Those who had (on admission) and developed (in the hospital stay) systemic bacterial (except mycobacterial) infections during the data collection period and for whom antibiotic therapy was prescribed, were strictly followed. However, those who did not satisfy the inclusion criteria and the intent of the data interpretation were excluded from the analysis (Figure 2).

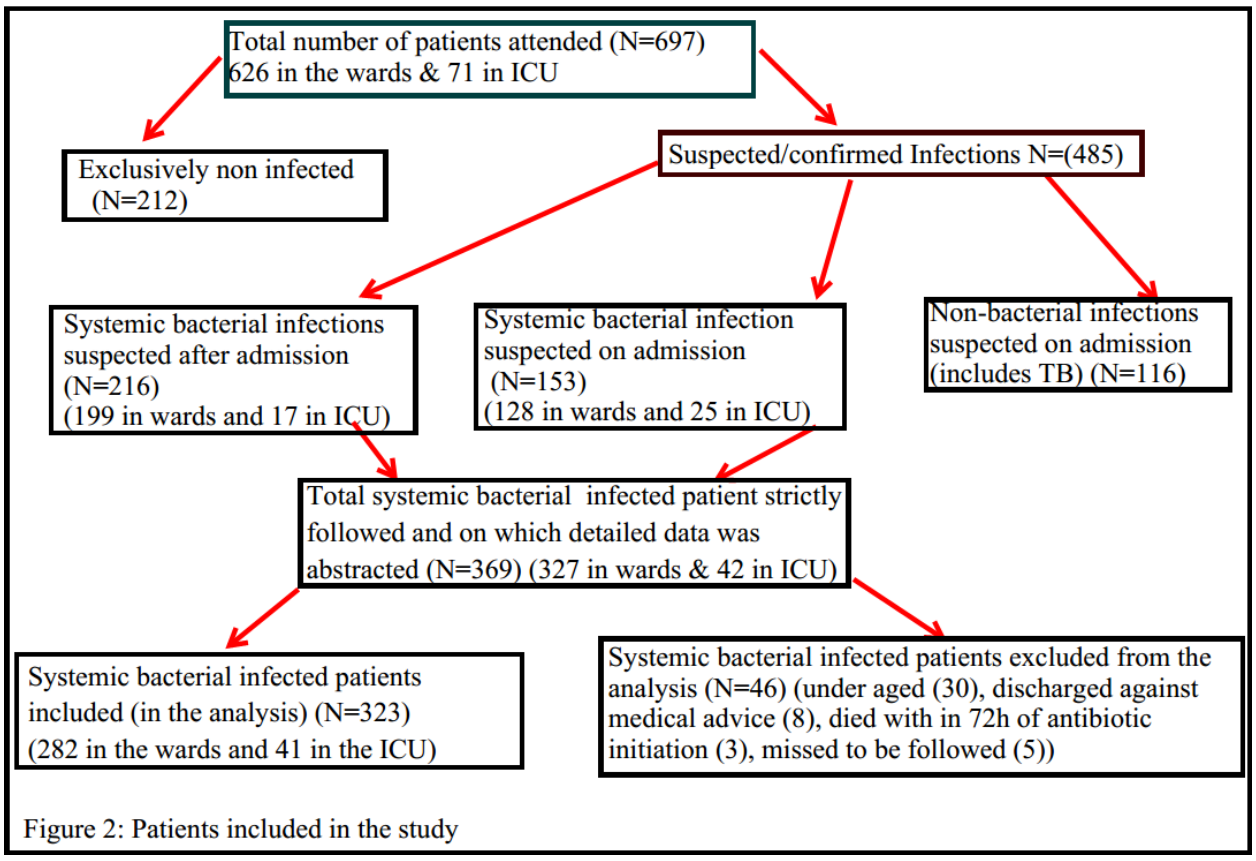

Figure 2: Patients included in the study

The required data was documented on preapproved abstraction sheet, daily. Demographic characteristics, primary/admission diagnosis, suspected infection diagnosis, laboratory procedures for the infection diagnosed (culture & gram stain), antibiotics administered, and any adjustments made on the antibiotic regimen were recorded properly. The dates' of each antibiotic initiation and microbiologic report were also included. Criteria used for diagnosis, microbiologic techniques, the decision to prescribe and modify antibiotics were left to the physician's discretion.

The primary admission diagnosis was classified based on the international classification of disease (ICD 10) criteria but the infectious diagnosis was reported intentionally as per the record of the prescribing physician. Using the recorded date values, microbiologic data relative to the start of new antibiotics was analyzed.

The decisions made on the adjustment of the empiric antibiotic regimen were classified as 'no change', 'discontinued' and 'modified'. The factors for adjustment were documented as per the basis of the change i.e., senior consultation, organ failure (kidney), availability of microbiologic results or any other reason. The other reasons for antibiotic changes recorded include clinical deterioration, new site of infection, antibiotic side effect, cost, discontinuation after ruling out infection. However, they were not extensively reported because of inconsistencies in some of the records. Since no directly/by name/ reported infectious disease consultations made in any stage of the infection management, the changes made by the senior physician leading the rounding team were reported as 'senior consultations' regardless of his or her specialty.

Patients with one of the following underling conditions were classified as being immunosuppressed: febrile neutropenia, cirrhosis, disseminated TB and HIV infection (O'Grady et al., 1998). On the other hand, severity of illness, surgical status, presence of medical devices, previous history of admission and/or antibiotic use and other important clinical parameters were not recorded and reported. Nevertheless, after data collection and to the extent the abstracted data allowed, the patients were categorized as 'community acquired', 'hospital acquired' and 'unknown' based on the source of the infection suspected by the physician. In addition, the patients were also classified into 'have', 'no' or 'no enough evidence' based on their risk of MDR infection. The criteria used for evaluation of infection or colonization with MDR bacteria were based on the Infectious Disease Society of America and the American Thoracic Society guideline (IDSA/ATS, 2005) for Ventilation associated, health care associated and hospital acquired infections and is extrapolated to other sites of infections (Robert *et al*., 2012; Tandon *et al*., 2012). Those criteria applied to the present study included: prior antibiotic receipt in the past 3 months, previous hospital admission during the last 3 months, late-onset hospital-acquired infections (HAIs) (as defined by the physicians and/or the date

of antibiotic administration relative to the admission date) (i.e. >5 days after admission), and presence of preexisting immunosuppressive disease.

After reviewing the patients' records and the collected data, five quality measures (see Annex III) were adopted as proposed by van den Bosch *et al*. for adult non-ICU (2014a) and for sepsis (2014b). The quality indicators are i) Empiric therapy is according to the guidelines, ii) Empiric therapy correctly changed according to culture sensitivity result reported within 72 h, iii) Empiric therapy discontinued within 7 days due to lack of culture evidence, iv) Dose and dosing interval adapted to renal function and v) IV to PO changes made within 7 antibiotic days. These quality indicators were developed to fit to our perspective based on the scientific requirements. The following were some of the modifications made from van den Bosch *et al*. (2014a and 2014b). In the absence of international guidelines, for some rare infections, recent studies were consulted to label the empiric treatments as 'guideline concordant or not'. In addition, in order to replicate real conditions as much as possible, all microbiologic cultures were analyzed but appropriateness of antibiotic therapy was only considered for culture and sensitivity reported within 48-72 h of antibiotic initiation. Though the change was taken to be correct (based on sensitivity report), positive cultures were not evaluated for true or false positivity. In case of microbiological (culture) negative reports, discontinuation of antibiotics within 7 days is reported as appropriate. Furthermore, given the inconsistency of clinical data records, since we did not involve any specialist in the specification of the exact date of intravenous to oral switch, it was generally assumed that any patients (except those with oral intake limitation and some infections) started with at least one intravenous medication deserves change unless lost to be followed. In this regard for all the patients stayed in the hospital with seven or longer antibiotic days and discharged healthy, only switches to the same drug or class of drugs were taken as appropriate.

The quality of antibiotic prescription (dose, intervals etc) according to pharmacokinetic/ pharmacodynamic criteria was not analyzed but only few major gaps were considered for some patient cases (like suboptimal ceftriaxone dose (1 gm) for infective endocarditis in the absence of other drugs and limiting factors).

