Title: A Retrospective Comparison of Broad Spectrum and Pathogen-Directed Antimicrobial Treatment of Acute Respiratory Distress Syndrome in HIV/AIDS patients.

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ABSTRACT

BACKGROUND: Globally, HIV (Human Immunodeficiency virus) prevalence is highest in Sub-Saharan Africa (WHO, 2015). Acute respiratory failure is the leading cause for admission and mortality in the ICU (Intensive Care Unit) for HIV infected patients (Sarkar and Rasheed, 2013). There appear to be no formal or standardized antimicrobial treatment guidelines for treating ARDS (Acute Respiratory Distress Syndrome) in patients with AIDS (Acquired Immunodeficiency Disease Syndrome).

METHOD: This retrospective descriptive comparative study employed chart review in order to compare patient outcomes of HIV infected patients, admitted with an ARDS diagnosis to the ICU of a private hospital in Richards Bay (Kwazulu-Natal) between January and December 2013, following one of two treatment regimens: 1) pathogen-directed antimicrobial treatment or 2) broad spectrum antimicrobial treatment. Total population sampling was performed for this study and data was collected by means of data collection sheets. The included patients (n=30) were allocated to either one of the two treatment groups based on the antimicrobial treatment they received in the ICU (broad spectrum antimicrobial treatment, n = 12 and pathogen-directed antimicrobial treatment, n = 18). The main outcome parameter for this study was survival rate to ICU discharge. The secondary outcome parameters were length of ICU stay and duration of antimicrobial therapy. The outcomes were compared both culture “blind” (without taking culture results into consideration) and cultures revealed (for patients with the same culture result).

RESULTS: From the sample of 30 included patients there were 18 survivors (broad spectrum antimicrobial treatment, n = 7 and pathogen-directed antimicrobial treatment, n = 11). For the culture “blind” analysis, there was a significant difference in patient outcome for the main outcome parameter ($p < \alpha$; $\alpha = 0.05$) as well as for the secondary outcome parameters ($H \geq 3.84$ (critical value); $\alpha = 0.05$). 50% surviving patients in the broad spectrum treatment group were discharged by 43 days in the ICU (median survival rate) and 50% surviving patients in the pathogen-directed treatment group were discharged by 17 days in the ICU. The median length of ICU stay was 43 days for the broad spectrum treatment group and 17 days for the pathogen-directed group. The median duration of antimicrobial treatment was

43 days for the broad spectrum group and 17 days for the pathogen-directed group. For the cultures “revealed” analysis no formal statistical tests were performed due to small sample size (five surviving patients). For the broad spectrum treatment group, 100% surviving patients were discharged by 7 days in the ICU and for the pathogen-directed group, 100% surviving patients were discharged by 32 days in the ICU. The median length of ICU stay was 11 days for the broad spectrum group and 21 days for the pathogen-directed group. The median duration of antimicrobial treatment was 11 days for the broad spectrum group and 21 days for the pathogen-directed group.

CONCLUSION: This study revealed that there is a difference in patient outcome for the two antimicrobial treatments (broad spectrum and pathogen-directed). The culture “blind” analysis indicated that the pathogen-directed antimicrobial treatment is the treatment with the best outcome for AIDS patients with ARDS in the ICU, but the cultures “revealed´ analysis indicated to opposite, with broad spectrum antimicrobial treatment the treatment with the best patient outcome. In the latter case, however, no formal statistical tests were performed due to small sample size. The pathogen-directed approach will be the recommended treatment approach for treating ARDS among AIDS patients in the ICU for the draft in-house guideline. This approach resulted in better patient outcomes for the culture “blind” analysis. It is also the approach that theoretically limits the risk of antimicrobial resistance (van der Eeden et al., 2005). However, a larger study is necessary in order to confirm these results.

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LIST OF ACRONYMS AND ABBREVIATIONS

AIDS	Acquired Immunodeficiency Disease Syndrome
ARDS	Acute Respiratory Distress Syndrome
BREC	Biomedical Research Ethics Committee
CD4	Cluster of Differentiation 4
COPD	Chronic Obstructive Pulmonary Disease
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
TB	Tuberculosis
WHO	World Health Organization

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CHAPTER 1. INTRODUCTION

1.1 BACKGROUND

Acute Respiratory Distress Syndrome:

Acute Respiratory Distress Syndrome (ARDS) is a serious reaction brought on by injury or acute infections of the lung, causing the leaking of more fluid than normal from the blood vessels into the alveoli (air sacs) and thus preventing the transport of oxygen from the atmosphere into the bloodstream. This leads to hypoxemia, multiple organ failure and eventually to death (American Thoracic Society, 2000).

Patients with AIDS (Acquired Immune Deficiency Syndrome) frequently present with a wide spectrum of pulmonary complications resulting from a variety of opportunistic infections. Opportunistic infections of the lungs can result in ARDS. Acute respiratory failure is the main cause for intensive care unit (ICU) admissions for patients with HIV (Human Immunodeficiency Virus) and is associated with mortality rates as high as 50-68 percent (Sarkar and Rasheed, 2013).

The most common infectious causes of acute respiratory failure in patients with AIDS are *Pneumocystis jirovecii* pneumonia and bacterial pneumonia (Sarkar and Rasheed, 2013 and Benito et al., 2012). In developed countries, the incidence for bacterial pneumonia is 60 percent and for *Pneumocystis jirovecii* pneumonia, 20 percent (Benito et al., 2012). *Streptococcus pneumoniae* is most frequently the cause of bacterial pneumonia (incidence of 70 percent) in HIV infected patients, followed by *Haemophilus influenza* (10%), *Staphylococcus aureus* (9%) and *Pseudomonas aeruginosa* (5%) (Benito et al., 2012). Fungal infections include *Histoplasma capsulatum, Crytococcus neoformans, Coccidioides immitis* and *Aspergillus.* Other causative pathogens of respiratory failure include *Mycobacteria,* viruses such *as Cytomegalovirus* and *Herpes Simplex* virus and parasites like *Toxoplasma gondii* (Benito et al., 2012).

According to the American Thoracic Society (2000) management of ARDS consists of treating the underlying cause or illness, supportive care and prevention of complications. Supportive care is done by means of mechanical ventilation in order to deliver enough air to ensure adequate oxygen levels. The necessity for mechanical ventilation indicates severe ARDS. ARDS is considered severe if the ratio of partial pressure arterial oxygen and fraction of inspired oxygen is equal to or less than 100mmHg (BMJ Best Practice, 2016). In order to treat the underlying cause of ARDS appropriately, causative pathogen(s) need to be identified and the most appropriate antimicrobial(s) should be used to treat the patient.

Most microbiological results only become available two to three days after cultures have been collected. Nonetheless, delayed treatment of ARDS – especially in combination with HIV – has potentially serious consequences, including increased mortality rates (Kollef, 2008 and Kumar et al., 2006). Therefore, it is common clinical practice to initiate empirical antimicrobial treatment as soon as a diagnosis of ARDS is established (Leekha et al., 2010). This approach can result in patients' excessive exposure to (often inappropriate) antimicrobials. Unnecessary or inappropriate antimicrobial treatment is known to lead to adverse events and increased healthcare costs (Glowacki et al., 2003) as well as increased antimicrobial resistance (Leone and Martin, 2008). No literature was found indicating a specific empirical antimicrobial treatment strategy for AIDS patients with ARDS.

Factors other than inappropriate antimicrobial treatment that can negatively affect the outcome for HIV infected patients with acute respiratory failure in the ICU include; mechanical ventilation, delayed ICU admission, increasing age, and the severity of illness (Sarkar, P. and Rasheed, HF. 2013).

Antimicrobial resistance:

Antimicrobial resistance is a pressing international concern (World Health Organization, 2013). The problem with antimicrobial resistance is that it reduces effectiveness of treatment. This leads to an increase in mortality rate, duration of treatment, healthcare costs and economic burden as more expensive therapies have to be used due to resistance to first-line treatment. The main contributing factor

to the emergence of antimicrobial resistance in hospitals is the excessive and prolonged antimicrobial treatment the patients receive. Another factor is the transmission of drug resistant pathogens among the large number of immunocompromised patients that are in close proximity to one another (MacDougall and Polk, 2005).

Bacterial pneumonia is the main cause of acute respiratory failure in HIV infected patients, with *Streptococcus pneumonia* as the most frequently causative pathogen (Benito et al., 2012). The first fully penicillin-resistant strains of *Streptococcus pneumonia* were detected in South Africa as early as 1977 and the first multi-drug resistant strains occurred in 1978. Since then, the prevalence of resistance has increased worldwide, along with an increase in resistance to other antimicrobial classes. In 2004, a third of all the pneumococcal isolates studied in South Africa displayed multi-drug resistance (Crowther-Gibson et al., 2011). In many other countries the once fully penicillin susceptible strains of *Streptococcus pneumonia* have declined by almost half to even less than a quarter in some (Okeke et al., 2005).

Global and local HIV Statistics:

According to the World Health Organization (2015), 36.9 million people were living with and 1.2 million have died from HIV in the year 2014. Sub-Saharan Africa is the worst affected by the epidemic, accounting for 70 percent of all new HIV infections worldwide.

The global HIV prevalence rate for adults between 15-49 years of age was 0.8 percent in 2014, with more than 10 percent of adults HIV positive in 9 countries. The highest adult HIV prevalence rate (4.8%) is in Sub-Saharan Africa, followed by the Caribbean (1.1%), Central Asia and Eastern Europe (0.9%), Latin America (0.4%), Central and Western Europe and North America (0.3%), the Pacific and Asia (0.2%) and North Africa and the Middle East with 0.1 percent. (Kaiser Family Foundation, 2015). This global HIV profile is illustrated in figure 1.1 below.

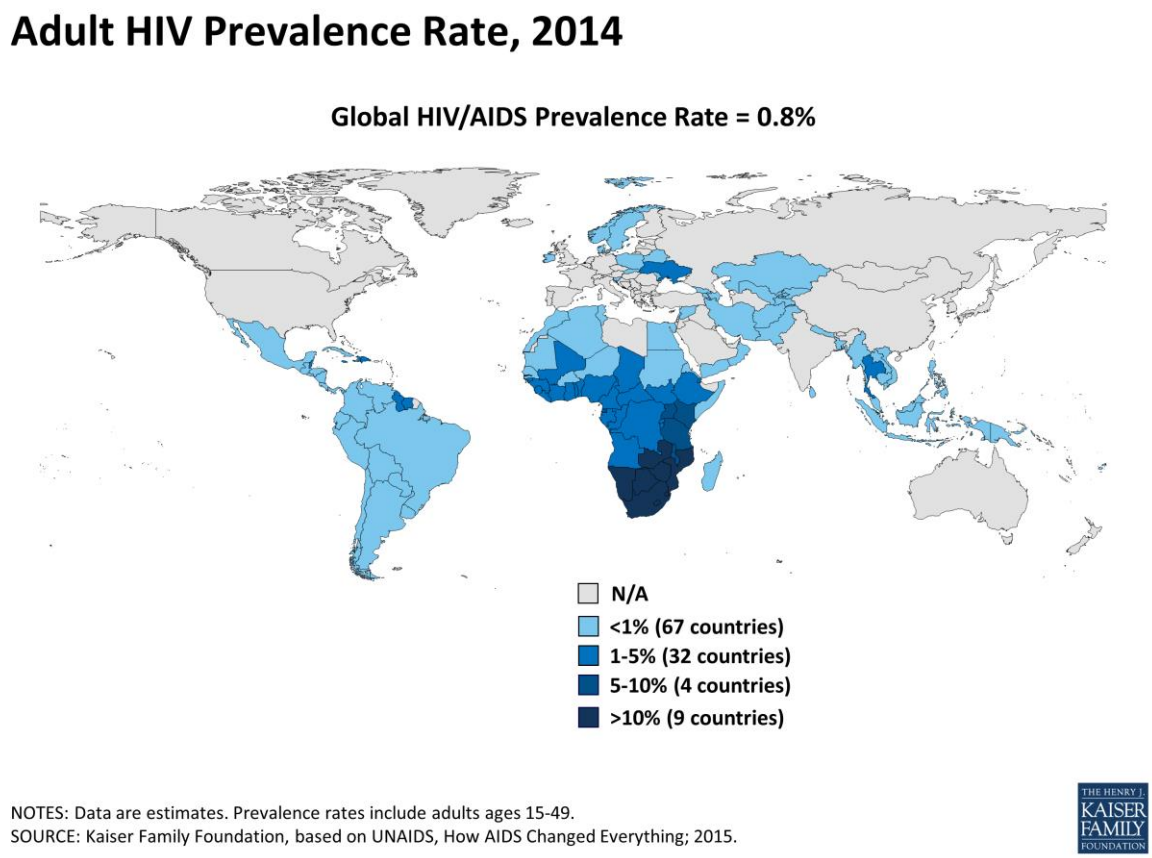


Figure 1.1 Adult HIV prevalence (15-49 years) 2014.

