Treatment outcomes in patients with Carbapenem Resistant Enterobactericeae bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India.

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT

OF M.D. GENERAL MEDICINE BRANCH I EXAMINATION OF

THE TAMIL NADU DR. M.G.R. UNIVERSITY, CHENNAI TO BE

HELD IN MAY 2019

CERTIFICATION

This is to certify that the dissertation “Treatment outcomes in patients with Carbapenem Resistant Enterobactericeae bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India” is a bonafide work of Dr. Nalini Sarah Newbigging, carried out under our guidance towards the M.D. Branch I (General Medicine) Examination of the Tamil Nadu Dr. M.G.R. University, Chennai to be held in May, 2019.

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DECLARATION

This is to certify that the dissertation "Treatment outcomes in patients with Carbapenem Resistant Enterobactericeae bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India" which is submitted by me in partial fulfillment towards M.D. Branch I (General Medicine) Examination of the Tamil Nadu Dr. M.G.R. University, Chennai to be held in May, 2019 comprises my original research work and information taken from secondary sources has been given due acknowledgement and citation.

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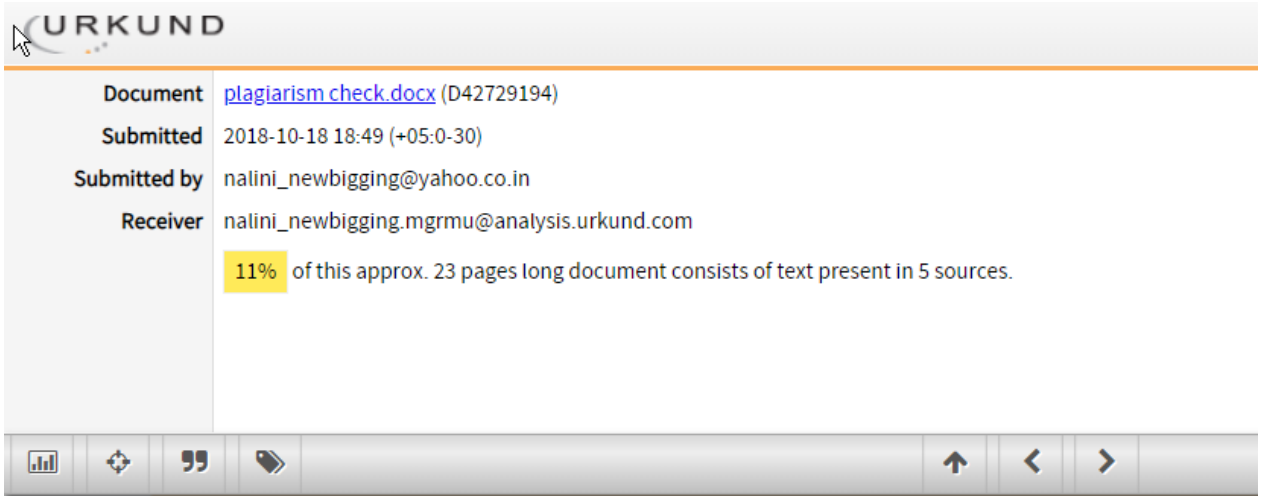
URKUND ANTIPLAGIRISM CERTIFICATE



This is to certify that this dissertation work titled “To study the clinical characteristics, risk factors and mortality outcomes of patients admitted with acute decompensated heart failure, admitted to general medical wards and intensive care units in a tertiary care hospital in South India” of the candidate Dr. Nalini Sarah Newbigging with registration number 201611463 in the branch of General Medicine. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 11 % of plagiarism in the dissertation.

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Lastly, I would like to thank God, my family and friends for their unrelenting support and help throughout the duration of the study.

Nalini Sarah Newbigging

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INTRODUCTION

Enterobacteriaceae are Gram-negative bacilli at are commensals in the intestine. They can however cause infections ranging from urinary tract infection (cystitis, pyelonephritis), septicaemia, pneumonia, meningitis and device related infections. They are a common source of community acquired and nosocomial infections, with *Escherichia coli* being the most common pathogen.