3.8. Statistical Analysis

The collected data was checked and cleaned for any deficit prior to data entry. Errors in data entry were also checked for accuracy using double data entry technique. Epi info 7 was used for data entry. The data was then exported to SPSS for windows version 21.0 for additional and advanced data analysis. Descriptive statistics such as means, medians, standard deviations, range and percentages were used to summarize patient characteristics and any changes made during the follow-up period. Binary logistic regression was carried out to see the association after all continuous variables were converted to categorical. Those who had a significant association in the univariate binary logistic regression were used in the final multivariate model. However, some of the variables that had association in other multivariate models were included in the final model despite the absence of association in the univariate analysis. Crude and Adjusted Odds Ratio (COR/ AOR) were calculated at 95% confidence level. Then the independent predictors for mortality and Prolonged LoS were identified. The association was declared significant at $p \leq 0.05$.

3.9. Ethical Consideration

Ethical approval for the protocol was obtained from the Ethics committee of the School of Pharmacy, College of Health Sciences, Addis Ababa University. In addition, the hospital management was requested for permission to conduct the study. Written informed consent was not obtained from patients and health personnels, since the study was strictly observational that did not

modify any clinical practice. Instead, information was given to the patients, their physicians and other health workers, as required. To ensure confidentiality, name and other identifiers of patients and prescribers were not recorded on the data abstraction formats. The collected data was kept in a locked cabinet and only the researchers had access to the data.

3.10. Operational Definitions

Length of stay (LoS): LoS was defined as the number of days between admission and discharge, regardless of the number of hours, because the precise time was often not available. Prolonged LoS is to mean the LoS above the median (> 16 days for the wards and > 10 days for the ICU).

Signs and symptoms of disease: based on ICD 10, it refers to the signs and symptoms of the underlying disease (e.g. hemiparesis, secondary to hypertension) that were not classified elsewhere under the primary admission diagnosis but which were the primary reasons for admission.

Antibiotics: in this study refers to any drugs used for systemic bacterial infection.

Initial antibiotic use (within 72 h of starting therapy): was defined as any antibiotic treatment initiated for empirical coverage while microbiologic results were pending or for definitive therapy in which the pathogens were already known.

Empiric antibiotic use: was defined as antibiotic use that occurred within 72 h of initiation of therapy while microbiologic culture results were pending or antibiotic use in situations after 72 h of initiation when microbiologic cultures did not yield a pathogen.

Definitive (therapeutic) antibiotic use: was defined as any antibiotic use at a time when microbiologic culture results and susceptibility data were available. This could have occurred at

initiation of therapy or after empirical antibiotic use was initiated, once microbiologic culture results were available.

Adjustment: any changes made on the antibiotic/regimen after 48-72 h of the initial therapy that refers to either of following.

- **Discontinued**: to mean any discontinuation of all antibiotics found to be unnecessary (e.g. no suspected infection)
- **Modified**: to mean either de-escalation (narrowing by either discontinuation of either agent or using the narrower spectrum option) or broadening (addition or using a much broader spectrum instead or starting a new regimen of treatment after a day and before 7 days of completion of the first course of treatment period) of therapy

Antibiotic metrics: refers to the following antibiotic use measures (Berrington, 2010).

- **Antibiotic courses**: any period during which the same agent (regardless of dose or route) was administered to the same patient on consecutive days;
- **Treatment periods**: a period of consecutive days on which any antibiotic or combination of antibiotics was administered to a patient;
- **Agent days**: the number of days that a patient received a particular agent during the ward admission period;
- **Antibiotic days**: the number of days on which a patient received any antibiotics during the ward admission period

4. RESULTS

4.1. Socio-Demographic and Disease Characteristics of Patient

Patients had a mean age of 41.8± 17.8 (range: 18-85), most of whom (40.9%) were between the age range of 25 and 44 years. Majority of them (58.5%) were from Addis Ababa region. Females accounted for about 52% of the study participants. Of all, 75.2% of the patients had infection during ward admission. Patients with circulatory diagnosis (34.4%) accounted for the second most category of primary admission diagnosis. Neoplasm in medical wards and different signs and symptoms in the medical ICU ranked third (Table 1).

Table 1: Socio-demographic and disease characteristics of hospitalized patients with bacterial infection in the internal medicine ward of Tikur Anbessa specialized hospital.

Variables	Wards,N=282(Freq, %)	ICU,N=41(Freq, %)	Total, N=323(Freq, %)
Age of patient (yr)			
18-24	51(18.1)	9(22.0)	60(18.6)
25-44	117(41.5)	15(36.6)	132(40.9)
45-64	70(24.8)	9(22.0)	79(24.5)
65 and above	44(15.6)	8(19.5)	52(16.1)
Average age(mean ± SD(range))	41.7± 17.7 (18-85)	42.9 ± 18.9 (18-84)	41.8± 17.8 (18-85)
Sex of patient			
Female	149 (52.8)	20(48.8)	169(52.3)
Male	133(47.2)	21(51.2)	154(47.7)
Region			
Addis Ababa	162(57.4)	27(65.9)	189(58.5)
Oromia	64(22.7)	7(17.1)	71(22.0)
Amhara	21(7.4)	4(9.8)	25(7.7)
SNNP	23(8.2)	1(2.4)	24(7.4)
Other regions♦	12(4.3)	2(4.8)	14(4.3)
Admission Diagnosis (ICD 10)†			
Infectious	209 (74.1)	34(82.9)	243(75.2)
HIV	45(16.0)	3(7.3)	48(14.9)
Circulatory	88(31.2)	23(56.1)	111(34.4)
Neoplasm	78(27.7)	2(4.9)	80(24.8)
Signs and symptoms of disease	77(27.3)	8(19.5)	85(26.3)
Endocrine & metabolic	33(11.7)	4(9.8)	37(11.5)
Digestive	18(6.4)	3(7.3)	21(6.5)
Genitourinary	23(8.2)	1(2.4)	24(7.4)
Blood related	22(7.8)	1(2.4)	23(7.1)
Respiratory	20(7.1)	6(14.6)	26(8.1)
Other Diagnosis††	19(6.7)	3(7.3)	22(6.8)
Abnormal organ functions			
Abnormal RFT**	35(12.4)	11(26.8)	46 (14.2)
GFR below 50 mL/min/1.73 m2	21(7.4)	6(14.6)	27 (8.4)
Microbiologic reports			
Gram stain reported	36 (12.8)	11(26.8)	47(14.6)
Culture reported	34(12.1)	4(10.81)	38 (14.9)
Sensitivity done***	9(81.8)	1(100)	10(83.3)

*†a given patient t may have ≥1 dignosis, based on International classification of disease (ICD); †† (Wards: Drug adverse outcomes (8), Seizure/Epilepsy (4), gynecology (3), Arthritis (2), Communicable hydrocephalus (1) & Cholestatic calculi (1); ICU: Injury (2) Drug related adverse outcomes (1)); ♦ (wards: Tigray (5), Gambela (1), Somali (3), Harare (1), Dre Dawa (2); ICU: Tigray (1) & Gambella (1)); *RFT-renal function test, based on serum creatinine value of > 1.2 g/dl; GFR-glomerular filtration rate; SD-standard deviation; HIV-human immunodeficiency virus; SNNP-southern nations, nationalities and peoples; ***Denominator-all positive culture reports-12 for the total, 11 in the wards and 1 in the ICU*

4.2. Rate of Infection

Using the total internal medicine ward admissions (697: 42 for ICU and 327 for wards) as the denominator, the systemic bacterial infection rate was 45.1% (282/626) for the wards and 57.7% (41/71) for the ICU. If the excluded patients with systemic bacterial infection were counted the rate increases to 52.2% (327/626) for the wards and 59.1% (42/71) for the ICU (Figure 2). This rate, however, did not indicate emergency department reported figures, since the data collection was exclusively undertaken after the patients were admitted to the internal medicine wards, including the medical ICU.

4.3. Infection Diagnosis and Infection Risk Status Indicators

Of all the patients, 48.0 % had pneumonia. Community acquired pneumonia in wards (25.2%) and aspiration pneumonia in ICU (36.6%) were the commonest types of pneumonia suspected. Patients with urinary tract infections (13.8%) in wards and with sepsis (12.2%) in ICU were the second most infections following pneumonia (Table 2).

Table 2: Types of infections suspected in hospitalized patients in the internal medicine ward of Tikur Anbessa specialized hospital.