Globally, South Africa has the largest number of people (6.8 million) living with HIV (Kaiser Family Foundation, 2015). HIV prevalence is estimated to be 10.2 percent, with 16.8 percent among adults between 15-49 years of age (Statistics South Africa, 2014). Of South Africa's nine provinces, Kwazulu-Natal, site of this research, has the highest prevalence of HIV in South Africa: 16.9 percent in the general population, and 27.6 percent among adults aged 15-49 years (Van der Linde, 2013).

1.2 PROBLEM STATEMENT

Globally, HIV prevalence is highest in Sub-Saharan Africa (WHO, 2015). Acute respiratory failure is the leading cause for admission and mortality in the ICU for HIV infected patients (Sarkar and Rasheed, 2013). There is an urgent need to examine appropriate antimicrobial strategies for treating ARDS in patients with AIDS as there appear to be no formal or standardized treatment guidelines. Empirical antimicrobial treatment for critically ill ICU patients ranges from a pathogen-directed to a broad

spectrum approach (Leekha et al., 2010). The concern with a pathogen-directed approach is the possibility of undertreating the patient (File, 2015). In contrast, the anticipated complication associated with a broad spectrum approach is the potential contribution to the emergence of antimicrobial resistance (Leone and Martin, 2008). Antimicrobial resistance is as much a problem in South Africa as it is globally and can largely affect the clinical outcome for patients (Mendelson, 2012). Identifying the most appropriate antimicrobial treatment strategy is necessary in order to both ensure optimal clinical outcomes for the AIDS patient with ARDS in the ICU and limit emergence of antimicrobial resistance.

1.3 HYPOTHESIS

There is no difference in patient outcomes when comparing broad spectrum antimicrobial and pathogen-directed treatment of ARDS among AIDS patients in the intensive care unit (ICU) setting.

The main outcome parameter for this comparison was survival rate to ICU discharge. Secondary outcome parameters included total length of ICU stay and total duration of antimicrobial treatment.

1.4 AIM AND OBJECTIVES

The aim of this study was to retrospectively compare patient outcomes for pathogen-directed with broad spectrum antimicrobial treatment in AIDS patients with ARDS admitted to a private hospital medical intensive care unit (ICU) in Kwazulu-Natal, South Africa.

The objectives of this study were:

1. To compare survival rate to ICU discharge of pathogen-directed with broad spectrum antimicrobial treatment over a 12 month period, January to December 2013, as measured by data collected from retrospective chart audits.

2. To compare length of ICU stay of pathogen-directed with broad spectrum antimicrobial treatment over a 12 month period, January to December 2013, as measured by data collected from retrospective chart audits.
3. To compare duration of pathogen-directed with broad spectrum antimicrobial treatment over a 12 month period, January to December 2013, as measured by data collected from retrospective chart audits.
4. To formulate a set of in-house guidelines regarding antimicrobial treatment of ARDS in AIDS patients admitted to the medical ICU based on study results.

1.5 STUDY DESIGN

This study had a retrospective descriptive design that employed chart review in order to compare patient outcomes following two treatment regimens: 1) pathogen-directed antimicrobial treatment and 2) broad spectrum antimicrobial treatment.

1.6 DEFINITION OF TERMS

AIDS (Acquired Immunodeficiency Disease Syndrome) – AIDS is known as the final stage of HIV infection. An HIV infected person has AIDS if the CD4-count is below 200 cells per cubic millilitre and/or if the individual manifests with one or more opportunistic infection (AIDSinfo, 2013).

Antibiotic - Drug that kills or inhibits bacterial growth (MedicineNet, 2015).

Antimicrobial drug – Drug that kills or inhibit the growth of microbes (MedicineNet, 2015).

Antimicrobial resistance – Antimicrobial resistance is resistance of a pathogen to an antimicrobial drug that was originally effective for treatment of infections caused by it (WHO, 2015).

ARDS (Acute respiratory distress syndrome) - ARDS is part of a major systemic immune response brought on by injury or acute infection of the lung. The body's response to injury or infection causes leaking of more fluid than normal from the blood vessels into the alveoli (air sacs); thus preventing efficient transport of oxygen through the bloodstream. This leads to hypoxemia, multiple organ failure and eventually to death (American Thoracic Society, 2000). ARDS is an extremely dangerous, life threatening condition.

Broad spectrum antimicrobial treatment - An antimicrobial treatment regimen with the intent to target multiple pathogens with the potential to be (causally) associated with a patient's presenting condition (Leekha et al., 2010). This is in contrast with a pathogen-directed treatment approach (see below).

Empirical antimicrobial treatment – An antimicrobial treatment that is initiated based on experience and guided by clinical presentation, without data (culture results) to support its use (Leekha et al., 2010).

HIV (Human Immunodeficiency Virus) – A retro virus that causes HIV infection by destroying or impairing the function of the immune system's cells. When the infection advances, the immune system becomes more fragile, and the infected person becomes more susceptible to infections (WHO, 2015).

Pathogen-directed antimicrobial treatment – An antimicrobial treatment regimen aimed specifically at the most likely causative pathogen(s) associated with a patient's presenting condition (Leekha et al., 2010). This is in contrast with a broad spectrum treatment approach (see above).

Survival rate - Percentage of study participants alive for a certain period of time after diagnosis or initiation of treatment (Gordis, 2000).

CHAPER 2. LITERATURE REVIEW

2.1 LITERATURE REVIEW

According to the American Thoracic Society (2000), in order to treat Acute Respiratory Distress Syndrome (ARDS), appropriate antimicrobial treatment is needed to eliminate underlying causative pathogens. Most microbiological results only become available two to three days after cultures have been collected. Therefore, it is common clinical practice to initiate empirical antimicrobial treatment as soon as a diagnosis of ARDS is established (Leekha et al., 2010). No literature was found indicating a specific empirical antimicrobial treatment strategy for AIDS patients with ARDS.

A common approach for empirical antimicrobial treatment of critically ill patients is the broad spectrum treatment; aimed at multiple (both typical and atypical) pathogens (Leekha et al., 2010). The main reason for so many clinicians opting for this approach is the fear of undertreating the critically ill patient, as delaying appropriate antimicrobial treatment is associated with a high mortality rate (Kollef, 2008 and Kumar et al., 2006). In a study by Kumar et al (2006), the authors found a 79.9 percent survival rate when appropriate antimicrobial therapy was initiated within the first hour of sepsis presentation. Survival decreased by an average of 7.6 percent for each hour of delay in the initiation of appropriate antimicrobial therapy. However, the broad spectrum approach can result in patients' excessive exposure to (often inappropriate) antimicrobials; resulting in more adverse events and increased healthcare costs (Glowacki et al., 2003) as well as increased antimicrobial resistance (Leone and Martin, 2008).

In an attempt to minimize the unwanted effects of a broad spectrum approach, Kollef (2008) advocates a de-escalation strategy where the broad spectrum antimicrobial treatment is narrowed down according to the pathogen(s) identified by microbiological tests. However, clinicians are often hesitant to follow this strategy for a variety of reasons. These include unwillingness to change antimicrobial treatment that appears to be effective, perceived lack of trust in the sensitivity and

specificity of the microbiological tests, not understanding the de-escalating strategy and insufficient high quality evidence (Khasawneh et al., 2014).

Another approach for empirical antimicrobial treatment of critically ill patients is pathogen-directed treatment. The advantage of a pathogen-directed approach is that it reduces risk of antimicrobial resistance and adverse events (van der Eeden et al., 2005) and thus also healthcare costs. However, limiting the antimicrobial coverage to a pathogen-directed spectrum might undertreat patients with concurrent atypical infections (File, 2015).

A prospective cohort study by Kollef et al (1999) described the relationship between inadequate antibacterial treatment and mortality for patients in the ICU with either community acquired or hospital acquired infections. The study was performed at Barnes-Jewish Hospital, a teaching hospital in St.Louis, Missouri. All infected patients admitted to this hospital's ICU were elegible for the study. Antimicrobial treatment was considered inappropriate if the pathogen in the blood culture was not treated effectively (according to antibiotic susceptibility) at the time of identification. The main outcome parameter for this study was hospital mortality. The results of this study showed a significantly higher hospital mortality rate for the patients that received inadequate antibacterial treatment than for the patients that received adequate antibacterial treatment.

The same conclusion was made by Valle's et al (2003), who performed a similar study than Kollef et al (1999). The authors of this study examined the impact of inappropriate antimicrobial treatment on the outcome of critically ill patients in 30 hospital ICUs in Spain. Adults admitted to these ICUs, with a minimum of one true positive blood culture, were eligible for this study. The outcome parameter for this study was survival. The authors found that inappropriate initial antimicrobial treatment was the most important determinant of survival for critically ill bacteremic patients in the ICU and the more severe the illness (presence of septic shock), the bigger the influence on survival rate (thus, reducing the survival rate).

Both these studies on inappropriate antimicrobial cover support the empirical broad spectrum antimicrobial strategy that aims to avoid the high mortality rate associated

with initial inadequate cover. They do recommend de-escalation after culture results if appropriate. Both studies included immunocompromised patients as well as patients diagnosed with ARDS.

However, studies that compared empirical broad spectrum and pathogen-directed antimicrobial treatment for hospitalised patients with community acquired pneumonia indicated no benefit in terms of clinical efficacy of initial broad spectrum antimicrobial treatment over pathogen directed antimicrobial treatment. One of these studies was a prospective randomised study by van der Eeden et al (2005). The study was performed at Alkmaar Medical Centre in The Netherlands. The authors decided on length of hospital stay as the main outcome parameter. Therapeutic failure on antimicrobial treatment, 30 day mortality and adverse events were the secondary outcome parameters. Statistical tests performed indicated no significant difference for the main and secondary outcome parameters between the two groups. The study did not limit its population to ICU patients only, but considered all patients admitted to the hospital with community acquired pneumonia. The study excluded patients with immunosuppression (HIV-infection) and did not disclose whether or not any of the study participants were diagnosed with ARDS.