Spread of infections can be by contaminated human hands, contaminated food and water. The bacteria acquire genetic material via horizontal gene transfer which is plasmid or transposon mediated and acquire multidrug resistance. (1)

Since the early 2000's Extended Spectrum Beta-Lactamases (ESBLs) have been reported worldwide. A study done in south India in 2007, where 131 episodes of bacteremia were studied as a prospective cohort revealed that 77.86% episodes were caused by *E.coli*, 62% of which were nosocomial acquired. Out of these isolates, 73.5% of the *E.coli* and 72.4% *Klebsiella* were ESBL. ESBL conf---ers resistance to all beta-lactams except Carbapenems.

Carbapenems were found to be most active among all antimicrobials tested, and conclusions were made that in patients with serious life threatening infection with ESBL empiric antibiotic of choice should be Carbapenem. (2) This finding has been corroborated by many studies in India and worldwide. This has led to the widespread use of Carbapenem.

Carbapenems (imipenem, meropenem, ertapenem, doripenem) are latest molecules with broad spectrum activity in beta lactams. Drawback of wide spread use of Carbapenem is the emergence of Carbapenem resistance.

Emergence of novel beta-lactamases with direct Carbapenem hydrolyzing activity has contributed to Carbapenem resistance .(3)

Carbapenem acquire resistance by:

1) Acquisition of carbapenemase genes that encode for enzymes capable of degrading Carbapenem.

2) A decrease in uptake of antibiotics by qualitative and/or quantitative deficiency of porin expression in association with over expression of Beta lactamases that poses very weak affinity for Carbapenem (1)

Since Carbapenem are now the first line of therapy in severe infections caused by multi drug resistant gram negative bacilli, the emergence of resistance to Carbapenem is proving to be a threat the heath and health care worldwide.

As per previous studies, exposure to health care and antimicrobials are the most important risk factors to developing CRE bacteremia. (3)

Patel et al found that invasive infections with *Klebsiella pneumoniae* was independently associated with recent organ/stem cell transplantation, mechanical ventilation and longer in hospital stay.(4) ICU stay and poor functional status have also been attributed as risk factors that cause increased mortality.(5)

Few therapeutic options remain available for the treatment of Carbapenem resistant Enterobactericeae, and are most often limited to colistin and tigecycline. (6) However , the treatment is often restricted by their side-effects as well as uncertain in vivo activity.(7)

The prevalence continues to grow globally while being subject to large regional variation. (7)

A case control study, the impact of finding *Klebsiella pneumoniae* isolates in bloodstream was estimated in patients with Carbapenem resistant *Klebsiella pneumoniae* infections. It was estimated that the mortality was 72% for blood stream infections compared to 22% in patients with infections at other sites.(8)

In a series of 60 cases of CR-KP BSI, 14 days and all cause in hospital mortality was 42% and 58% respectively.(7)

Optimal therapy for CRE BSI is still under dispute and development of newer antibiotic molecules are underway. Retrospective comparisons favour combination therapy over single agent therapy with absolute differences in mortality ranging from 20.2% to 46.7%.(9) (10)

A study done in a tertiary hospital in Mumbai revealed that colistin monotherapy may be non-inferior compared to combination therapy for treating CRE BSI , however combined use of colistin with Carbapenem can provide good therapeutic option and needs further investigation.(11)

Therefore, investigation of risk factors for development of CRE bacteremia and appropriate antibiotic therapy is warranted.

PROPOSED STUDY

In this prospective cohort study, we plan to assess the clinical profile and outcome of patients, with Carbapenem Resistant Enterobactericeae (Klebsiella spp and *Escherichia coli)* blood stream infection requiring admission into a medical, surgical ward or ICU in a tertiary care centre in South India.

AIM

To assess treatment outcomes in patients with Carbapenem resistant Enterobactericeae (CRE) bloodstream infections (BSI) being treated in the medical ward, surgical ward and ICU in tertiary care hospital in South India

OBJECTIVES

1) To determine the rate of 14-day all-cause mortality in patients with CRE BSI who are admitted to general wards or medical and surgical ICU and HDU.