Bacterial Diagnosis*	Wards, N=282(Freq, %)	ICU,N=41(Freq, %)	Total, N=323(Freq, %)
Pneumonia	124(44.0)	31(75.6)	155(48.0)
Community acquired	71(25.2)	7(17.1)	78(24.2)
Aspiration	27(9.6)	15(36.6)	42(13.0)
Hospital acquired	21(7.5)	8(19.5)	29(9.0)
Ventilation associated	0	1(2.4)	1(0.3)
Other Pneumonia	5(1.8)	0	5(1.6)
Urinary Tract Infection	39(13.8)	3(7.3)	42(13.0)
Sepsis	34(12.1)	5(12.2)	39(12.1)
Fever of neutropenia	34(12.1)	1(2.4)	35(10.8)
Meningitis	18(6.4)	2(4.9)	20(6.2)
Abscess	15(5.3)	0	15(4,6)
Spon. Bacterial Peritonitis	11(3.9)	2(4.9)	13(4.0)
Gastroenteritis	11(3.9)	0	11(3.4)
Diabetic foot ulcer	10(3.5)	0	10(3.1)
Infective endocarditis	9(3.2)	0	9(2.8)
Skin infections	7(2.5)	1(2.4)	8(2.5)
Unknown infections	7(2.5)	0	7(2,2)
Paranumonic effu/empyema	6(2.1)	0	6(1.9)
Tetanus	0	2(4.9)	2(0.6)
Surgical site infections	0	1(2.4)	1(0.3)
Other Bacterial infections**	23(8.2)	1(2.4)	24(7.4)

** a given patient may have ≥ 1 diagnosis; **Acute bronchitis (1), Acute Post Streptococcal Glomerulonephritis (1) , Acute febrile illnesses (2) , Chronic diarrhea (2) , Cough (1) , Emphysema (1) , H. pylori (1) , Intra-abdominal infections (3), IBD (2) , lymphadenitis (Pyogenic) (1), Odontogenic infections (4), Osteomyletis (1), Otitis Media (1), Pneumothorax (1), RF (Rheumatic fever)(1) and Sore throat (1);for ICU: acute bronchitis; ICU: Intensive care unit*

Based on immunity status, source of infection, and previous clinical encounters, potential risk of colonization to more resistant bacterial strains varies among patients. About two fifth of the patients were immunosuppressed having higher risk for resistant infections. Despite the absence of evidence to classify most of the patients, about 10% of ward and 29% of ICU patients had risk of colonization with MDR infections. On the other hand, more than half of infected patients were not classified based on their source of infection. However, above one fifth had community onset and the remaining had hospital onset infections (12% of the wards and 24% of the ICU) (Figure 3).

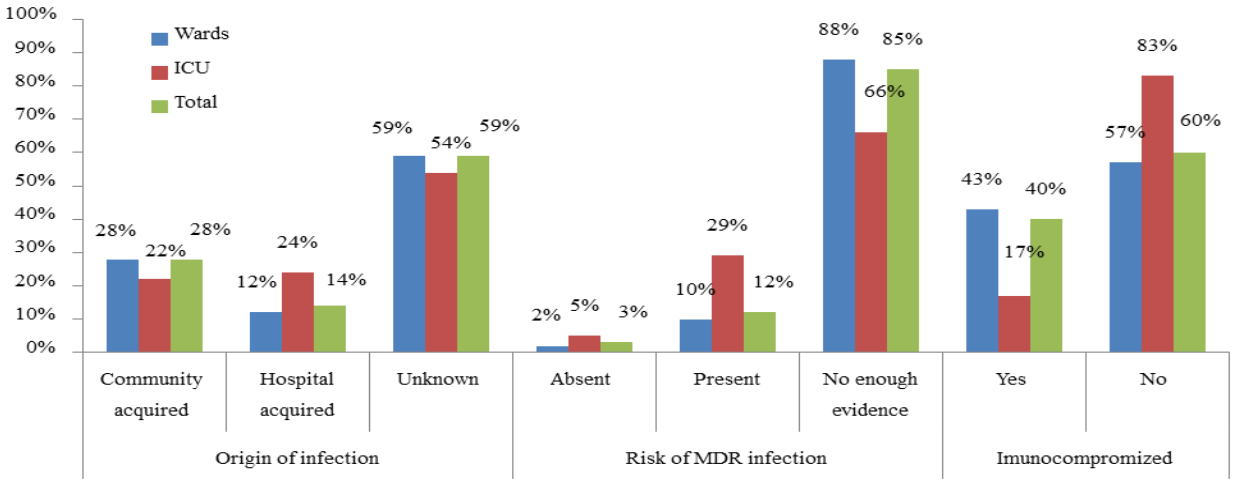

Figure 3: Infection risk status indicators for colonization with resistant strains, among patients with bacterial infections admitted to the internal medicine ward of Tikur Anbesa Specialized Hospital.

4.4. Antibiotics and Antibiotic Related Factors

4.4.1. Class of and Specific Antibiotics Used

Comparatively (ward vs. ICU); cephalosporin (41% vs. 43%), anti-anaerobic (15% vs. 19%) and glycopeptides (vancomycin only) (12% vs. 19%) were prevalently used class of drugs across the settings (Figure 4).

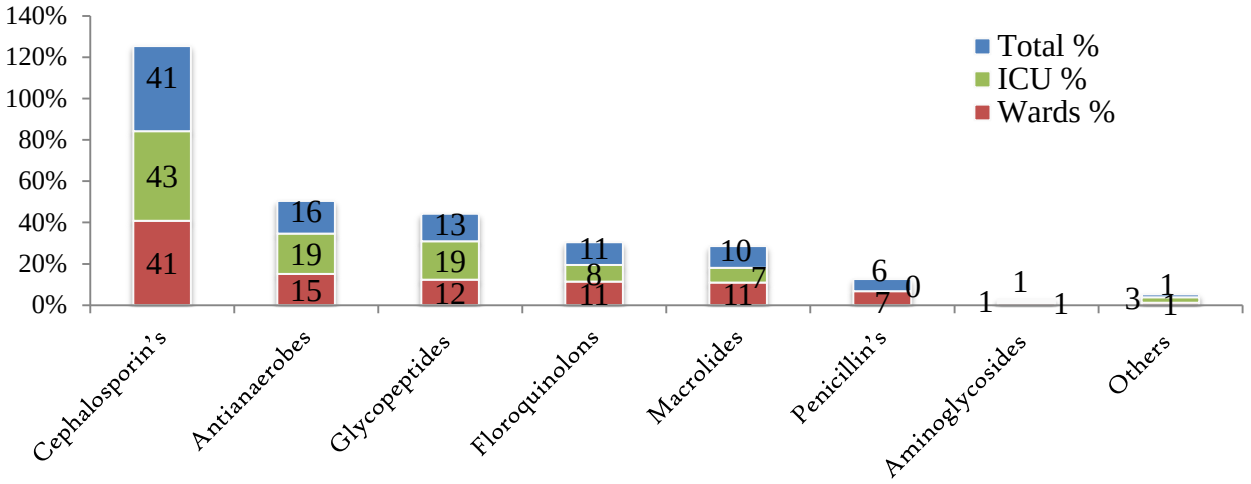

Figure 4: Types of antibiotic classes used in hospitalized patients with bacterial infection in the internal medicine wards of Tikur Anbessa specialized hospital. *Others: wards: Doxycycline (3), Chloramphenicol (3) and Meropenum (2); ICU: Doxycycline(1), imipenum(1)and cotrimoxazole (1); ICU, intensive care unit.*

The most frequently prescribed antibiotics were (ward vs. ICU) ceftriaxone (32% vs. 27%), metronidazole (14% vs. 19%) and vancomycin (12% vs. 19%) (Figure 5).