Another study was a retrospective cohort study by Williams et al (2013). The authors used data obtained from the Paediatric Health Information System database. This database contains clinical data of 43 tertiary care children's hospitals in the United States. The main outcome parameter for this study was length of hospital stay and secondary outcome parameters were admission to the ICU after the first two days in hospital, a 14 day readmission rate and total cost for hospital admission. Again, statistical tests indicated no significant difference between the outcomes for the two groups. The study population was however children between the ages of 2 and 18 years and not adults. They did not mention whether or not they included or excluded immunocompromised patients. They included patients admitted to both the general hospital wards and the ICU. However, they excluded patients that were admitted to the ICU or that were mechanically ventilated before two days of stay in hospital in order to exclude children with severe pneumonia.

According to the results of these two studies, pathogen-directed treatment seems to be the treatment of choice. This approach contributes less to the emergence of antimicrobial resistance and the increase in healthcare costs, without compromising the outcome of the patient. However, these studies did not focus on immunocompromised patients with ARDS and included patients in both the general ward and the ICU. Further studies that focus in specific on immunocompromised patients with ARDS in the ICU setting are needed in order to draw a valid conclusion. So far it appears as if none exists.

CHAPTER 3. METHOD

3.1 STUDY SETTING

This study was conducted at a general private hospital in Richards Bay, Kwazulu-Natal North Coast. The hospital has 263 beds and serves an urban as well as a peri-urban population. Richards Bay's population consists of 57387 people; 48.01 percent black African, 30.1 percent White, 18.22 percent Indian, 3.25 percent Coloured and 0.42 percent other (Frith, 2011). Figure 3.1 below is an image of a map that indicates Richards Bay's location in Kwazulu-Natal.

Figure 3.1 Richards Bay's location in Kwazulu-Natal (SA Places, 2015).

The hospital is situated in the centre of Richards Bay and offers the following specialities: Anaesthesiology, bio kinetics, dentistry, diagnostic radiology, ophthalmology, psychiatry, urology, audiology, cardiology, dermatology, neurology, gynaecology, physiotherapy and nephrology. The hospital also have the following surgeons: general surgeons, a neurosurgeon, orthopaedic surgeons, an ear, nose

and throat surgeon and a maxillo-facial and oral surgeon. Other specialists include physicians, intensivists, paediatricians and a neonatologist. Additional services include: general practitioners, 24-hour accident and emergency unit, wound care clinic, diabetic clinic, laboratories, retail pharmacy and stork's nest. It is the only private hospital in Richards Bay and has three intensive care units (one medical, one surgical and one neonatal intensive care unit), a high care ward, two surgical wards, two medical wards, a paediatric ward, orthopaedic ward, cardiac ward, maternity ward and a day ward. The hospital has six theatres as well as a gastro-intestinal unit.

The hospital has an Antimicrobial Stewardship team as well as a Drug and Therapeutics Committee. The Antimicrobial Stewardship team consists of a pharmacist, an infectious diseases physician, an infection control nurse and a microbiologist. The Drug and Therapeutics Committee consists of the Antimicrobial Stewardship team, a representative clinician from each major speciality, the pharmacy manager, unit/ward managers of the hospital, the hospital manager and a laboratory technician. It is the function of this committee to develop in-house antimicrobial use guidelines, monitor the implementation of these guidelines, assess feedback and outcomes, and conduct reviews and potential revisions of these guidelines every year.

3.2 STUDY POPULATION

The population for this study was all HIV/AIDS infected patients admitted to the medical ICU of a private hospital in Richards Bay, KwaZulu-Natal with an ARDS diagnosis at time of admission or soon thereafter, between January 2013 and December 2013.

3.3 STUDY SAMPLE

Total population sampling, a type of purposive sampling technique, was performed for this study. This is a nonprobability sampling method that may be utilized when a target study population is small in size (Laerd Statistics, 2012). For this work, the hospital records of all HIV-infected medical ICU patients with an admitting (or soon

after admission) diagnosis of ARDS, between January 2013 and December 2013, that met study inclusion and exclusion criteria, were included in the study sample.

3.4 INCLUSION AND EXCLUSION CRITERIA

Hospital records of potentially eligible patients were reviewed according to a set of inclusion and exclusion criteria. The inclusion criteria for this study were that the patient: 1) had a confirmed diagnosis of AIDS, with a CD-4 count of less than 200 cells per cubic millilitre blood; 2) had an admitting diagnosis/diagnosis soon after admission of ARDS; 3) was mechanically ventilated as a result of this diagnosis; 4) received either broad spectrum or pathogen-directed antimicrobial treatment; 5) was between the age of 18-65 years (to exclude age-related effects on prognosis); and 6) was admitted directly from Casualty into the medical ICU. This final criterion was instituted to exclude patients who had previously failed first line antimicrobial treatment and to exclude the effect of delayed ICU care on prognosis. All criteria had to be met in order for a patient (record) to be included in the study.

Exclusion criteria for the study were that the patient: 1) did not meet the defined criteria above; 2) was pregnant at admission; 3) had an existing malignancy; 4) had a known antimicrobial drug allergy, or 5) had any of the following co-morbidities: COPD (chronic obstructive pulmonary disease), any other organ failure (apart from the lungs) or a pulmonary embolism. These criteria can influence the decision of antimicrobial choice other than expert opinion and/or can contribute to a worse prognosis for the patient other than the effect of the admission diagnosis, hence exclusion criteria.

3.5 PARTICIPANT RECORD SCREENING, SELECTION, and TREATMENT GROUP ALLOCATION

According to the medical ICU's admission records, for the period January to December 2013, there were one hundred and seven patients with a diagnosis of ARDS. Sixty three of these patients were between the ages of 18 and 65 years and were admitted directly from Casualty into the ICU. Thirty patients met the remaining inclusion and exclusion criteria of the study. Based on the antimicrobials the patients

were initiated on, they were allocated to one of the two treatment groups. Twelve patients received treatment A (broad-spectrum) and eighteen patients treatment B (pathogen-directed). Specific antimicrobials included in each group are described in the following section. See patient selection and screening flow-chart below (figure 3.2).

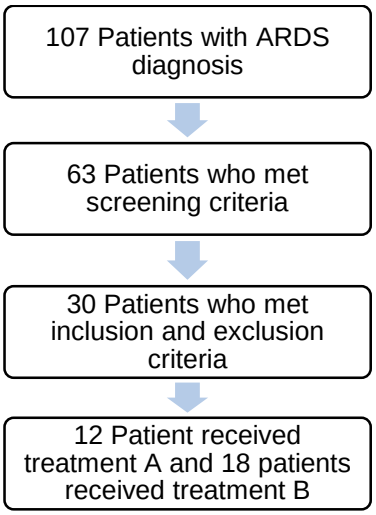


Figure 3.2 Participant record screening, selection and allocation to treatment groups.

3.6 TREATMENT GROUPS

At the hospital where this work was undertaken, the decision to treat with either broad spectrum or pathogen-directed treatment is based on clinician opinion regarding appropriate empirical antimicrobial treatment strategies for critically ill patients in the ICU. The broad spectrum approach is informally called “IV domestos*” by the facility’s clinicians. This approach consists of antimicrobials that cover multiple possible ARDS causative pathogens (both typical and atypical). This includes cover for gram positive bacteria, gram negative bacteria*, Pneumocystis jirovecii*, other fungal infections and, sometimes, viral infections. This broad spectrum approach consists of a minimum of four antimicrobials prescribed concurrently in order to cover this kind of microbial spectrum (Dr D Kelbe 2013, pers. comm, 13 June).

*Domestos is a South African household cleaning product. It is marketed as a cleaning product that kills “all known germs” in the house. In the study facility, broad spectrum intravenous antimicrobial treatment is informally referred to by clinicians as “IV Domestos” in recognition of the fact that the treatment is aimed at the potential eradication of as many microbes as possible.

The most common causative pathogens of ARDS are *Pneumocystis jirovecii* and *Streptococcus pneumonia* (Benito et al., 2012). The pathogen-directed approach at the study hospital is aimed at only these two pathogens. *Pneumocystis jirovecii* is treated with Suxamethonium-Trimethoprim and *Streptococcus pneumonia* with a combination of a beta-lactam antibiotic + macrolide/fluoroquinolone. The latter combination is based on the guideline for the treatment of community acquired pneumonia in the ICU of the American Thoracic Society (2007). At the hospital, the pathogen-directed approach consists of a maximum of three antimicrobials prescribed concurrently in accordance to this guideline (Dr D Kelbe 2013, pers. comm, 13 June). Table 3.1 and table 3.2 below summarize the antimicrobial combinations used for the two treatment groups, based on conventional clinician practice at the study hospital.

Table 3.1 Treatment A.

Treatment A (broad spectrum)
Beta-lactam[1] antibiotic + Macrolide/Fluoroquinolone[2] + Antifungal[3] + Aminoglycoside + Suxamethonium-Trimethoprim + Anti-viral [1]Ceftriaxone (3rd generation cephalosporin) or Amoxycillin+clavulanic acid/Piperacillin+ tazobactam (beta-lactamase resistant penicillins). [2]Levofloxacin or Moxifloxacin
Patients allocated to this treatment group concurrently received a minimum of any 4 of the above antimicrobials.

Table 3.2 Treatment B.

Treatment B (pathogen-directed)
Beta-lactam[1] antibiotic + Macrolide/fluoroquinolone[2] + Suxamethonium-Trimethoprim [1]Ceftriaxone (3rd generation cephalosporin) or Amoxycillin+clavulanic acid/Piperacillin+ tazobactam (beta-lactamase resistant penicillins). [2]Levofloxacin or Moxifloxacin
Patients allocated to this treatment group concurrently received a maximum of any 3 of the above antimicrobials.

3.7 DATA COLLECTION TOOLS

Data collection sheets were used for the selecting and screening of patient records and to display the data extracted from these records. A total of six data collection sheets were derived. Examples of all data collection tools are available in Annexure A.

Tool #1

The first data collection sheet was designed in order to screen the Medical ICU's admission records. This sheet allowed screening for patients with an admission diagnosis of ARDS (or soon thereafter), that were admitted directly from Casualty into the ICU and that were between 18 and 65 years of age.

Tool #2

The second data collection sheet was designed for a second level of screening. Patient records (that met the criteria on the first data collection sheet) were screened for remaining inclusion and exclusion criteria. The criteria had to be answered with either a "yes" or a "no". The answers had to be all "yes" for the inclusion criteria and all "no" for the exclusion criteria in order to be included in this study.

Tool #3

The third data collection sheet was designed in order to specify the antimicrobial treatment the patient received for easy classification of patients to either treatment group A or treatment group B. The broad spectrum treatment approach was named "treatment A" and the pathogen-directed approach "treatment B".

Tool #4

The fourth data collection sheet was designed for comparing the patient characteristics of the two treatment groups. The patient characteristics that needed to be collected included: patient age, sex, any other co-morbidities not listed under exclusion criteria, smoking status as well as TB (tuberculosis) status.

Tool #5

The fifth data collection sheet was designed in order to compare culture results of the two treatment groups. Information on the data collection sheet included: organism(s) cultured, culture source, time from initiation of antimicrobial treatment until culture results were received and if de-escalation of treatment took place after culture results.

Tool #6

The sixth data collection sheet was designed to collect the outcome results of the patients of the two treatment groups. The main outcome parameter for this study was survival rate to ICU discharge. The secondary outcome parameters were total length of ICU stay and total duration of antimicrobial treatment. The following questions on the data sheet had to be answered per included patient regarding the outcome parameters:

- Did the patient survive until discharged from the ICU: Yes/No
- What was the total length of ICU stay: Measured in number of days.
- What was the total duration of antimicrobial treatment in the ICU: Measured in number of days.

3.8 DATA COLLECTION PROCESS

Objectives 1 to 3:

The data collection process for the first three objectives of this study took place in four phases.