2) To assess factors associated with mortality in patients with CRE BSI.

MATERIALS AND METHODS

SETTING

The Christian Medical College is a 2400 bed teaching hospital in Vellore, South India. Though it caters to approximately 1 million citizens of the town it also serves patients from all over India and South-East India.

This study has been conducted among patients with CRE bacteremia in all Medical wards, Medical ICU and HDU, surgical ICU and HDU, certain approved Surgical and specialty wards.

Duration: May 2017 till July 2018 as a prospective study.

STUDY DESIGN

Prospective observational study

INCLUSION CRITERIA

1. Patient age more than or equal to 18 years, who have given written informed consent
2. Patients who are currently admitted in CMC Hospital, Vellore
3. Patient with monomicrobial CRE BSI
4. Current CRE bacteremia being the first episode of BSI, patients with second episode of CRE during the same admission were registered only once.

EXCLUSION CRITERIA

1. Patients below the age of 18
2. Patients who are not currently admitted in the hospital
3. Patients who do not give consent
4. Patients with previous bacteremic illness during the current admission

METHODS

Patients with confirmed CRE BSI (*Klebsiella spp*. or *Escherichia coli*) were identified through a registry in the Department of Microbiology. Blood cultures were predominantly drawn from peripheral venipuncture after observing aseptic precautions. In patients with CLABSI, a paired peripheral venipuncture sample was also obtained. Sequential patients with CRE BSI were then enrolled in the study if they met the inclusion criteria as specified above. In all patients only the first episode of bacteremia was included for analysis.

A study questionnaire with relevant information was formulated. This included demographic details, severity of illness (APACHE II score and Pitt's bacteremia score), INCREMENT CPE score (12) co- morbidities such as underlying Diabetes Mellitus and systemic hypertension, the Charlson Comorbidity Index was also assessed, immune status (Sero-positive status, underlying Hepatitis B or Hepatitis C infection) and primary source of bacteremia.

Pitt's Bacteremia Score is a score that takes into account vital signs, mechanical ventilation and mental status, a score of more than 4 is suggestive of severe infection.

The Acute Physiology and Chronic Health Evaluation (APACHE II), is a tool used to estimate acute severity of illness and mortality. The APACHE II score is made of both physiological variables and disease-related variables. The APACHE II score can have a value from the range of 0 to 71 points.

During the study period, the administration of antibiotics and other therapy related decisions, were made solely by the treating physician and were not influenced by this study.

Demographic details, and parameters for assessment were documented from the patient's hospital chart, after written informed consent was obtained from the patient or their relatives. Details used in assessment of severity of illness, including temperature, presence of hypotension and laboratory parameters were obtained of the day that the blood culture that grew the isolate of interest had been taken.

Primary source of the infection was defined as pneumonia, urinary tract infection, surgical wounds and primary bloodstream infections, with catheter related blood stream infections included with primary blood stream infections in accordance with the definitions that have been established by the Centers for Disease Control and Prevention.(13)

MICROBIOLOGICAL METHODS

For all patients enrolled in the study, 5-8 ml of blood was collected, using standard precautions, in adult blood culture bottles (BacTAlert). This was then processed by semi-automated blood culture system (BacT/Alert; BioMérieux, Marcyl' Etoile, France). Standard microbiological methods were used to identify the causative organism. Disk diffusion method was used to for antibiotic susceptibility testing (AST). The interpretation was based on Clinical Laboratory Standards Institute (CLSI) recommendations.

Disk diffusion by Kirby-Bauer method

CLSI recommends this method for routine testing. Accuracy and reproducibility is insured by maintaining a standard set of procedures.