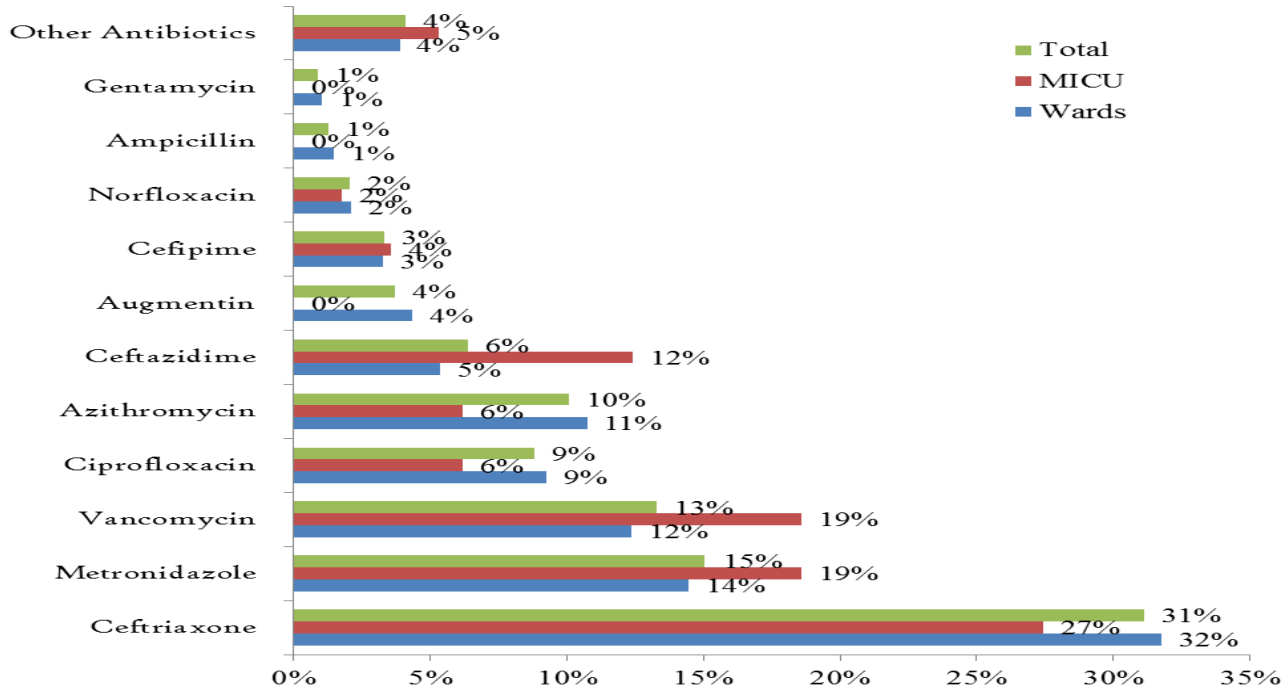

Figure 5: Types of antibiotics used in hospitalized patients with bacterial infection in the internal medicine ward of Tikur Anbessa specialized hospital. *Other Antibiotics : Wards: Clindamycin (5), Cloxacillin- (4), Gemifloxacin- (1), Cefotaxime (2), Cephalexin (1), Crystaline penicillin (1), Doxicycline (3), Meropinem (2), Chloramphenicol (3), Clarithromycin (2), Amoxicillin (2);ICU: Clindamycin(1), Clarithromycin(1), Amikacin(1), Doxycycline(1), Imipenem(1), Cotrimoxazole(1)*

4.4.2. Antibiotic Metrics

A given patient with a bacterial infection was exposed to 1-7 antibiotic courses with a mean of greater than two (Table 3). On average, a given patient with an infection had about two antibiotics simultaneously for both settings. The number of days that elapsed while the patient was on any antibiotic varied between the two settings, being 13.5 for the wards and 9.5 for the medical ICU. Likewise, there was a variation in the average number of agent days, 23.2 for the wards and 18.5 for the medical ICU (Table 3)

Table 3: Antibiotic use based on different metrics for hospitalized patients with bacterial infection in the internal medicine ward of Tikur Anbessa specialized hospital

Variable		Wards	ICU
Agent days, Mean ± SD (R)		23.2±19.5(2-135)	18.5±11.9(5-55)
Antibiotic days, Mean ± SD (R)		13.5±19.6(2-51)	9.5±5.9 (3-30)
Antibiotics course, Mean ± SD (R)		2.4 ±1.1 (1-7)	2.7±1.4 (1-7)
Maximum no. of antibiotics at a time, Mean ± SD (R)		1.9±0.6 (1-4)	2.2±0.8(1-5)
Treatment periods	One	237(84.0%)	38(92.7%)
	Two	39(13.8%)	2 (4.9%)
	Three	6(2.1%)	1(2.4%)

ICU: intensive care unit, SD: standard deviation, R: range

4.4.3. Changes to Initial Therapy

This portion specifically deals with the initial therapy and its adjusted component. Adjustments not related to this were not addressed here. Almost all (99.6%) patients in the wards were started with empiric therapy, except one (0.4%). On the other hand, all 41 of the ICU therapies were empiric. The initial therapy was discontinued in 8 (3.0%) of the wards and 2 (3%) of the ICU patients, and modified in 81 (29.0%) of the wards and 10 (24%) of the ICU patients (Figure 6).

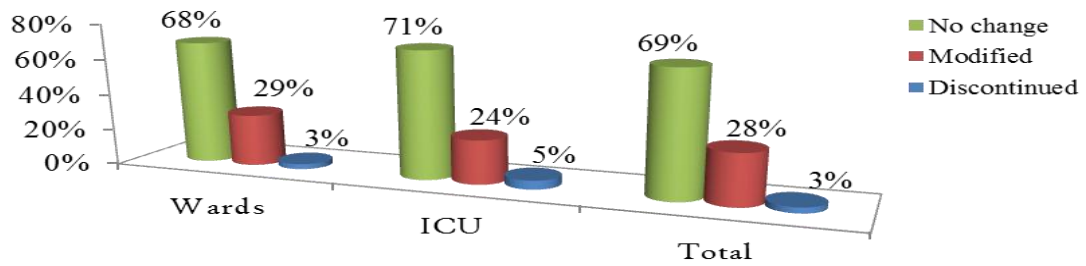

Figure 6: Adjustments to the initial antibiotic therapy for hospitalized patients with bacterial infection in the internal medicine ward of Tikur Anbessa specialized hospital

4.5. Appropriateness of Antibiotic Use

About 80% of patients in the wards and 90% of patients in the ICU had empiric antibiotics prescribed according to international guidelines. On the other hand, among the total 34 culture reports originated from the wards (Table 1), only 5 of them were available within 72 h of antibiotic initiation. Three of the available reports were negative and thus sensitivity was done for the two positive cultures only. The changes made for these 2 were based on the sensitivity report and thus taken as appropriate. However, no discontinuation of the empiric antibiotic therapy was performed for negative culture reports in all of the wards within 5- 7 days, thus all inappropriate.

Dose and dosing interval was adapted to renal failure (glomerular filtration below 50 mL/min/1.73 m^2) for eight of 21 (38.1%) in wards and 1 of 6 (16.7%) of the ICU patients (Table 4). Although 238 ward admitted patients with an intravenous antibiotic survived to the required date, 20 were not candidates for oral therapy (see Annex III for limiting conditions). Among the 218 candidates, only 15 (6.9%) of them had oral switches (Table 4).

Table 4**:** Appropriateness of antibiotic use based on the five quality indicators of antibiotic use

Quality indicators for appropriate antibiotic usage	**Appropriate (Frequency(Percentage))**	
	Wards	**ICU**
Empiric therapy is according to the guidelines	226 of 281 = 80.4%	37 of 41=90.2
Empiric therapy correctly changed according to culture sensitivity result reported within 72 h	2 of 2 Sensitivity reports= 100%	-
Empiric therapy discontinued within 7 antibiotic days due to lack of culture evidence	0 of 3 culture negative reports	-
Dose and dosing interval adapted to renal function	8 of 21 with GFR < 50 mL/min/1.73 m^2= 38.1%	1 of 6= 16.7%
IV to PO changes made within 7 antibiotic days	15 of 218 patients who had $\geq$7 antibiotic days= 6.9%	-

4.6. Hospital Outcome Indicators

There was high mortality in the hospital, 27.13% in the wards and 58.5% in the ICU. The length of stay (mean $\pm$ SD (range)) for wards and ICU was 18.5$\pm$12.2 (3-60) and 8.9$\pm$4.9 (3-23), respectively. However, ICU patients spent 6.3$\pm$9.7 (2-41) days in non-ICU internal medicine wards, before or after their admission to the medical ICU (Table 5).

Table 5: Hospital outcome indicators in hospitalized patients with systemic bacterial infection

Variables	Wards, n=282 (Freq, %)	ICU, n=41(Freq, %)	Total, n=323 (Freq, %)
Final status of patient			
Dead	78(27.7)	24(58.5)	102(31.6)
Discharged	204(72.3)	17(41.5)	221(68.4)
LoS, mean ± SD(R)	18.5±12.2(3-60)	8.9±4.9(3-23)	17.3±11.9(3-60)
LoS outside (for ICU only)	0	6.3±9.7(2-41)	-

LoS: length of stay; ICU: intensive care unit; SD: standard deviation; R: range

4.7. Predictors of Hospital Outcome

The predictors presented below were for the wards only.

4.7.1. Predictors of Mortality

The presence of HIV infection, signs & symptoms of disease, digestive (liver-cirrhosis), neoplasm, sepsis, meningitis, immunosuppression, vancomycin use, increased antibiotic courses (≥2) were positively associated with mortality in the univariate logistic regression, but prolonged LoS mainly favored discharge of patients (Table 6).