Phase #1

The first phase was the initial screening of medical ICU admission records for patients with an admitting ARDS diagnosis or for whom this diagnosis was made soon thereafter. Eligible patient records included those for patients between the ages of 18 and 65 years who were admitted directly from Casualty into the ICU. The records of the patients that met this initial set of criteria were then requested from the hospital's patient record storage location.

Phase #2

The second phase was a second level of screening. The requested patient records were further screened according to the remainder inclusion and exclusion criteria of this study.

Phase #3

Phase three was allocation of the included patient records to one of the two treatment groups. The allocation was based on the antimicrobial treatment the patient was initiated on during the first 24 hours following admission. Patients that received broad spectrum antimicrobial treatment were allocated to treatment group A and patients that received pathogen-directed treatment were allocated to treatment group B.

Phase #4

Phase 4 was the collection of information from the included patient records per treatment group. Information collected included information regarding patient characteristics, co-morbidities, culture results and the outcome parameters set for this study.

Objective 4:

The fourth objective of this study was to formulate a set of in-house guidelines regarding antimicrobial treatment of ARDS in AIDS patients admitted to the medical ICU. The guidelines derived from study results were drafted taking into account hospital requirements for adopting new treatment guidelines.

The prerequisites for recommending an antimicrobial guideline to the hospital's Drug and Therapeutics Committee (and in accordance with the WHO's prerequisites for treatment guidelines, 2011) are: 1) the choice of the antimicrobials recommended should be based on the hospital's microbiological test results, 2) it should be syndrome based, 3) the clinical setting must be specified as well as the rationale for recommending the guideline, 4) it should provide the strength (evidence-based) of the recommendation and it should involve the hospital's clinicians in order to bring

ownership to the guidelines. The guideline should lead to appropriate use of antimicrobials and limit the emergence of antimicrobial resistance (WHO, 2011).

3.9 DATA MANAGEMENT

The raw data were stored electronically on a password protected computer on the hospital's premises and will be kept for a duration of 5 years from the time of study write up. Only the author of this study will have access. After 5 years, the raw data will be deleted from the researcher's computer hard drive and any hard copies will be destroyed.

3.10 ETHICAL CONSIDERATIONS AND CONFIDENTIALITY

Permission to conduct the research was obtained from the study hospital itself as well as from the hospital's Research Operational Committee. Ethics approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal. Only the hospital's patient record numbers were used on data sheets, and no patient can be identified by name. Electronic records of data collected during the study were stored securely and strict access control measures were in place.

CHAPTER 4. DATA ANALYSIS AND RESULTS

4.1 DATA ANALYSIS

The software package STATISTICA (StatSoft Inc. 2013) was used for the analysis of the data collected for this study.

Participants' socio-demographic profile:

The first step in data analysis was to compare the socio-demographic profiles of the two treatment groups. Median age and gender ratios were determined for each treatment group. The median age was determined instead of the proposed mean due to the small sample size (thirty patients) and small sample size in treatment groups (twelve patients in treatment group A and eighteen patients in treatment group B). Gender is nominal data and these values were counted and presented as a ratio for each treatment group. Co-morbidities are also nominal data and the percentage for each identified co-morbidity as well as for tuberculosis and smoking status were calculated.

Patient outcome by objective:

Data analysis for the first three objectives of the study was done in two ways: 1) culture "blind" and 2) cultures "revealed". For the culture "blind" analysis, the outcome parameters were compared between the two treatment groups based on an approach where antimicrobial therapy is initiated empirically (thus, before culture results are known) and that the physicians do not de-escalate broad spectrum antimicrobial treatment after culture results for a variety of reasons (Khasawneh et al., 2014). For the cultures "revealed" analysis, outcomes were compared between the two treatment groups for patients with the same culture result. Further, choice to initiate either pathogen-directed or broad spectrum treatment is very often based on clinician opinion. This was also borne out in informal discussions with clinicians at the study hospital (Dr D Kelbe 2013, pers. comm, 14 June).

Culture "blind":

Objective 1 - Comparing survival rate to ICU discharge between broad spectrum and pathogen-directed antimicrobial treatment:

The first objective for this study was to compare the survival rate to ICU discharge (main outcome parameter) between broad spectrum and pathogen-directed antimicrobial treatment of ARDS among patients with AIDS in the ICU setting. Survival rate is defined as a percentage of study participants alive for a certain period of time after diagnosis or initiation of treatment (Gordis, 2000).

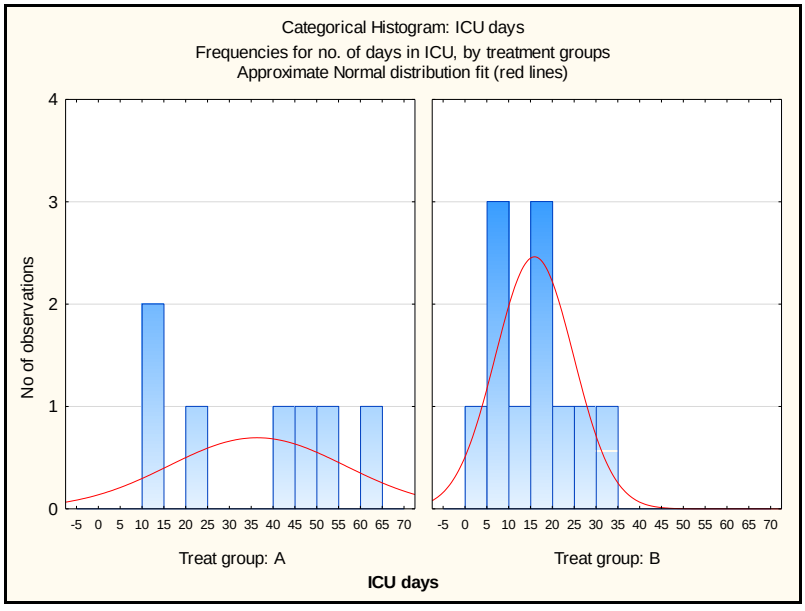
Survival analysis is a method for analysing data where the outcome variable has two components: time to event and event status (censored or uncensored). The event of interest for this study was ICU discharge. For this analysis, the earlier the exit/time to event of interest (discharge from ICU) the better the patient outcome. When study participants do not experience the event of interest (e.g. if the patient died), the observations are called "censored", as the information on the survival time is incomplete. Although censoring indicates a type of missing data, certain survival methods (e.g. Kaplan-Meier) can accurately incorporate censored and uncensored observations.

The Kaplan-Meier method is a nonparametric estimator of the survival function, and is used to estimate and graph survival percentages as a function of time (Despa, 2005). In this graphical depiction, the y-axis represents cumulative survival percentages and the x-axis time after initiation of treatment (Goel, Khanna and Krisha, 2010). In order to compare two Kaplan-Meier curves statistically for two treatment groups, the null hypothesis of "no difference" can be tested. This can be done by means of various available tests, with the log-rank test (also called the Mantel-Cox test) being the most popular (Despa, 2005). This nonparametric test, with significance level of alpha (α) = 0.05, was used in this study. If the calculated p-value is $\leq \alpha$, then the null hypothesis is rejected. If $p > \alpha$, then the null hypothesis is not rejected. The log-rank test was used, instead of the commonly used student-t test for the equivalence of means, as the data were non-normally distributed.

Objective 2 - Comparing length of ICU stay between broad spectrum and pathogen-directed antimicrobial treatment:

The second objective for this study was to compare the length of stay in the ICU (secondary outcome parameter) between pathogen-directed and broad spectrum antimicrobial treatment of ARDS among AIDS patients in the ICU.

In order to determine the distribution of the data, the values for length of stay in ICU in days (x-axis) for the surviving patients were graphed (graph 4.1) as a histogram (number of observations (y-axis)). This was important in order to determine whether parametric or non-parametric tests were appropriate to use. Data distribution is considered normal if the histogram creates a curve with a bell-shape (Roberts, 2012). This illustrates the state in which most values cluster in the centre of the data range (this creates a central peak and is also the mean of the data); with the remaining values tapering off symmetrically towards the data extremes (Rouse, 2013). In graph 4.1 below, it is clear that the data of this study were non-normally distributed, as the histograms did not create a bell-shaped curve.



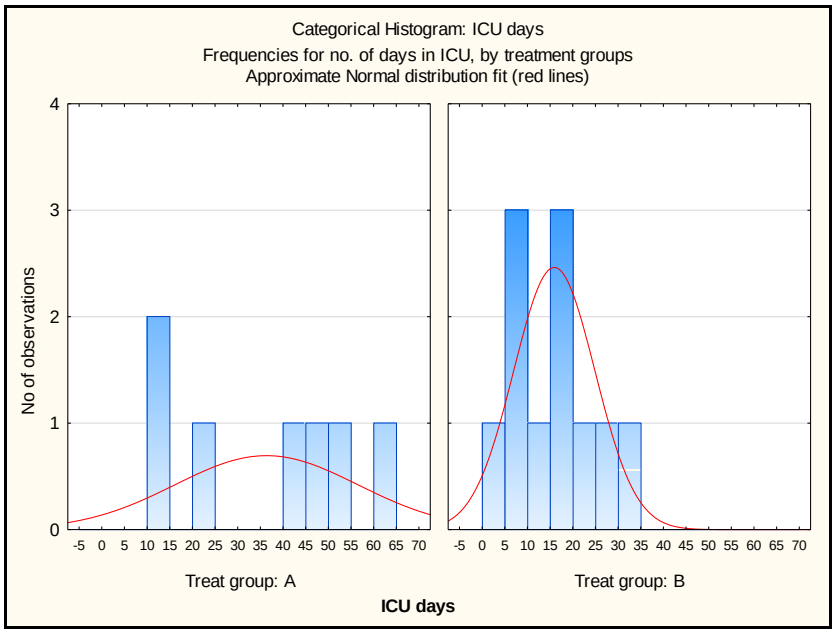
Graph 4.1 Distribution of the data values for length of stay in ICU (in days) for treatment groups A and B.

For this objective the difference in median number of days in the ICU was analysed between the surviving patients of the two treatment groups (seven patients in treatment group A and eleven patients in treatment group B). The median value was used instead of the mean because of the non-normal distribution of the data. The most suitable test for comparing the two medians for the two independent samples was the Kruskal-Wallis H test with significance level alpha (α) = 0.05. This test is a rank-based, nonparametric test that does not require the assumption of normality and can be used to test if there are statistically significant differences between two or more groups of an independent variable on a continuous or ordinal dependent variable (Laerd Statistics, 2012). If the calculated H statistic of the Kruskal-Wallis test is less than the critical value (read off from the Kruskal-Wallis H distribution table), then the null hypothesis cannot be rejected. If the calculated H statistic is greater than the critical value, then the null hypothesis can be rejected at the specified alpha level (Statistics Solutions, 2015). The treatment that resulted in a shorter length of stay in the ICU was the treatment with the better patient outcome.

Objective 3 - Comparing duration of antimicrobial treatment between broad spectrum and pathogen-directed antimicrobial treatment:

The third objective for this study was to compare the duration of antimicrobial treatment (secondary outcome parameter) between broad spectrum and pathogen-directed antimicrobial treatment of ARDS among AIDS patients in the ICU.

In order to determine the distribution of the data, the values for duration of antimicrobial treatment in ICU in days (x-axis) for the surviving patients were graphed (graph 4.2) as a histogram (number of observations (y-axis)). In graph 4.2 below, it is clear that the data of this study were non-normally distributed, as the histograms did not create a bell-shaped curve.



Graph 4.2 Distribution of the data values for duration of antimicrobial treatment in ICU (in days) for treatment groups A and B.