Requirements:

1. Sterile broth medium in 1.5 ml quantities (nutrient broth / Mueller Hinton broth)
2. MHBA for *S. pneumoniae* and other Streptococci
3. MHA for Non-fastidious organisms.
4. HTM for *Haemophilus spp*.
5. GC agar with 1% growth supplements for *Neisseria spp*.
6. Calibrated loop of 2 mm diameter
7. Antibiotic solution
8. Sterile filter paper disks / Commercial disks

9. Pasteur pipettes sterile
10. Cotton swabs sterile
11. Normal saline and / Nutrient broth
12. McFarland BaSO4 turbidity standard 0.5
13. Sterile forceps / needle / disk dispenser
14. 12 x 100 mm sterile test tubes
15. Measuring scales / sliding calipers
16. Table lamp
17. Zone diameter interpretation charts
18. Quality control reference strains
19. Discard jar with disinfectant

Antimicrobials:

Antimicrobials for testing may be prepared in house (from pure substance) or are also available as commercial disk of standard size and strength.

Commercial disk:

1. Each particular agent recommends the proper temperature for storage of the disk cartridges. Certain specific agents like imipenem, cefaclor, and clavulanic acid combinations should be frozen till day of testing, in view of their labile nature.
2. For cartridges that are stored in a freezer, they should be removed from storage one or two hours prior to testing to bring it at room temperature. This is done in order to prevent condensation forming on the disks.
3. Discard all disks that are past the expiry date.

Preparation of antimicrobial solution in-house:

Preparation of stock solution:

1. Pure substance of antimicrobial agents may be received in powder or tablet form. **Preparations intended for parenteral injections should not be used.**
2. Using sterile glassware, required concentrations of the stock solution are obtained by accurately weighing the powders and dissolving them in appropriate diluents.
3. Antibiotic stock solution should be evaluated against standard strains of stock cultures. The stock can be aliquoted in 5 ml volumes and frozen at -20ºC or -60ºC, if satisfactory.
4. Antibiotic solution can be prepared with the following formula:

$$\textit{Weight}\ (\text{mg}) = \frac{\textit{Volume}\ (\text{mL}) \bullet \textit{Concentration}\ (\mu\text{g/mL})}{\textit{Potency}\ (\mu\text{g/mg})}$$

Or

$$\textit{Volume}\ (\text{mL}) = \frac{\textit{Weight}\ (\text{mg}) \bullet \textit{Potency}\ (\mu\text{g/mg})}{\textit{Concentration}\ (\mu\text{g/mL})}$$

Preparation of inoculum:

Either growth method or direct suspension method can be used to prepare the inoculum.

For non-fastidious organisms the growth method is preferred. This is also preferred when smooth suspension of the organism cannot be made.

1. Touch 8 or 10 well isolated colonies that are of the same morphological type with a sterile needle / loop.
2. Inoculate into 1.5 ml of a sterile suitable broth.
3. To produce a bacterial suspension of moderate turbidity, the inoculum should be incubated at 35 – 37ºC for 2 – 6 hours.
4. Adjust the turbidity of the broth to McFarland barium sulphate standard 0.5 with sterile saline / broth. This results in a suspension containing approximately 1 to 2 x 10^8 CFU/ml for *E.coli* ATCC 25922.

Inoculation of test plates

1. According to the number of antibiotics used, mark the plates into five sections (100 mm petri-dish).
2. The plates need to be inoculated within 15 minutes of preparation of suspension in order to avoid change in the density.
3. Removes excess fluid by dipping a sterile cotton swab into the suspension.
4. By streaking the swab over the sterile agar surface, inoculate the dried surface of a Mueller-Hinton agar plate.

5. The lid may be left ajar for 3 to 5 minutes, to allow for excess surface moisture to be absorbed before applying the drug impregnated disks.

Application of antimicrobial disk

1. Within 15 minutes of inoculation of the culture, the antimicrobial disks should be dispensed on the agar plate.
2. Complete contact with the agar surface needs to be ensured by pressing each disk down individually.
3. A disk should not be relocated once it has come into contact with the agar surface.
4. For antimicrobial solution that is prepared in house, a 2 mm calibrated loop is used to deliver 5µl of the solution into 6 mm disk that is prepared from Whatmann No.2 filter paper, and placed on the surface of the plate.
5. After the disks are applied, incubate the plates in an inverted position in an incubator set to 35±2ºC within 15 minutes.