All variables having $p \leq 0.05$ in the univariate and those which had association in other multivariate logistic regression (despite lack of association in the univariate) models were included in the final model of multivariate logistic regression. In addition, since the model omitting outliers was more accurate in classifying cases than the one with all cases, the logistic regression model without the outliers was used for predicting mortality. Consequently, presence of HIV (AOR=5.639, 95% CI: 1.828-17.399), $p<0.01$), digestive diseases (AOR=56.09, 95% CI: 10.926-287.955, $p<0.001$), different signs and symptoms of disease (AOR=5.197, 95% CI: 2.28-11.82, $p<0.001$) and neoplasm (AOR=4.23, 95% CI: 1.36-13.13, $p<0.01$) were independent predictors among the primary admission diagnosis. Sepsis (AOR=5.20, 95% CI: 1.69-15.99, $p<0.01$), meningitis (AOR=5.36, 95% CI: 1.28-22.53, $p<0.05$) and renal failure (GFR below 50 mL/min/1.73 m^2) (AOR=4.544, 95% CI: 1.17-17.67, $p<0.05$) were also independent predictors. Vancomycin use (AOR=2.88, 95% CI: 1.07-7.76, $p<0.05$) was the only independent predictor among several antibiotics used. Whilst prolonged antibiotic days (>10) (AOR=0.19, 95% CI: 0.1-.496, $p<0.001$) and ≥3 simultaneous antibiotic uses (AOR=0.053, 95% CI: 0.01-.55, $p<0.01$) were negatively associated, increased antibiotic courses (each with $p<0.05$) were positively associated with mortality among the drug related factors (Table 6).

Table 6: Binary logistic regression analysis for predictors of mortality for hospitalized patients with bacterial infection

Variables	Ward mortality		COR (95% CI)	AOR (95% CI)
	Yes (%)	*No (%)*		
Admission Dx of HIV infection				
No	58(24.5)	179(75.5)	1.00	(Reference)
Yes	20(44.4)	25(55.6)	2.47(1.28, 4.77)**	5.64(1.83, 17.40)**
Admissions Dx of Signs & symptoms				
No	49(23.9)	156(76.1)	1.00	(Reference)
Yes	29(37.7)	48(62.3)	1.92(1.20, 3.37)*	5.20(2.28, 11.82)***
Admissions Dx of digestive problems				
No	67(25.4)	197(74.6)	1.00	(Reference)
Yes	11(61.1)	7(38.9)	4.62(1.72, 12.40)**	56.09(10.93, 287.96)***
Admissions Dx of Neoplasm				
No	51(25.0)	153(75.0)	1.00	(Reference)
Yes	27(34.6)	51(65.4)	1.59(0.90-2.79)	4.23(1.36, 13.13)**
Sepsis				
No	60(24.2)	188(75.8)	1.00	(Reference)
Yes	8(44.4)	10(55.6%)	3.525(1.69, 7.34)***	5.20(1.70, 15.99)**
Meningitis				
No	70(26.5)	194(73.5)	1.00	(Reference)
Yes	8(44.4)	10(55.6)	2.22(0.84-5.84)	5.36(1.28, 22.53)*
GFR below 50mL/min/1.73 m2				
No	69(26.3)	193(73.7)	1.00	(Reference)
Yes	9(45.0)	11(55.0)	2.29(0.91, 5.76)	4.54(1.1, 17.68)*
Immunosuppressed				
No	35(21.7)	126(78.3)	1.00	(Reference)
Yes	43(35.5)	78(64.5)	1.98(1.17, 3.37)**	0.92(0.32, 2.61)
Length of stay				
≤ 16 years	51(33.3)	102(66.7)	1.00	(Reference)
>16 years	27(20.9)	102(79.1)	0.53(0.31, 0.91)*	0.45 (0.18, 1.11)
Vancomycin				
No	46(22.9)	155(77.1)	1.00	(Reference)
Yes	32(39.5)	49(60.5)	2.20(1.27, 3.83)**	2.88(1.07, 7.76)*
Cefepime				
No	69(26.4)	192 (73.6)	1.00	(Reference)
Yes	9(42.9)	12(57.1)	2.09(0.84-5.17)	1.64(0.36, 8.53)
Antibiotic course				
1	8(16.0)	42(84.0)	1.00	(Reference)
2	40(29.4)	96(70.6)	2.19(.94, 5.07)	25.42(2.32, 278.87)**
3	17(29.3)	41(70.7)	2.18(.85, 5.60)	34.69(2.67, 451.11)**
4	6(26.1)	17(73.9)	1.85(.56, 6.15)	37.85(2.04, 701.48)*
≥ 5	7(46.7)	8(53.3)	4.59(1.30, 16.28)*	95.14(4.61, 196.96)**
Maximum no of antibiotics at a time				
One	11(19.0)	47(81.0)	1.00	(Reference)
Two	55(29.7)	130(70.3)	1.81(.87-3.75)	0.43(0.06, 2.95)
≥3	12(30.8)	27(69.2)	1.90(0.74-4.89)	0.05(0.01, 0.55)**
Antibiotic days				
≤10	47(33.8)	92(66.2)	1.00	(Reference)
> 10	31(21.7)	112(78.3)	0.54(0.32, 0.92)	0.19(0.08, 0.50)**

**p < 0.05; **p< 0.01; ***p<0.001; Dx: Diagnosis; COR: crud odds ratio; AOR: Adjusted odds ratio; CI: confidence interval*

4.7.2. Predictors of Prolonged Length of Stay

Age, on admission diagnosis of infection, aspiration pneumonia and hospital acquired pneumonia, meningitis, hospital origin of infection, and mortality were the disease related predictors of prolonged LoS in the Univariate logistic regression. Among the drug and related predictors, ceftazidime, vancomycin, ciprofloxacin, norfloxacin, antibiotic courses of 5 or more, agent days of $\geq$ 21, treatment periods, and modification to the empiric therapy were also associated with prolonged LoS (Table 7).

All predictors in the univariate model ($p \leq 0.05$) were included for analysis in the mulitivariate logistic regression model. The analysis revealed that age range of 25-44 (AOR=2.68, 95% CI: 1.10-6.53), $p<0.05$), presence of hospital acquired infection (AOR=2.39, 95% CI: 1.08-5.29, $p<0.05$) and prolonged agent days beyond 21 days (AOR=15.87, 95% CI: 4.56-55.24), $p<0.001$) were positively associated with prolonged LoS. Presence of on admission infection was negatively associated with prolonged LoS (AOR=.40, 95% CI: 0.18-.87, $p<0.05$), (Table 7).

Table 7: Binary logistic regression analysis for predictors of prolonged length of stay for hospitalized patients with bacterial infections

Variables	LoS		COR (95% CI)	AOR (95% CI)
	≤ *16 days* (%)	> *16 days* (%)		
Age groups (year)				
18-24	28(54.9)	23(45.1)	1.00	(Reference)
25-44	49(41.9)	68(58.1)	1.69(.87, 3.28)	2.68(1.10, 6.53)*
45-64	41(58.6)	29(41.4)	0.861(.42, 1.78)	2.35(0.90, 6.14)
≥65	35(79.5)	9(20.5)	0.313(.13, .78)**	0.42(0.13, 1.31)
Admission Dx of Infection				
No	32(43.8)	41(56.2)	1.00	(Reference)
Yes	121(57.9)	88(42.1)	0.57(.895, 5.44)	0.40(0.18, 0.87)*
Aspirational pneumonia				
No	133(52.2)	122(47.8)	1.00	(Reference)
Yes	20(74.1)	7(25.9)	0.38(.16, .93)*	0.53(0.14, 1.98)
Hospital acquired pneumonia				
No	149(57.1)	112(42.9)	1.00	(Reference)
Yes	4(19.0)	17(81.0)	5.65(1.85, 17.26)**	2.59(0.50, 13.33)
Meningitis				
No	138(52.3)	126(47.7)	1.00	(Reference)
Yes	15(83.3)	3(16.7)	0.22(.06, .77)*	0.20(0.03, 1.13)
Origin of infection				
Unknown	98(58.7)	69(41.3)	1.00	(Reference)
CAI	44(55.0)	36(45.0)	1.16(.68, 1.99)	1.63(0.53, 5.03)
HAI	11(31.4)	24(68.6)	3.20(1.42, 6.74)**	2.39(1.08, 5.29)*
Ceftazidime				
No	144(58.5)	102(41.5)	1.00	(Reference)
Yes	9(25.0)	27(75.0)	4.23(1.91, 9.39)***	3.39(0.93, 12.35)
Vancomycin				
No	122(60.7)	79(39.3)	1.00	(Reference)
Yes	31(38.3)	50(61.7)	2.49(1.47, 4.23)***	1.21(0.43, 3.43)
Ciprofloxacin				
No	130(58.6)	92(41.4)	1.00	(Reference)
Yes	23(38.3)	37(61.7)	2.27(1.27, 4.08)**	0.88(0.37, 2.10)
Norfloxacin				
No	149(55.6)	119(44.4)	1.00	(Reference)
Yes	4(28.6)	10(71.4)	0.05(.96, 10.23)	3.36(0.74, 15.36)
Antibiotic courses				
1	27(54.0)	23(46.0)	1.00	(Reference)
2	90(66.2)	46(33.8)	0.60(0.31, 1.16)	0.33(0.11, 1.01)
3	28(48.3)	30(51.7)	1.26(0.59, 2.68)	9.23(0.05, 1.00)
4	7(30.4)	16(69.6)	2.68(0.94, 7.65)	0.54(0.07, 4.04)
≥ 5	1(6.7)	14(93.3)	16.44(2.01, 134.69)**	0.52(0.03, 9.23)
Agent days				
< 10 days	44(69.8)	19(30.2)	1.00	(Reference)
11-20 days	78(70.9)	32(29.1)	0.95(0.48, 1.87)	1.86(0.62, 5.56)
≥ 21 days	31(28.4)	78(71.6)	5.83(2.95, 11.5)***	15.87(4.56, 55.24)***
Treatment periods				
1	139(58.6)	98(41.4)	1.00	(Reference)
2	13(33.3)	26(66.7)	0.14(0.02, 1.23)	0.56(0.03, 9.30)
3	1(16.7)	5(83.3)	0.40(0.04, 3.79)	0.19(0.01, 3.18)
Adjustment to Empiric therapy				
No change	119(61.7)	74(38.3)	1.00	(Reference)
Modified	27(33.3)	54(66.7)	3.22(1.86. 5.55)***	2.31(0.77, 6.90)
Discontinued	7(87.5)	1(12.5)	0.23(0.03, 1.91)	0.26(0.02, 3.25)