For this objective the difference in median number of treatment days in the ICU was analysed between the surviving patients of the two treatment groups (seven patients in treatment group A and eleven patients in treatment group B). The median value was used instead of the mean because of the non-normal distribution of the data. The Kruskal-Wallis H test with significance level set at alpha (α) = 0.05 was again the most suitable test to compare the two medians for the two independent samples. The treatment that resulted in the shortest duration of antimicrobial treatment was the treatment with the better patient outcome.

Box-and Whisker plots, a type of graph that shows the shape of the data distribution (Easton and McColl, 1997), were used to describe the median length of ICU stay and duration of antimicrobial treatment for treatment groups A (broad spectrum) and B (pathogen-directed) respectively.

Cultures "revealed":

The first step in analysis under cultures "revealed" was comparison of culture results. For culture results (nominal data) for the two treatment groups, a percentage was calculated for patients for whom cultures were done, the organisms cultured, the culture source and the percentage of de-escalation that took place after culture results. Time is ratio data (which is interval data with an absolute zero point (Easton and McColl, 1997)) and therefore the minimum and maximum times from initiation of antimicrobial treatment until culture results were received were determined.

Objective 1 - Comparing survival rate to ICU discharge between broad spectrum and pathogen-directed antimicrobial treatment:

The first objective for this study was to compare the survival rate to ICU discharge (main outcome parameter) between broad spectrum and pathogen-directed antimicrobial treatment of ARDS among ICU patients with AIDS. Due to the small sample size (five surviving patients – one in treatment group A and four in treatment group B) for the cultures "revealed" analysis, it was not viable to perform any formal statistical tests for this data. Because of this, the two treatment groups were compared by only looking at the percentage of surviving patients, with *Pneumocystis jirovecii* cultured, discharged at certain points in time (the number of days spent in the ICU per patient); with the focus on the number of days it took to achieve a 100 percent discharged percentage. The shorter the duration to achieve a 100 percent discharged percentage, the better the patient outcome.

Objective 2 - Comparing length of ICU stay between broad spectrum and pathogen-directed antimicrobial treatment:

The second objective for this study was to compare the length of stay in the ICU (secondary outcome parameter) between pathogen-directed and broad spectrum antimicrobial treatment of ARDS among AIDS patients in the ICU. Again, no formal statistical tests were performed due to small sample size (five surviving patients – one in treatment group A and four in treatment group B). The median length of ICU stay (in number of days) were calculated for the patients in treatment group A and

B with *Pneumocystis jirovecii* cultured. The shorter the length of stay in the ICU, the better the patient outcome.

Objective 3 - Comparing duration of antimicrobial treatment between broad spectrum and pathogen-directed antimicrobial treatment:

The third objective for this study was to compare the duration of antimicrobial treatment (secondary outcome parameter) between broad spectrum and pathogen-directed antimicrobial treatment of ARDS among AIDS patients in the ICU. No formal statistical tests were performed due to small sample size (five surviving patients – one in treatment group A and four in treatment group B). The median duration of antimicrobial treatment (in number of days) was calculated for the patients in treatment group A and B with *Pneumocystis jirovecii* cultured. The shorter the duration of antimicrobial treatment, the better the patient outcome.

Objective 4 - Formulation of an In-House Set of Guidelines:

The fourth objective of this study was to formulate an in-house set of guidelines. The compilation of a set of draft guidelines took place based on the analysis of all data collected during the study period.

The steps followed to formulate the draft in-house antimicrobial guideline were based on the prerequisites set by the Drug and Therapeutics committee of this hospital. These steps included: 1) Writing the guideline in specific for the antimicrobial treatment of HIV infected patients with ARDS in the ICU of the study site hospital; 2) specifying and describing the clinical setting in the guideline; 3) indicating that the guideline was based on this hospital's microbiological test and study results; 4) describing the rationale for recommending this guideline; 5) specifying the recommended antimicrobial treatment (based on this study's results) as well as the strength (evidence-based) of the recommendation. The next step would then be to 6) arrange the presentation and recommendation of the draft guideline onto the agenda of the next Drug and Therapeutics committee meeting and then finally 7) presenting the guideline to the Drug and Therapeutics committee in 2016.

4.2 RESULTS

Participants' socio-demographic profile:

The median age for treatment group A (broad spectrum) and group B (pathogen-directed) was 38 and 40 years respectively. With respect to gender, half (50%) of treatment group A were male and half (50%) female patients. In treatment group B 38.9 percent were male and 61.1 percent were female. There were no smokers in either of the two treatment groups. This information is presented below in table 4.1.

Table 4.1 Participants' socio-demographic profile.

	Total sample size n=30					
	Group A (broad spectrum) n=12			**Group B (pathogen-directed) n=18**		
	Minimum	**Median**	**Maximum**	**Minimum**	**Median**	**Maximum**
Age in years	23	38	47	25	40	64
Gender Male : Female	50% : 50%			39% : 61%		

With respect to co-morbidities, nearly all (91.7%) patients in treatment group A had some form of tuberculosis. Among those with tuberculosis, two thirds (66.7%) had pulmonary tuberculosis, 16.7 percent had multi-drug resistant pulmonary tuberculosis and 8.3 percent had abdominal tuberculosis. In treatment group B, 72.2 percent of the patients had pulmonary tuberculosis. See the comparative percentage tuberculosis for the two treatment groups in table 4.2 below.

Table 4.2 Comparative percentage tuberculosis for treatment groups A and B.

Tuberculosis (TB) %			
Total sample size n=30			
Group A (broad spectrum) n=12		**Group B (pathogen-directed) n=18**	
Pulmonary TB	66.7%	**Pulmonary TB**	72.2%
Multi drug resistant pulmonary TB	16.7%	**Multi drug resistant pulmonary TB**	0%
Abdominal TB	8.3%	**Abdominal TB**	0%
Total % with TB	91.7%	**Total % with TB**	72.2%
Total % without TB	8.3%	**Total % without TB**	27.8%

In treatment group A, 16.6 percent patients had other co-morbidities. These included: diabetes (8.3 percent of the patients) and anaemia (8.3%). In treatment group B there were 33.3 percent patients with other co-morbidities; including hypertension (5.6 percent of the patients), pericardial effusion (5.6%), deep vein thrombosis (5.6%), psychosis (5.6%), hypertension and diabetes (5.6%) and hypertension, diabetes and asthma (5.6%).

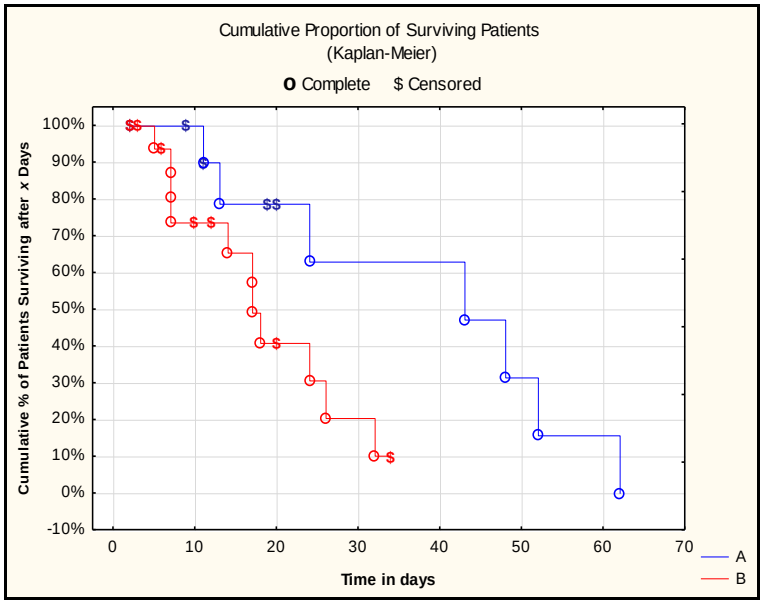
Patient outcome by objective:

Culture "blind":

Objective 1 – Comparing survival rate to ICU discharge of pathogen-directed with broad spectrum antimicrobial treatment:

The first objective of this study was to compare survival rate to ICU discharge (main outcome parameter) between pathogen-directed and broad spectrum antimicrobial treatment for ARDS among ICU patients with AIDS. To reiterate, survival rate is defined as a percentage of study participants alive for a certain period of time (until event of interest; in this case survival to ICU discharge) after diagnosis or initiation of treatment (Gordis, 2000). In this study, twelve of the thirty included patients died

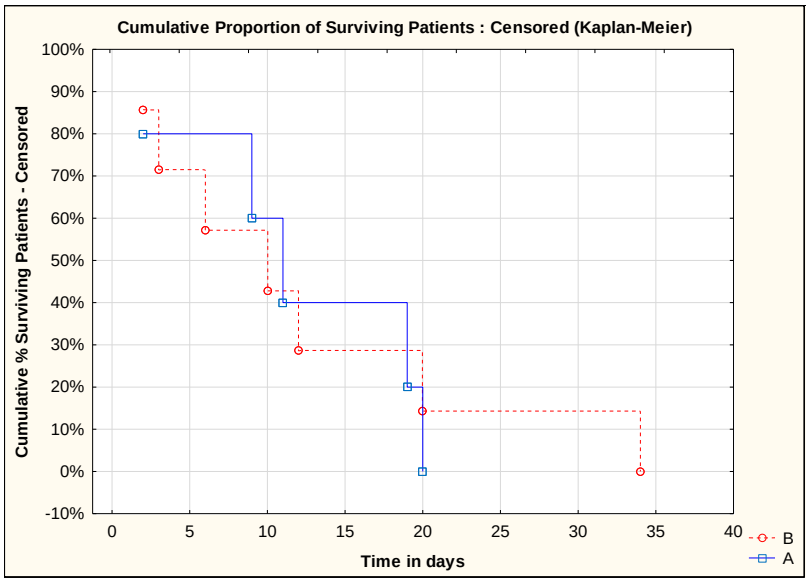
prior to discharge/while in the ICU. Thus data analysis for this section was right censored. Although the Kaplan-Meier analysis can take right-censored data into account, these censored observations skewed the survival curve(s) in the sense that it appeared to shorten the time to discharge. For example, when the Kaplan-Meier curves for the two treatment groups were compared (with censored data included) using Cox's F test, a p-value of 0.24 was obtained (at significance level of alpha = 0.05). This suggests a non-significant difference. Moreover, examination of the survival curve (graph 4.3) shows that most patients in treatment group B experienced the event of interest (ICU discharge) within 30 days (horizontal/x-axis). By comparison, for most patients in treatment group A, ICU discharge only occurred by 50 to 60 days. See graph 4.3 below.



Graph 4.3 Kaplan-Meier survival curves demonstrating cumulative percentage of patients surviving after x number of days in the ICU for both censored and uncensored patients of treatment groups A and B.