Reading and interpretation of results:

1. Only when the zone size for the QC organism is within the expected zone size range should reading for the test isolate be taken.
2. Each plate is examined after 16 – 18 hours of incubation.
3. Resulting zones of inhibition will be clear and there will be a confluent lawn of growth if the inoculum was correct and the plate was accurately streaked.
4. Zone edge: is the point of abrupt diminution of growth.

5. Measure the diameters of the zones of complete inhibition, including the diameter of the disk.
6. Zones are measured to the nearest whole millimeter.

The area where no obvious, visible growth can be detected is the zone margin.

DEFINITIONS

1. An **episode of bacteremia** is defined as the period of 14 days from the time of collection of the first blood culture positive for *E. coli* or *Klebsiella* spp.
2. **Nosocomial bacteremia:** defined as *E. coli* or *Klebsiella* spp. bacteremia occurring among patients more than 48 hours after admission to the hospital or among those patients who had an invasive procedure done (minor surgical procedure, intravenous administration of drugs or placement of a urinary catheter) as an outpatient and the bacteremia was attributable to that procedure.
3. **Previous antibiotic therapy** is defined as antibiotics given for at least 2 days within the 14 days before an episode of *E. coli* or *Klebsiella spp*. bacteremia.
4. Mortality was death from any cause within 14 days from the date of the first positive blood culture for *E. coli* or *Klebsiella* spp.
5. **Empiric antibiotic treatment** was the antibiotic(s) administered from the time of obtaining blood culture, and continued till availability of AST report
6. **Targeted antibiotic treatment** was defined as antibiotics started once the AST report was available.
7. **Appropriate antibiotic treatment** (empirical and targeted) was defined as receipt of at least one antimicrobial to which the bacterial isolate was susceptible in-vitro.
8. **Inappropriate therapy** was defined as administration of antimicrobials that did not have in-vitro activity against the isolate of interest.

SAMPLE SIZE CALCULATIONS

Based on a previous study the mortality of patients with CRE is described to be 42.6%.

Based on this information, the sample size was calculated for:

Objective (1) using the formula, n=4p (1-p)/d2 = (4*.43*.57)/ (.07*.07) =164. Here p is the expected proportion of mortality and d is the absolute precision.

Objective (2), to find the significant predictors of mortality, the required number is approximately 224.

Hence the sample size of this study is decided to be 250.

INSTITUTIONAL REVIEW BOARD

The institutional review board and ethics committee approved this study. The research funding was obtained from the fluid research grant of the institution.

IRB Minute Number: 10566 (OBSERVE) (8/3/2017)

REVIEW OF LITERATURE

Bloodstream infections are a major cause of morbidity and mortality. Bacteremia due to Gram-negative bacilli is a significant problem encountered as both community acquired and hospital acquired infections. These organisms present problems with regards to antibiotic therapy because of the increasing drug resistance (14). Gram-negative bacteremia with septic shock has been estimated to have a mortality rate of 12 to 38 percent; depending, on whether the patient receives timely and appropriate antibiotic therapy (15).

EPIDEMIOLOGY

Gram-negative bacilli cause approximately a quarter to a half of all bloodstream infections, whether the infection is hospital or community acquired, depending on geographic region, and other patient risk factors.

Community-acquired infections

Gram-negative bacilli cause a high proportion of community-acquired BSI, as they are more likely related to primary infections of the urinary tract, abdomen, and respiratory tract.

In a study conducted in two tertiary care centers in the United States, community-acquired bloodstream infections were due to Gram-negative bacilli in 45% cases, whereas they caused 31 percent of hospital-acquired infections (16). A systematic

review of studies from South and Southeast Asia , wherein among community-acquired BSI, Gram-negative organisms were the causative in 60 percent of patients (17).

Gram-negative BSI as a community-acquired infection is commonly seen in the elderly population. This was evidenced in a retrospective review of 238 patients, 65 years of age and above, wherein a Gram-negative organism was the etiologic agent in 36 percent of cases (18).