**p < 0.05; **p< 0.01; ***p<0.001; Dx: Diagnosis; CAI-community acquired infection; HAI-hospital acquired infection; COR: crud odds ratio; AOR: Adjusted odds ratio; CI: confidence interval*

5. DISCUSSION

In the previous decades, several studies have reported changes in epidemiology, microbiology and outcomes in adults with infections and addressed variable clinical presentation of infectious diseases (Weinstein *et al*., 1983; Lark *et al*., 2001; Diekema *et al*., 2003).

Unlike other studies (Storey *et al*., 2012), in the present study, infection was the primary diagnosis for admission followed by circulatory disorders. Consistent with reports by Camins *et al***. (**2009) and Storey *et al*. (2012) pneumonia was the most common source of infection in hospitalized patients. In line to Hall *et al***. (**2007 and 2010), majority (24.2%) of the pneumonia cases were community acquired. Although there is dearth of evidence in adults in our country, the Ethiopian demographic health survey stated pulmonary infections as the leading cause of morbidity and mortality (CSA and ICFI. 2012). Cephalosporins were the most commonly used drugs followed by the anti-anaerobic and glycopeptides (vancomycin) for such infections in the hospital. A study conducted in other countries reported floroquinolones or penicillins as the major prescribed drugs (Storey *et al.,* 2012). Unlike this study, most studies conducted in regional hospitals of Ethiopia reported penicillins as the top prescribed drugs **(**Zeresenay *et al.*, 2002*;* Endale *et al.*, 2013; Woldu *et al*., 2013**).** Comparable to studies by Ayele *et al*. (2013) and Sileshi *et al*. (2015), in the present study, empiric therapy was initiated for 99.6% of patients in the wards and all patients in the ICU. Including the current, all these studies conducted in TASH were in complete disagreement with a study performed in one teaching hospital (Mettler *et al*., 2007), where empiric therapy was initiated only in 19.4% of the patients.

One of the important issues in stewardship is the need assessment performed in line with hospital outcome indicators. Being one of the outcome indicators, prolonged LoS was enormously associated

with higher hospital costs (Mauldin et al., 2010). The mean LoS reported for the medical wards in this study was four times higher than reported by Usman *et al*. (2011) and Ghods *et al*., (2014) for the general patients, and about 2 times higher than reported by Battleman *et al*. (2002) and Suter-Widmer *et al*. (2012) for pneumonia cases. The most probable reasons for an extended LoS observed in TASH might be related to the hospital system gaps like waiting for diagnostic or therapeutic procedures, or delay in discharge (Ghods *et al*., 2014). Another possible explanation could be due to the presence of MDR bacterial strains that could potentially extend the in-hospital day care (Zilberberg *et al.*, 2009; Lye *et al*., 2012). On the other hand, the present study showed about a three-fold and four-fold higher ICU mortality than reported in high (20%) and low (15.4%) antibiotic resistance countries, respectively (Hanberger et al., 2014). A study conducted among pneumococcal bacteremia patients in 21 hospitals in 10 countries (including developed and developing countries) reported a mortality rate of 16.9% (Yu *et al*., 2003). This was lower than the ward mortality found in the current study (27.7 %). Another study conducted in a Gambian hospital (Hill *et al*., 2007) reported an overall mortality of 6% and bacteremia attributed mortality of 8.3%, which is above 3 times lower than reported in this study. All these collectively indicate that the mortality in the current study was incomparably high, seeking an immediate attention. As to our understanding, the absence of effective antimicrobial use polices in the hospital may be one of the reasons for the high mortality and prolonged length of stay reported in our study.

Since the predictors in the medical ICU did not reach statistical significance (may be because of the small sample size that decrease the statistical power), the values in the subsequent discussion were solely performed for the medical wards, unless otherwise indicated. The analyses indicated that patients with prolonged LoS tended to survive, while those with shorter LoS tended to die, as more than half of the non-survived patients with systemic bacterial infection died under the median day of

in-hospital stay in both the wards and ICU. In other words, the increased survival observed in the prolonged care attendants might be attributed to the prolonged antibiotic treatment periods as evidenced by the benefit of survival for > 10 antibiotic days ($p<0.01$) and prolonged LoS observed with prolonged agent days (≥21 days) (*$p<0.001$*). However, this inverse relation between mortality and prolonged LoS failed to reach statistical significance in the multivariate model. This finding is in line with Lagu *et al*. (2011), where no significant association was found between hospital stay and mortality.

Among the socio-demographic characteristics of patients, only age categories showed an association with LoS. Unlike previous studies (Yu *et al*., 2003; Nakamura *et al*., 2006; Robenshtok *et al*., 2006), older age was not significantly associated with mortality, in the current study. Furthermore, in disagreement with other findings (Maguire *et al*., 1986; Gordon 2003; Suter-Widmer *et al*., 2012) that reported association of advanced age with prolonged LoS, this study found independent association of middle age (25-45) with prolonged LoS as compared to young age (18-24) (*$p<0.05$*). Since, middle-aged people form immunologically competent group of the population that require shorter in-hospital care, other hospital-based factors like waiting for diagnostic or therapeutic procedures or delay in discharge might contribute for the observed association (Ghods et al., 2014). In other words, since there was no association of age with prolonged LoS in the linear regression analysis, the result for binary regression may be attributed to the increase in the figures (since most (40.8%) of the populations were classified under this category) that pooled the association.

Prolonged LoS did not have association with primary admission diagnoses (except with infectious admission) and consecutive infection diagnosis in the multivariate analysis. This finding is in contrast with an observational study by De Buyser *et al*. (2014) performed in geriatric and internal medicine acute care wards of Italian hospitals, where primary reason of admissions like metastasized

cancer, renal failure or dialysis and infection as independent predictors of LoS. In contrast to De Buyser *et al*. (2014) again, neoplastic disease had independent association with mortality in this study, despite the association was not revealed in the univariate model.

Other strong independent predictors of mortality were the presence of different signs and symptoms of diseases and digestive disorders (both with $p<0.001$). The former was in agreement with a study conducted in the medical wards of Queen Elisabeth Central Hospital in Malawi (Gordon, 2003), where hypotension and level of consciousness were shown to be important predictors of mortality in patients with pneumococcal meningitis or bacteremia. Similarly, Diekema *et al*. (2003) also reported association of hypotension with mortality in community onset blood stream infected patient groups. Based on the ICD 10 criteria, digestive disorders encompass liver disorders, which might be the most probable reason for death in the current study. In this regard, the study was in agreement with other published reports (Tumbarello *et al*., 2007; Fernández *et al*., 2012). The mortality might be attributed to various reasons like the presence of resistant bacterial strains. Indeed, several studies (Fernández *et al*., 2012; Ariza *et al*., 2012; Tandon *et al*., 2012) conducted in cirrhotic patients reported the contribution of development of antibiotic resistant infections to increased mortality. Furthermore, this study also found independent association with HIV in line with other studies (McCabe *et al*., 2009). These groups of population are often nutritionally or immunologically impaired, making them an easy target for infection and its associated complications (Greenberg *et al*., 2012). However, analysis of association using immunosuppressed group as a factor failed to produce any association with mortality. This could most probably be because of the masking effect of one on another, as the group included several diseases (cirrhosis, febrile neutropenia, HIV and disseminated TB) that exhibited opposite association with mortality.