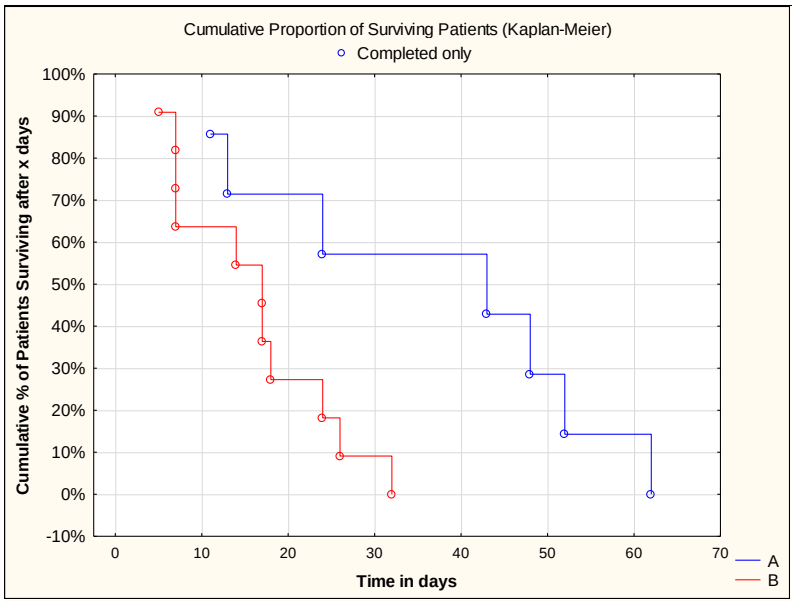
When comparing the Kaplan-Meier curves (graph 4.4) of the two treatment groups for only the censored patients (those who died in ICU – five patients in treatment group A and seven patients in treatment group B), the Log-rank test, yielded p=0.82 (alpha = 0.05). This indicates that there is no significant difference between the survival curves for the two treatment groups. Thus, removing these 12 censored

observations should not have an impact on the remainder of the data. See graph 4.4 below.



Graph 4.4 Kaplan-Meier survival curves demonstrating cumulative percentage of patients surviving after x number of days in the ICU for censored patients of treatment groups A and B.

The focus now lies on the uncensored patients (seven surviving patients in treatment group A and eleven surviving patients in treatment group B). The statistical Log-rank test, with significance level alpha = 0.05, indicated a significant difference between the outcomes for treatment A and B (Log-Rank p = 0.02), thus rejecting the null hypothesis of equality. The period of time until the event of interest occurred for 50 percent surviving patients (also known as median survival rate) was 43 days for treatment group A and 17 days for treatment group B (as read off from graph 4.5). This means that the period of time for treatment group B (pathogen-directed) to have 50 percent surviving patients discharged, was shorter than the period of time for treatment group A (broad spectrum) to have 50 percent surviving patients discharged. See graph 4.5 below.

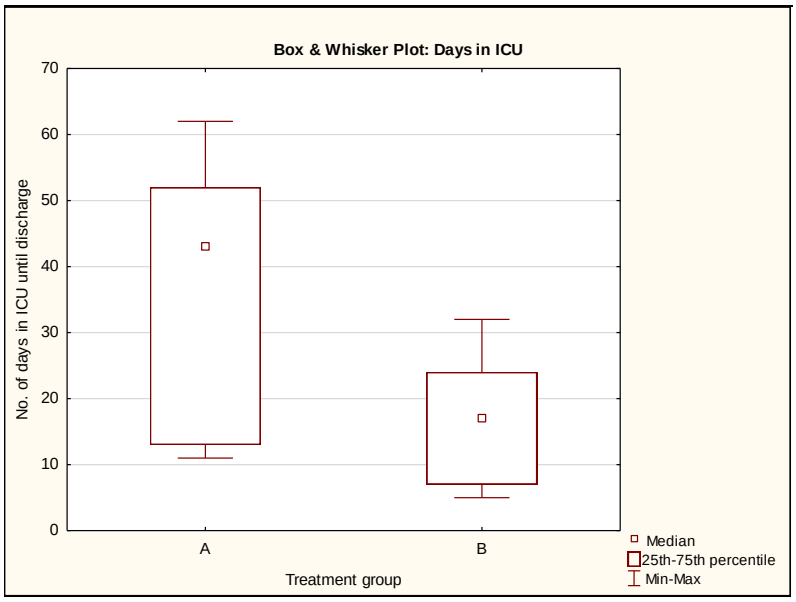


Graph 4.5 Kaplan-Meier survival curves demonstrating cumulative percentage of patients surviving after x number of days in the ICU for uncensored patients of treatment groups A and B.

Objective 2 - Comparing length of ICU stay between broad spectrum and pathogen-directed antimicrobial treatment:

The second objective focused on a comparison of the length of ICU stay between pathogen-directed and broad spectrum antimicrobial treatment. Total length of ICU stay was one of the secondary outcome parameters for this study.

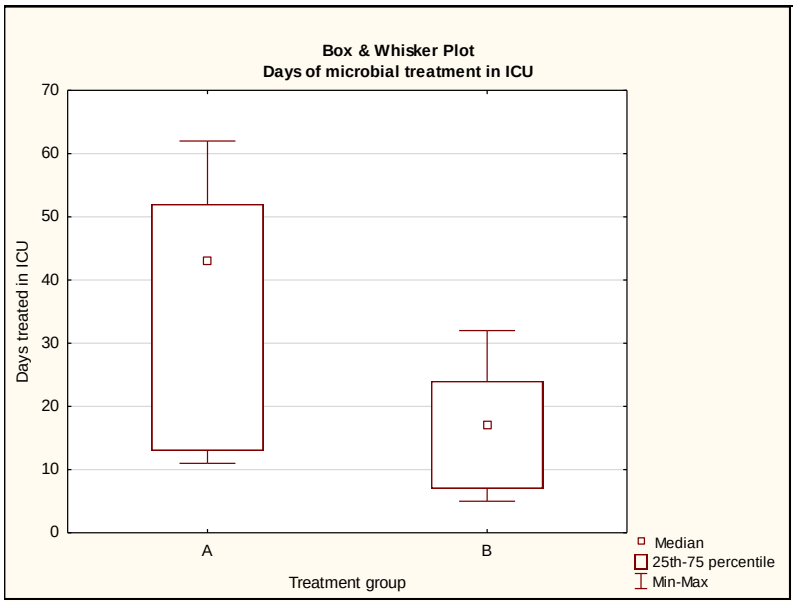
The Kruskal-Wallis test, with significance level of alpha = 0.05 and critical value 3.84, confirmed a significant difference (calculated test statistic H = 3.97) between the length of ICU stay for the survivors in treatment groups A and B (seven in treatment group A and eleven in treatment group B). The median length of stay in the ICU was 43 days for treatment group A (broad spectrum) and 17 days for treatment group B (pathogen-directed). Thus, treatment group B had a shorter length of ICU stay than treatment group A. Median, minimum and maximum values, and inter-quartile (25^{th} (Q1) to 75^{th} (Q3) percentile) ranges are shown in the Box- and -Whisker plots (graph 4.6) below.



Graph 4.6 Box-and –Whisker plots demonstrating median, minimum and maximum values, and inter-quartile (25th (Q1) to 75th (Q3) percentile ranges for length of ICU stay (in days) for treatment groups A and B.

Objective 3 - Comparing duration of antimicrobial treatment between broad spectrum and pathogen-directed antimicrobial treatment:

Comparing the duration of antimicrobial treatment between pathogen-directed and broad spectrum treatment when treating ARDS in patients with AIDS in the ICU was the third objective for this study. Total duration of antimicrobial treatment was also one of the secondary outcome parameters for this study. The Kruskal-Wallis test, with significance level of alpha = 0.05 and critical value 3.84, confirmed a significant difference (test statistic H = 3.97) between the duration of antimicrobial treatment for the survivors in treatment group A and B (seven in treatment group A and eleven in treatment group B). The median duration of antimicrobial treatment was 43 days for treatment group A (broad spectrum) and 17 days for treatment group B (pathogen-directed). Thus, treatment group B had a shorter duration of antimicrobial treatment than treatment group A. Median, minimum and maximum values, and inter-quartile (25th (Q1) to 75th (Q3) percentile) ranges are shown in the Box-and - Whisker plots (graph 4.7) below.



Graph 4.7 Box-and –Whisker plots demonstrating median, minimum and maximum values, and inter-quartile (25th (Q1) to 75th (Q3) percentile ranges for duration of antimicrobial treatment (in days) for treatment groups A and B.

Cultures "revealed":

Participants' culture results:

Cultures were done for all patients in both treatment groups. The minimum amount of time it took from initiation of treatment until cultures were received for both treatment groups was 1 day and the maximum amount of time for treatment group A (broad spectrum) was 5 days and for treatment group B (pathogen-directed) 6 days. For treatment group A, organism growth was detected for 41.7 percent of patients. *Pneumocystis jirovecii* was cultured for 8.3 percent of the patients with sputum the culture source. *Pneumocystis jirovecii* and *Staphylococcus aureus* were cultured for 16.7 percent of the patients and sputum was again the culture source, except for one patient where a nasal swab was the culture source for the cultured *Staphylococcus aureus*. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were cultured for 8.3 percent of the patients and sputum was the culture source. *Staphylococcus epidermidis* and *Klebsiella pneumoniae* were cultured for 8.3 percent of the patients and the culture source for *Staphylococcus epidermidis* was

blood and the axilla for *Klebsiella pneumoniae.* There was no organism growth for 58.3 percent of the patients in treatment group A.

For treatment group B, organism growth was detected for 44.4 percent of patients. *Pneumocystis jirovecii* was cultured for 33.3 percent of the patients with sputum the culture source, except for one patient where the bronchial washings was the culture source. *Candida albicans* was cultured for 5.6 percent of the patients with sputum the culture source. *Staphylococcus epidermidis* and *Pneumocystis jirovecii* were cultured for 5.6 percent of the patients with blood the culture source for *Staphylococcus epidermidis* and sputum for *Pneumocystis jirovecii*. There was however no organism growth for 55.6 percent of the patients in treatment group B. Table 4.3 below shows the comparative culture results for the two treatment groups.

Table 4.3 Comparative culture results for the two treatment groups.

	Participants' culture results			
	Total sample size n=30			
	Group A (broad spectrum) n=12		**Group B (pathogen-directed) n=18**	
Organisms cultured	**% of patients with specified organism growth**	**Source**	**% of patients with specified organism growth**	**Source**
Pneumocystis Jirovecii	8.3%	Sputum	33.3%	Bronchial washings : Sputum (1 : 5)
Pseudomonas Aeruginosa and Klebsiella Pneumonia	8.3%	Sputum		
Staphylococcus Aureus and Pneumocystis Jirovecii	16.7%	Nasal swab : Sputum (1 : 3)		
Staphylococcus Epidermidis and Klebsiella Pneumonia	8.3%	Blood : Axilla (1 : 1)		
Staphylococcus Epidermidis and Pneumocystis Jirovecii			5.6%	Blood and sputum
Candida Albicans			5.6%	Sputum
Total % growth	41.7%		44.4%	
Total % no growth	58.3%		55.6%	

At the hospital where this study was undertaken, both pathogen-directed and broad spectrum antimicrobial treatments are initiated empirically (before culture results are known). Most clinicians at this hospital do not de-escalate broad-spectrum treatment after culture results, because they want to ensure cover for both multiple (typical and atypical) pathogens at all times as they fear undertreating their critically ill patient (Dr D Kelbe 2013, pers. comm, 13 June). The clinicians that treat with the pathogen-directed treatment also do not change treatment after culture results, unless an organism that causes an infection is cultured that is not covered by the pathogen-directed antimicrobial spectrum. The organism cultured most for the pathogen-directed treatment group in this study was *Pneumocystis jirovecii*. Although *Streptococcus pneumonia* was not cultured for any patients in this group,

the clinicians continued with antimicrobial treatment aimed at this organism. Explanations for this include a lack in trust in the sensitivity and specificity of the diagnostic tests as well as a reluctance to change antimicrobial treatment that appears to be effective (Dr D Kelbe 2013, pers. comm, 13 June).

Another problem regarding culture result "trust" at this hospital is that antimicrobial treatment is often initiated before adequate cultures are taken (Sr L Maurel 2014, pers. comm, 30 October). Obtaining cultures after antimicrobial treatment has been initiated can cause inconclusive culture results, because organisms that would otherwise be detected may not necessarily grow after antimicrobial exposure (Rojo, 2006). This could also be a possible explanation for the high percentage of "no growth" culture results that were seen with this study.

Objective 1 – Comparing survival rate to ICU discharge of pathogen-directed with broad spectrum antimicrobial treatment:

For reasons related to small sample size (n=5), comparison of survival rate to discharge was undertaken only through examination of percentage of patients discharged at certain points in time, with the focus on the number of days it took to achieve a 100% discharged percentage. For treatment group A (broad spectrum), all (100%) survivors with *Pneumocystis jirovecii* cultured were discharged by 7 days. For treatment group B (pathogen-directed), 25 percent of survivors with *Pneumocystis jirovecii* cultured were discharged by 7 days, 50 percent by 18 days, 75 percent by 24 days and 100 percent by 32 days only. As noted above, no formal statistical tests were performed due to small sample size (five surviving patients – one in treatment group A and four in treatment group B).

Objective 2 - Comparing length of ICU stay between broad spectrum and pathogen-directed antimicrobial treatment:

The median length of ICU stay for the patients with *Pneumocystis jirovecii* cultured in treatment group A, was 11 days. The median length of ICU stay for the surviving patients with *Pneumocystis jirovecii* cultured in Treatment group B, was 21 days. No formal statistical tests were performed due to small sample size.

Objective 3 - Comparing duration of antimicrobial treatment between broad spectrum and pathogen-directed antimicrobial treatment:

The median duration of antimicrobial treatment for the patients with *Pneumocystis jirovecii* cultured in treatment group A, was 11 days. The median duration of antimicrobial treatment for the survivors with *Pneumocystis jirovecii* cultured in treatment group B, was 21 days. No formal statistical tests were performed due to small sample size.

See table 4.4 below for a summary of results for both the culture “blind” and cultures “revealed” analyses for objectives 1 to 3.

Table 4.4 Summary of results; culture “blind” and cultures “revealed”.

	Culture “blind” results **Total sample:** n=30 **Uncensored:** n=18 **Censored:** n=12	**Cultures “revealed” results** **Total sample:** n=7 **Uncensored:** n=5 **Censored:** n=2
Objective 1 – Comparing survival rate to ICU discharge of pathogen-directed with broad spectrum antimicrobial treatment	**Total survivors:** n=18 **Group A:** n=7 **Group B:** n=11 **Results:** Null hypothesis rejected ($p < \alpha$; $\alpha = 0.05$). Group A: 50% surviving patients discharged by 43 days (median survival rate). Group B: 50% surviving patients discharged by 17 days (median survival rate).	**Total survivors:** n=5 **Group A:** n=1 **Group B:** n=4 **Results:** Group A: 100% surviving patients discharged by 7 days. Group B: 100% surviving patients discharged by 32 days.
Objective 2 - Comparing length of ICU stay between broad spectrum and pathogen-directed antimicrobial treatment:	**Total survivors:** n=18 Group A: n=7 Group B: n=11 **Results:** Null hypothesis rejected ($H \geq 3.84$ (critical value); $\alpha = 0.05$). Group A: Median length of ICU stay was 43 days. Group B: Median length of ICU stay was 17 days.	**Total survivors:** n=5 Group A: n=1 Group B: n=4 **Results:** Group A: Median length of ICU stay was 11 days. Group B: Median length of ICU stay was 21 days.
Objective 3 - Comparing duration of antimicrobial treatment between broad spectrum and pathogen-directed antimicrobial treatment:	**Total survivors:** n=18 Group A: n=7 Group B: n=11 **Results:** Null hypothesis rejected ($H \geq 3.84$ (critical value); $\alpha = 0.05$). Group A: Median duration of antimicrobial treatment was 43 days. Group B: Median duration of antimicrobial treatment was 17days.	**Total survivors:** n=5 Group A: n=1 Group B: n=4 **Results:** Group A: Median duration of antimicrobial treatment was 11 days. Group B: Median duration of antimicrobial treatment was 21 days.

Objective 4 - Formulating a set of in-house guidelines:

The fourth objective of this study was to formulate an in-house guideline regarding antimicrobial treatment of ARDS among AIDS patients admitted to the ICU based on study results.

This draft in-house treatment guideline was written specifically for the antimicrobial treatment of HIV infected patients with ARDS in the ICU of the study site hospital. The clinical setting was described and it was indicated that the guideline was based on this hospital's microbiological test results. The rationale for recommending this guideline was also explained. The recommended antimicrobial treatment was based on this study's results.

Retrospective comparative therapeutic studies, investigating the results of treatment, are considered level three evidence according to the Levels of Evidence chart by De Vries and Berlet (2010). This study was a retrospective comparative study and therefore it was graded as level three evidence. The study was started after treatment was completed and participants were identified for the study based on the treatment they received.

Hospital management's secretary will be contacted in order to schedule the presentation and recommendation of this draft in-house guideline onto the agenda of the next Drug and Therapeutics Committee meeting in 2016. See Annexure B for a draft of this guideline.

CHAPTER 5. DISCUSSION

5.1 DISCUSSION

The null hypothesis for this study was as follow:

There is no difference in patient outcomes when comparing broad spectrum antimicrobial and pathogen-directed treatment of ARDS among AIDS patients in the intensive care unit (ICU) setting.

Objectives 1 - 3:

Culture "blind":

For the **first objective** of this study, there was a significant difference in patient outcome between the two treatment groups. Treatment group B (pathogen-directed) showed a better median **survival rate** (main outcome parameter) than treatment group A (broad spectrum), since the time it took (in number of days) to have 50 percent patients discharged was shorter than for treatment group A.

The broad spectrum approach also did not show a better outcome than the pathogen-directed approach in studies by van der Eeden et al (2005) and Williams et al (2013). These authors compared pathogen-directed with broad spectrum antimicrobial treatment for patients with community acquired pneumonia and found no significant difference in 30 day mortality rate between the two treatment groups.

Antimicrobial resistance is a pressing international concern (World Health Organization, 2013) with excessive and prolonged antimicrobial treatment the main contributing factors in hospitals (MacDougall and Polk, 2005). Pathogen-directed antimicrobial treatment is aimed at the most likely causative pathogen(s) associated with a patient's presenting condition (Leekha et al., 2010) and reduces the risk of antimicrobial resistance and adverse events (van der Eeden et al., 2005) and also healthcare costs (Glowacki et al., 2003).

The concern with limiting the antimicrobial coverage to a pathogen-directed spectrum is the possibility of undertreating patients with concurrent atypical infections (File, 2015). Initial inadequate antimicrobial cover can result in a higher hospital mortality rate (Kollef et al., 1999 and Valle's et al., 2003) and that is the reason why many clinicians at the study site hospital treat ARDS among patients with AIDS in the ICU with the broad spectrum antimicrobial approach (Dr D Kelbe 2013, pers. comm, 13 June).

However, the results for the first objective of this study indicated that excessive antimicrobial coverage (broad spectrum approach) did not give a better outcome in terms of survival when treating ARDS among AIDS patients in the ICU at this hospital. Thus, the pathogen-directed antimicrobial approach was the treatment that resulted in a higher survival rate and theoretically contributed the least to the emergence of antimicrobial resistance.

For the **second objective** of this study, there was also a significant difference in patient outcome between the two treatment groups. The median **length of ICU stay** (secondary outcome parameter) for the surviving patients in treatment group B (pathogen-directed) was shorter than for those in treatment group A (broad spectrum). The shorter length of ICU stay indicated that the event of interest, discharged from the ICU, was reached sooner for the pathogen-directed treatment group.

In a study by van der Eeden et al (2005), the authors compared pathogen-directed with broad spectrum antimicrobial treatment for patients with community acquired pneumonia and found no significant difference in length of stay between the two treatment groups. Again, the broad spectrum approach did not show a better outcome than the pathogen-directed approach.

For the **third objective** of this study, there was also a significant difference in patient outcome between the two treatment groups. The median **duration of antimicrobial treatment** for the surviving patients in treatment group B (pathogen-directed) was shorter than for those in treatment group A (broad spectrum). The shorter duration of antimicrobial treatment indicated that the event of interest, discharge from the

ICU, was reached sooner for the pathogen-directed treatment group. A shorter duration of antimicrobial treatment also theoretically contributes less to the emergence of antimicrobial resistance (MacDougall and Polk, 2005).

Treatment group B (pathogen-directed) showed a better outcome regarding both the main and secondary outcome parameters of this study. The sample size of this analysis was small. A larger study is necessary to confirm the results of this analysis. If a larger study confirms that the pathogen-directed approach is the approach that results in better patient outcomes and this approach is approved by the Drug and Therapeutics committee for an in-house antimicrobial treatment guideline for AIDS patients with ARDS in the ICU, it will ensure optimal patient outcome and theoretically reduce the emergence of antimicrobial resistance in this hospital.

Cultures "revealed":

Due to the small sample size for this analysis, it was not viable to perform any formal statistical tests for the data of objectives 1- 3.

For **objective one**, there was a difference in patient outcome between the two treatment groups. Treatment group A (broad spectrum) showed a better outcome than treatment group B as 100 percent survivors, for whom *Pneumocystis jirovecii* was cultured, were discharged after a shorter duration of stay in the ICU.

For **objective two**, there was a difference in patient outcome between the two treatment groups. The median **length of ICU stay** (secondary outcome parameter) for the surviving patients for whom *Pneumocystis Jirovecii* was cultured, was shorter for treatment group A (broad spectrum) than for treatment group B (pathogen-directed).

For **objective three**, there was a difference in patient outcome between the two treatment groups. The median **duration of antimicrobial treatment** (secondary outcome parameter) for the surviving patients, for whom *Pneumocystis Jirovecii* was cultured, was shorter for treatment group A (broad spectrum) than for treatment group B (pathogen-directed).

The treatment that resulted in a higher survival rate (main outcome parameter), shorter length of ICU stay and duration of antimicrobial treatment (secondary outcome parameters), was the treatment with the better patient outcomes according to the outcome parameters set for this study. Thus, for the cultures "revealed" analysis, the broad spectrum approach resulted in better patient outcomes than the pathogen-directed approach. This analysis was done for patients for whom *Pneumocystis jirovecii* was the only cultured organism. The results for this analysis highlights the possibility of co-infection with atypical pathogens and the importance of appropriate antimicrobial cover on patient outcome (File, 2015).

The results for the **cultures "revealed"** analysis were thus the opposite of what were found for the **culture "blind"** analysis. Sample size was small (especially for the cultures "revealed" analysis) and could be a reason for the contradicting results. A larger study is thus necessary in order to make a valid conclusion.

Objective 4:

The fourth objective of this study was to formulate a set of in-house guidelines regarding antimicrobial treatment of ARDS in AIDS patients admitted to the medical ICU based on study results.

According to the results for the **culture "blind"** analysis the pathogen-directed approach resulted in better patient outcomes according to the outcome parameters set for this study. The pathogen-directed antimicrobial treatment was directed at the most common causative pathogens of ARDS; *Pneumocystis jirovecii* and *Streptococcus pneumoniae*. See table 5.1 below.

Table 5.1 Treatment B.

Pathogen-directed antimicrobial treatment
Beta-lactam[1] antibiotic + Macrolide/Fluoroquinolone[2] + Antifungal[3] + Aminoglycoside + Suxamethonium-Trimethoprim + Anti-viral
[1]Ceftriaxone (3rd generation cephalosporin) or Amoxycillin+clavulanic acid/Piperacillin+ tazobactam (beta-lactamase resistant penicillins). [2]Levofloxacin or Moxifloxacin

According to the results of the **cultures "revealed"** analysis the broad-spectrum antimicrobial treatment showed better patient outcomes according to the outcome parameters set for this study. This analysis was done for patients for whom *Pneumocystis jirovecii* was the only cultured organism. The broad spectrum antimicrobial treatment was directed at both typical and atypical causative pathogens of ARDS in HIV infected individuals. See table 5.2 below.