Among the infection diagnoses, sepsis had profound association with mortality both in the univariate (*p<0.001*) and multivariate (*p<0.01*) models. Similarly, several studies across the world reported the deadly nature of sepsis (Kang *et al*., 2004*;* Gaieski *et al*., 2013; McPherson *et al*., 2013). Accordingly, ASPs make it their prime concern (Storey *et al*. 2012). Another infection diagnosis that had significant association (*p<0.05*) in the multivariate model with mortality is meningitis. In agreement with this, different studies also revealed the deadly nature of meningitis (Berkley *et al*., 2001; Scarborough *et al*., 2007; Wall *et al*., 2013). This implies that the two infections should be the focus of future stewardships.

Different observational studies found an independent link between cefepime use and mortality (Chopra *et al*., 2012). In the current study, however, among all patients who used different antibiotics, only those with vancomycin were more than 2 times more likely to die (39.5%) both in the unvariate and multivariate binary logistic models (COR=2.20, 95% CI: 1.27-3.83, *p<0.01*; AOR= 2.88 95% CI: 1.07-7.76), *p<0.05*). Although no studies were found with similar methodological approach in support of our evidence, this could possibly be explained by the inappropriate use of the drug in the hospital as evidenced by its guideline non-concordant use. From guideline non-concordant empiric therapy uses, inappropriate vancomycin use was among the top (34 % inappropriate empiric therapy uses were vancomycin misuses). In support of this, vancomycin use evaluation conducted in the internal medicine ward of TASH also revealed that vancomycin dose was not adjusted or adjusted inadequately in 96.5 % of the cases (Zeleke *et al*., 2013). Another possible explanation may be attributed to the different complications that are inherent with the drug's pharmacology (Moore *et al*., 2011) and the emergence of resistant strains that potentially decrease the drug's outcome (Bhavnani *et al*., 2000; Carmeli *et al*., 2002; Moore *et al*., 2011; Minejima *et al*., 2014).

Measurement of drug consumption using antibiotic days, agent days and other metrics is an important component of antimicrobial stewardship (Berrington A., 2010). In the current study, patients with prolonged antibiotic days beyond the median (10) day were more likely to survive than to die *(p<0.01*). This point, however, should be interpreted cautiously, as prolonged antibiotic exposure is associated with multiple costs like emergence of antibiotic resistance (Dennesen *et al*., 2001). Several studies attempted to address this concern and compared shorter (one week) verses longer treatment durations, and found no difference in outcome (Chastre *et al*., 2003; Moussaoui *et al*., 2006; Havey *et al*., 2011). The difference observed between the current and these studies might be attributed to methodological differences, including setting cut-off date for mortality. The fact that majority of our patients had pneumonia and other infections that could have been treated effectively with shorter courses of antibiotics points to the possibility that patients might have survived because of other reasons. Hence, using cut-off date mortality, correlational timing relative to antibiotic initiation and death, and using other advanced statistical options could best reveal this association.

On the other hand, patients treated with three and more antibiotics simultaneously, were more likely to survive than single antibiotic users (*p<0.01*). This is in line with the advantages of combination therapy reported in different observational studies (Tamma *et al*., 2012). In general, however, meta-analyses of observational studies have shown a benefit of combination therapy, while those including randomized controlled trials (RCTs) have not demonstrated such benefits (Marcus *et al*., 2011). Hence, because of fear of emergence of resistance, toxicity and the absence of clear significant advantage with combination therapy in randomized studies, guidelines restrict such treatment approaches for certain group of patients (Dellinger *et al*., 2013). Patients at risk of MDR gram-negative infections including patients with compromised immune systems, those with previous ICU admissions, or recent recipients of broad-spectrum antibiotics could be candidates for such

combinations. However, such regimens should be promptly de-escalated based on the patient's clinical course, and culture & susceptibility test results in order to avoid further emergence of resistance and adverse side effects (Marcus *et al*., 2011; Tamma *et al*., 2012, Dellinger *et al*., 2013). Despite this concept and Mettler *et al*. (2007) report, though almost all our patients started with broad-spectrum combination empiric therapies, modification was done only for quarter of the patients (29% for wards vs. 24% for ICU). Even these modifications did not necessarily indicate streamlining (lowering the estimate), since majority of the modifications involved addition of therapy for clinical deterioration, identification of new site of infection, and for culture positive microbiologic reports.

Other important predictors addressed were those indicating exposure to more resistant strains of infection like hospital onset and MDR infection. Despite these patients are at high risk of resistant bacterial infection, they also usually experience delays in receipt of appropriate antibiotics compared to low risk patients (Cardoso *et al*., 2013; Moehring *et al*., 2013) leading for their poor hospital outcome (Schwaber *et al*., 2007, Cardoso *et al*., 2013). Unlike the current study, Diekema *et al*. (2003) and Zilberberg *et al.,* (2009) reported association of nosocomial origin of infection with mortality. Nevertheless, the current study is in agreement with Zilberberg *et al.* (2009) with the statistically significant association found between hospital acquired infections and prolonged LoS. On the other hand, though studies (Schwaber *et al*., 2007, Lye *et al*., 2012) reported the profound effect of MDR infection in the outcome of hospitalized patient, this study was not expressed in that way neither in the univariate nor in the multivariate logistic regression models for both mortality and prolonged LoS. The study performed by Lye *et al*. (2012) reported an independent association of MDR risk with prolonged LoS in survivors. A similar study (Lye *et al*., 2012) reported the association of MDR with 30-day mortality, despite the absence of such evidence in the multivariate

analysis. This difference may be attributed to the partial identification of patients, since above 85% of the patients were not known with respect to their MDR risk status, which could have potentially decreased the statistical power.

Among the 5 quality indicators, only concordance to the guideline and intravenous to oral switch were tested for statistical association and found to be associated neither in the univariate nor in the multivariate model with both outcome indicators. The remaining 3 quality indicators had too low observations to test, with profoundly different denominators. Descriptively 6.9% of the wards and none of the ICU admitted patients had intravenous to oral conversions in this study. This was in disagreement with the findings reported by Sevinc *et al*. (1999) who reported 54% switch and Mertz *et al*. (2009) who reported 61.4%. On the other hand, as per a study (Ayele *et al*., 2013) done on third generation cephalosprins in the internal medicine ward of TASH using IDSA guideline, the empiric antibiotic use was guideline non-concordant in most of the cases than reported in the current study. This difference was mainly attributed to the criteria used in labeling non-concordance. In the current study, only initial drug class recommendations were used irrespective of their specific dosage regimens, unless there is an overt deviation. However, Ayele et al. (2013) also addressed dose, dose adjustment and culture-sensitivity reports. Furthermore, 99.3% of the wards and all of the ICU antibiotic uses were inappropriate, when availability of culture-sensitivity report to initiate and/or modify empiric therapy was used as a sole quality indicator in the current study. Incomparably, a study using correct changes to culture-sensitivity reported only 22% of the new antibiotic initiations as inappropriate (Montravers *et al*., 2011). As per another study reported by Erbay *et al.* (2005) in Turkey, antibiotics ordered empirically were found to be less appropriate than those ordered with evidence of culture and susceptibility results, signifying the necessity of such reports.

6. LIMITATIONS OF THE STUDY

Since this study was a 3 month long prospective observational, unlike to the previous works, it has made timely, relevant, unique and comprehensive contribution in uncovering the facts for the prudent use of antibiotics. Being an observational analysis, however, it had some limitations. Given its prospective nature, an attempt was made to fill the information gaps in the charts through seeking assistance from physicians on the spot. On the other hand, the study was conducted in only one hospital, and practice patterns, patients' characteristics and microbiology resistance patterns may vary among hospitals, which may limit the generalizability of the research. Use of international guidelines might also under or overestimate the report. Because of the initial different design of the data abstraction sheet, there were some partially addressed factors and the recommendations based up on these partial data may possibly introduce some bias. In connection to this, the reports about the origin of infection and MDR risk factors should be interpreted cautiously.