Table 5.2 Treatment A.

Broad spectrum antimicrobial treatment
Beta-lactam antibiotic + Macrolide/Fluoroquinolone + Antifungal + Aminoglycoside + Suxamethonium-Trimethoprim + Anti-viral
[1]Ceftriaxone (3rd generation cephalosporin) or Amoxycillin+clavulanic acid/Piperacillin+ tazobactam (beta-lactamase resistant penicillins). [2]Levofloxacin or Moxifloxacin

Identifying the most appropriate antimicrobial treatment strategy was necessary in order to both ensure optimal clinical outcomes for the AIDS patient with ARDS in the ICU and limit emergence of antimicrobial resistance. For this study, the pathogen-directed treatment resulted in better patient outcomes for the culture "blind" analysis. This approach also theoretically reduces the risk of antimicrobial resistance as opposed to the broad spectrum approach (van der Eeden et al., 2005). The pathogen-directed antimicrobial approach will therefore be presented in 2016, in the form of a draft in-house treatment guideline, as a recommended antimicrobial

treatment approach, to the Drug and Therapeutics committee of the study site hospital for treating ARDS among AIDS patients in the ICU.

The results of the cultures “revealed” analysis will also be shared with this committee. The results of this analysis were the opposite of what were found for the culture “blind” analysis. A possible explanation for the contradicting results between the two analyses is small sample size (especially the cultures “revealed” analysis). The importance of and need for a larger study for confirmation of the analyses’ results will be stressed.

CHAPTER 6. CONCLUSION

6.1 CONCLUSION

Globally, HIV prevalence is highest in Sub-Saharan Africa (WHO, 2015). Acute respiratory failure is the leading cause for admission and mortality in the ICU for HIV infected patients (Sarkar and Rasheed, 2013). There appear to be no formal or standardized antimicrobial treatment guidelines for treating ARDS in patients with AIDS. Identifying the most appropriate antimicrobial treatment strategy was necessary in order to both ensure optimal clinical outcomes for the AIDS patient with ARDS in the ICU and limit emergence of antimicrobial resistance.

Data analysis for the first three objectives of the study was done in two ways: 1) culture “blind” and 2) cultures “revealed”. For the culture “blind” analysis, the outcome parameters were compared between the two treatment groups based on an approach where antimicrobial therapy is initiated empirically (thus, before culture results are known) and that the physicians do not de-escalate broad spectrum antimicrobial treatment after culture results for a variety of reasons (Khasawneh et al., 2014). For the cultures “revealed” analysis, outcomes were compared between the two treatment groups for patients with the same culture result, namely *Pneumocystis jirovecii*.

For the culture “blind” analysis, treatment B (pathogen-directed) showed better patient outcomes than treatment A (broad spectrum) for both the main and secondary outcome parameters. For the cultures “revealed” analysis, treatment A (broad spectrum) showed better patient outcomes than treatment B (pathogen-directed) for both the main and secondary outcome parameters. Sample size was small for this study (especially for the cultures “revealed” analysis) and this could be the reason for the contradicting results.

The findings of this study as well as a draft in-house treatment guideline will be presented in 2016 to the Drug and Therapeutics committee of the hospital at which this study was conducted. The pathogen-directed approach will be the recommended treatment approach for treating ARDS among AIDS patients in the

ICU for the draft in-house guideline. This approach resulted in better patient outcomes for the culture “blind” analysis. It is also the approach that theoretically limits the risk of antimicrobial resistance (van der Eeden et al., 2005). However, a larger study is necessary in order to confirm these results.

6.2 SIGNIFICANCE OF THE STUDY

Acute respiratory failure is the main cause for admission and mortality in the ICU for HIV infected patients (Sarkar and Rasheed, 2013). There appear to be no formal or standardized treatment guidelines for the antimicrobial treatment of the underlying causative pathogens of this condition. Antimicrobial resistance is a pressing international concern (World Health Organization, 2013). The problem with antimicrobial resistance is that it reduces effectiveness of treatment. This leads to an increase in mortality rate, duration of treatment, healthcare costs and economic burden as more expensive therapies have to be used due to resistance to first-line treatment. This study represents the first step in identifying the most appropriate antimicrobial treatment strategy in order to both ensure optimal clinical outcomes for the AIDS patient with ARDS in the ICU and limit emergence of antimicrobial resistance.

6.3 STUDY LIMITATIONS

The small sample size was a limitation for this study. Small sample size lowers statistical power i.e. the probability of accepting a false null hypothesis; and the results may not be reliable (Verial, 2015). In this study, the sample size for the cultures “revealed” analysis was too small to perform any formal statistical tests or to draw inference from the data.

6.4 RECOMMENDATIONS

A much larger study of this nature is recommended in order to confirm this study’s results. The choice of the significance level (alpha) at 0.05 or less and the use of appropriate statistical test(s) is important in order to ensure reliability. The effectiveness of the outcomes of the tests i.e. not only the conclusion (reject or

accept at specified level alpha), but the size of the difference that the intervention made, plays a large role in clinical studies.

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ANNEXURE A:

Tool 1 Screening of admission records.

SCREENING OF THE MEDICAL ICU'S ADMISSION RECORDS:				
Indicate Yes or No for each of the criteria. Answer should be Yes for all criteria to be considered for the study				
Patient number for ARDS diagnosis	***Admission via Casualty***	***2013 Admission***	***Age between 18 and 65***	***Considered for the study***

Tool 2 Inclusion and exclusion criteria.

Record no. of patient admitted to ICU with ARDS	*Inclusion Criteria (indicate Yes or No for each of the criteria)*					*Exclusion Criteria (indicate Yes or No for each of the criteria)*						*Included (Yes or No)*
	Answer should be Yes for all criteria to be included in the study					*Answer should be No for all criteria to be included in the study*						
	CD4 count <200	*HIV Positive*	*Ventilated*	*Admitted directly from Casualty*	*Received antimicrobial treatment*	*Antimicrobial drug allergy*	*COPD*	*Organ failure (other than lungs)*	*Pulmonary embolism*	*Presence of malignancy*	*Pregnant*	

Tool 3 Treatment group allocation.

Record number of patient that meets inclusion and exclusion criteria	***Antimicrobial treatment received*** ***(Specify the antimicrobials received)***	***Treatment A (tick this column if patient is allocated to "Treatment A received" group)***	***Treatment B (tick this column if patient is allocated to "Treatment B received" group)***

Tool 4 Treatment group participant's characteristics.

TREATMENT GROUP A: PARTICIPANT'S CHARACTERISTICS				
Record no. of patient	***Any co-morbidities not listed under exclusion criteria (answer Yes or No and specify)***	***Smoking status***	***Age***	***Sex***
TREATMENT GROUP B: PARTICIPANT'S CHARACTERISTICS:				
Record no. of patient	***Any co-morbidities not listed under exclusion criteria (answer Yes or No and specify)***	***Smoking status***	***Age***	***Sex***

Tool 5 Culture results.

TREATMENT GROUP A:					
Record no. of patient	***Cultures done for patient? Answer Yes or No***	***Organism(s) cultured (If there were no growth, write "no growth.")***	***Culture source***	***Time (in days) from initiation of treatment until culture results were received***	***Did de-escalation take place where applicable? (answer Yes ,No or Not applicable)***
TREATMENT GROUP B:					
Record no. of patient	***Cultures done for patient? Answer Yes or No***	***Organism(s) cultured (If there were no growth, write "no growth.")***	***Culture source***	***Time (in days) from initiation of treatment until culture results were received***	***Did de-escalation take place where applicable? (answer Yes or No)***

Tool 6 Main and secondary outcome parameters.

TREATMENT GROUP A:			
Record no.. of patient	***Did the patient survive until ICU discharge? (answer Yes or No)***	***What was the total duration of stay in the ICU? (in days)***	***What was the total duration of antimicrobial treatment in the ICU? (in days)***
TREATMENT GROUP B:			
Record no.. of patient	***Did the patient survive until ICU discharge? (answer Yes or No)***	***What was the total duration of stay in the ICU? (in days)***	***What was the total duration of antimicrobial treatment in the ICU? (in days)***

ANNEXURE B:

The draft recommended in-house antimicrobial guideline:

A DRAFT IN-HOUSE ANTIMICROBIAL TREATMENT GUIDELINE FOR AIDS PATIENTS WITH ARDS IN THE ICU

DRAFT FOR RECOMMENDATION: 2016

PRESENTED BY MARNA BASSON

Content:

1. Clinical setting:

This guideline is recommended for antimicrobial treatment of ARDS among AIDS patients in the medical ICU (intensive care unit) of a general private hospital in Richards Bay, Kwazulu-Natal North Coast.

2. Rationale for this guideline:

Globally, HIV prevalence is highest in Sub-Saharan Africa (WHO, 2015). Acute respiratory failure is the main cause for admission and mortality in the ICU for HIV infected patients (Sarkar and Rasheed, 2013). There is an urgent need to examine appropriate antimicrobial strategies for treating ARDS in patients with AIDS as there appear to be no formal or standardized treatment guidelines. Empirical antimicrobial treatment for critically ill ICU patients ranges from a pathogen-directed to a broad spectrum approach (Leekha et al., 2010). The concern with a pathogen-directed approach is the possibility of undertreating the patient (File, 2015). In contrast, the anticipated complication associated with a broad spectrum approach is the potential contribution to the emergence of antimicrobial resistance (Leone and Martin, 2008). Antimicrobial resistance is as much a problem in South Africa as it is globally and can largely affect clinical outcome for patients (Mendelson, 2012). Identifying the most appropriate antimicrobial treatment strategy was necessary in order recommend an in-house treatment guideline that would ensure optimal clinical outcomes for the AIDS patient with ARDS in the ICU and limit emergence of antimicrobial resistance.

3. Strength of the recommendation:

Retrospective comparative therapeutic studies, investigating the results of treatment, are considered level three evidence according to the Levels of Evidence chart by De Vries and Berlet (2010). This study was a retrospective comparative study and therefor it was graded as level three evidence. The study was started after treatment was completed and participants were identified for the study based on the treatment they received.

4. Recommended antimicrobial treatment:

Based on this hospital's microbial test results and the results of the study "A Retrospective Comparison of Broad Spectrum and Pathogen-Directed Antimicrobial Treatment of Acute Respiratory Distress Syndrome in HIV/AIDS patients" that was performed at this hospital by Basson (2016), the following pathogen-directed antimicrobial treatment is recommended for the treatment of ARDS among AIDS patients in the ICU:

Table 4.1 Pathogen-directed antimicrobial treatment.

Pathogen-directed antimicrobial treatment
Beta-lactam antibiotic + Macrolide/fluoroquinolone + Suxamethonium-Trimethoprim Ceftriaxone (3rd generation cephalosporin) or Amoxycillin+clavulanic acid/Piperacillin+ tazobactam (beta-lactamase resistant penicillins). [2]Levofloxacin or Moxifloxacin

The above treatment is aimed at the two most common causative pathogens of ARDS in HIV-infected patients, *Pneumocystis jirovecii* and *Streptococcus pneumonia* (Benito et al, 2012). This treatment (pathogen-directed) resulted in better patient outcomes than the broad spectrum approach for the culture "blind" analysis of the performed study (Basson, 2016). This pathogen-directed approach also limits the risk of antimicrobial resistance (van der Eeden et al., 2005).

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