Although the use of multivariate analysis helped to control a substantial proportion of any confounding variable, data related to some important variables like severity of the illness, the presence of medical devices, previous ICU admission and antibiotic exposure status were not reported, and thus not included in the multivariate analysis. Therefore, all these might have affected the outcomes.

7. CONCLUSION

This observation showed that more than half of the patients had suspected infection and received antibiotics on empiric basis in which almost none were justified based on microbiologic cultures. Different patient, disease and drug related characteristics were identified to be strong and independent predictors for mortality and Prolonged LoS. Since pulmonary infections were the most frequent type and infections such as sepsis and meningitis were the most life-threatening ones, local guidelines or any other stewardship activities should give priority to these issues. Among the drugs, vancomycin, cephlosporins and other broad spectrums need special emphasis. Generally, these observations call for the establishment of local antibiotic use protocols to initiate an appropriate antibiotic immediately, to de-escalate in line to microbiologic reports, and to stop irrational use of antimicrobials as a whole. Therefore, in view of the limited number of publications on this topic, the results should be of interest to clinicians and other concerned stakeholders in the field.

8. RECOMMENDATION

- ☞ TASH should immediately established Antimicrobial stewardship program and make it functional to facilitate appropriate use of antimicrobials.
- ☞ ASPs would rather address ICU infections and those with febrile neutropenia, separately.
- ☞ A subsequent intervention involving development of local guideline, formulary restriction, and clinician education should be introduced by TASH, FMHACA, MOH and other stakeholders to reduce antibiotic exposure, decrease health care costs, and improve patient safety.
- ☞ Antimicrobial stewardship programs can use this model of needs assessment to identify focus areas of quality improvement.
- ☞ Future researchers should better use advanced statistical options to prove real association.

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ANNEXES

Annex I: Data Abstraction Format

1. Bed no: _____ Patient card no: _____
2. Age of patient: _____; Region where patient came from; _____
3. Sex of patient: A) Male B) female
4. Final status of the patient: A) Discharged B) Dead
5. Length of stay, days: _____(including the admission and discharge dates)
6. Primary(Admission) Diagnosis, may be more than one: _____
7. Patient have immunosuppressive disease (HIV, disseminated TB, febrile neutropenia & cirrhosis) A) Yes B) No
8. Type of Infection diagnosed (it may be primary or developed after admission):
   A) Bacterial (specify)
   B) Viral (specify)
   C) Fungal (specify)
   D) Parasitic (specify)
9. Presence or development of surgical site infections A) Yes B) No
10. If the infection is bacterial, in question 8 and 9 above, write the detail of the drug/s given as follows:

Antibiotics (AB)	AB_1	AB_2	AB_3	AB_4	AB5	AB6
Date started						
Date stopped						
Name						
Dose prescribed						
Frequency of use						
Route of administration						
Duration of treatment						
Indication of treatment						
Nature of the drug use						
A Primary treatment (Rx)						
B Extension/alternative Rx						
C Reason for B (resistance / toxicity/organ failure/DI/CI)						
Cost (pharma purchase data)						

11. No of antibiotics at a time as a primary treatment (A) : A) One B) Two;_____, C) There_____, D) four _____, D) > four
12. No of antibiotics at a time as an extension/alternative treatment (B): A) One B) Two;_____ C) There _____ D) four _____, D) > four
13. Which laboratory technique/s is/are used to aid the diagnosis
    A) I) No; II) yes: Gram stain report date _____ Result: (A) positive (B) negative)
    B) I) No; II) yes: Culture result report date: _____ Result: (A) positive (B) negative
    C) I) No; II) yes: Serologic/other test (result: (A) indicative (B) not indicative of infection)
    If, indicative: Temp_____ CBC _____, Chest X ray_____, Others:_____
14. If culture was done, write the specific pathogen identified and the sensitivity for the given drugs (if done)_____
15. Was any action made based on the cultureresult? A) yes B) No
16. If yes, for the above question, what was done?
    A) Discontinue agent(s) (specify the drug/s discontinued) ----------
    B) Limit duration (specify the duration----------)
    C) Optimize dose (specify the dose----------)
    D) Broadening the spectrum, adding/changing the drug) (write the change----------)
    E) Others (specify----------)
17. Was an IDconsultation made? A) yes B) No
    If yes, specify any change made:_____
18. Was the drug discontinued by any reason other than mentioned in qn 13, 14 & 15 A) Yes (specify the reason----------) B) No
19. Was any intravenous (IV) to oral (PO) change made? A) yes B) No
    i) If yes, for which drug/s? (Specify the drug/s, the dose & its IV treatment duration)
    _____
    ii) Is there any conditions that limit oral intake and gastrointestinal absorption? A)yes B) No
20. Major organ dysfunction identified (highest lab values during the period of antibiotic use should be used)
    A) I) No;II) yes: RFT report date_____ values: Scr/CrCl_____, BUN_____ GFR: ___
    B) I) No; II) yes: LFT report date_____ values: ALT/SGPT/_____ AST/SGOT/:_____ Others _____

21. Was any adjustment for renal function done? A) yes B) No

If yes, specify the drug, the changes made and the GFR/SCr/Cr_{CL} value?

_____

22. Was any adjustment for any other reasons done? A) yes B) No

If yes, specify the drug, the changes made and the reason of change?

_____

23. Specify any other information necessary, which may be related to previous antibiotic use, hospital admission, infection history etc. (*please note the date of the event too*)

_____

Annex II: Weekly Data Crosschecking Sheet

Helped to know the denominator, avoid errors, & maximize completeness and Effectiveness.

Ward* B5 (32 functional beds)

		First patient on the given bed					
Bed		Card no	Date of admission	Primary Diagnosis	Infectious Diagnosis	Antibacterial agent	Date of discharge
B 505	1						
	2						
	3						
	7						
	4						
	5						
	6						
B 506	1						
	2						
B 507	1						
	2						
	3						
	7						
	4						
	5						
	6						
B 513	1						
	2						
	3						
	7						
	4						
B 515	5						
	6						
	3						
	7						
	4						
	5						
	6						
B 525	1						
	2						

Total no of admissions per week:_____

**Similar sheet was used for Ward B8 (30 functional beds), Ward C8 (28 functional beds), Ward D8 (28 functional beds) and Medical ICU (6 functional beds)*

Annex III: Quality Indicators

s.no.	**Quality indicator** All patients are: adults, admitted to ICU and non-ICU internal medicine wards with > 24 h of systemic antibiotics because of a suspected systemic bacterial infection	**Numerator description** All patients are: adults, admitted to ICU and non-ICU internal medicine wards with > 24 h of systemic antibiotics because of a suspected systemic bacterial infection	**Denominator description** All patients are: adults, admitted to ICU and non-ICU internal medicine wards with > 24 h of systemic antibiotics because of a suspected systemic bacterial infection
1.	Empirical systemic antibiotic therapy should be prescribed according to internationally widely used guidelines, IDSA based (since no local guidelines)	Number of patients who started with empirical systemic antibiotic therapy according to the guideline	Total number of patients who started with empiric systemic antibiotic therapy
2.	Empiric antibiotic therapy should be changed to pathogen directed as soon as culture results become available **Culture reports for the adjustment were expected to be available within 48-72 hours of empiric therapy initiation, otherwise not considered*	No of patients with empiric systemic antibiotics whose culture reported positive within 48-72 hours and changing to pathogen directed therapy was done appropriately ** Appropriate is when the infective organism is also sensitive for a narrow spectrum antibiotic changed*	Total no of patients with empiric systemic antibiotics whose culture reported positive within 48-72 hours *and in whom changing to pathogen directed therapy was done.* .
3.	Dose and dosing interval of systemic antibiotic should be adapted to renal function	No of patients with a compromised renal function who started with an empirical systemic dose adjusted to renal function.	Total number of patients who started with empirical systemic antibiotic therapy and who had a compromised renal function, **defined as an estimated Glomerular filtration rate (GFR) < 50 ml/min/1,73m*
4.	Empiric antibiotic therapy for presumed bacterial infection should be discontinued within 7 days if culture was reported to be negative	No of patients whose empiric antibiotic therapy is discontinued within 7 days, because of lack of microbiological evidence of infection.	Total number of patients who started empirical systemic antibiotic therapy, but lacked microbiological evidence of infection.
5.	Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 7 days of antibiotic initiation for all patients surviving to this date and continued with the treatment unless there is limiting conditions, **Limiting conditions, When oral intake and gastrointestinal absorption are inadequate, (exceptions like endocarditis, meningitis)*	Number of patients with intravenous antibiotics for 7 and greater days, in whom changes to oral agent was done.	Total number of patients with intravenous antibiotics for 7 and greater days, in whom changing to oral antibiotic therapy was expected.