Hospital-acquired infections

In the United States of America, the National Nosocomial Infections Surveillance (NNIS) System reported that from 1986 to 2003 the proportion of gram negative BSI in ICU patients remained static at approximately 25 to 30 percent (19).

However, several single centre studies have shown an increase in the proportion of Gram-negative infections among patients with catheter-related BSI. A single large United States tertiary care hospital reported a significant increase in the proportion of gram-negative BSI from 15.9 percent in 1999 to 24.1 percent in 2003 (20). Several subsequent reports from Europe have shown a similar trend in the proportion of Gram-negative catheter-related BSI (21,22). Increasing proportions of Gram-negative catheter-related bloodstream infections, may be related to improved prevention efforts aimed at Gram-positive central line infections, increasing antimicrobial resistance, and/or changes in surveillance practices (23–25). Many of these factors are impacted by local infection prevention practices and the geographical prevalence of drug-resistance.

Globally, the proportion of bloodstream infections caused by Gram-negative bacilli differs by geographic region.

Data from the SENTRY Antimicrobial Surveillance Program from 1997 to 2002 demonstrated that the proportion of Gram-negative bacteremia was greater in Europe (43 percent) and Latin America (44 percent), than that identified in North America (35 percent) (26). A study from the European Antimicrobial Resistance Surveillance System, reported that the frequency of bacteremia due to *Escherichia coli* increased by 8.1 percent per year from 2002 to 2008. The additional caseload was being attributed to increasing antimicrobial resistance (27).

Seasonality and the effect of warmer climates may partially explain these geographical differences. Several studies have demonstrated seasonal trends in gram-negative bacteremia in multiple continents and involving various pathogens, including *Acinetobacter* spp., *E. coli*, *Enterobacter* spp., *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (28–30).

Risk factors associated with Gram-negative bacteremia

Most hospitalized patients with Gram-negative bacteremia have at least one comorbid condition (31). In a study of 326 patients with Gram-negative bacteremia, comorbid conditions were identified in (97 percent) (32). Conditions identified in this study included(32–35):

- Haematopoietic stem cell transplant
- Liver failure
- Serum albumin <3 G/dL
- Solid organ transplant
- Diabetes mellitus
- Pulmonary disease
- Chronic hemodialysis
- HIV infection
- Treatment with glucocorticoids

SOURCE OF INFECTION

Determining the source of infection is critical to make appropriate therapeutic decisions. This includes assessment of the most likely pathogen, and subsequently initiation of appropriate empiric therapy depending on the site of the primary infection. Among critically ill patients, common sources of Gram-negative BSI include the respiratory tract and central venous catheters (36). Several studies of elderly patients in the community, have identified the urinary tract as the most frequent source of Gram-negative BSI (37,38). Infections of the gastrointestinal tract, biliary tract, and skin or soft tissues are less frequent sources of bloodstream infections.

MICROBIOLOGY

The frequency of specific Gram-negative bacilli responsible for BSI differs depending on whether the onset of the infection, is in the hospital or community and the likely primary source of infection.

Hospital-acquired gram-negative bacillary BSI identified from a large database of acute care hospitals in the United States, distribution of pathogens was noted as follows(39):

E. coli – 18 percent

K. pneumoniae – 16 percent

P. aeruginosa – 8 percent

Proteus spp – 1 percent

Other Gram-negative bacteria – 56 percent

Patients in the ICU generally are on empiric antibiotics, which increases the risk of infections with *P. aeruginosa* and other non-fermenting Gram-negative bacilli.

Infections with *E. coli* predominate in cases of community-onset Gram-negative BSI. This was depicted in a study done in Italy wherein the following distribution was noted. (40) *E. coli* – 76 percent

P. aeruginosa – 7.9 percent

K. pneumoniae – 5.4 percent

Proteus mirabilis – 4.2 percent

Enterobacter spp – 3.7 percent

ANTIBIOTIC RESISTANCE

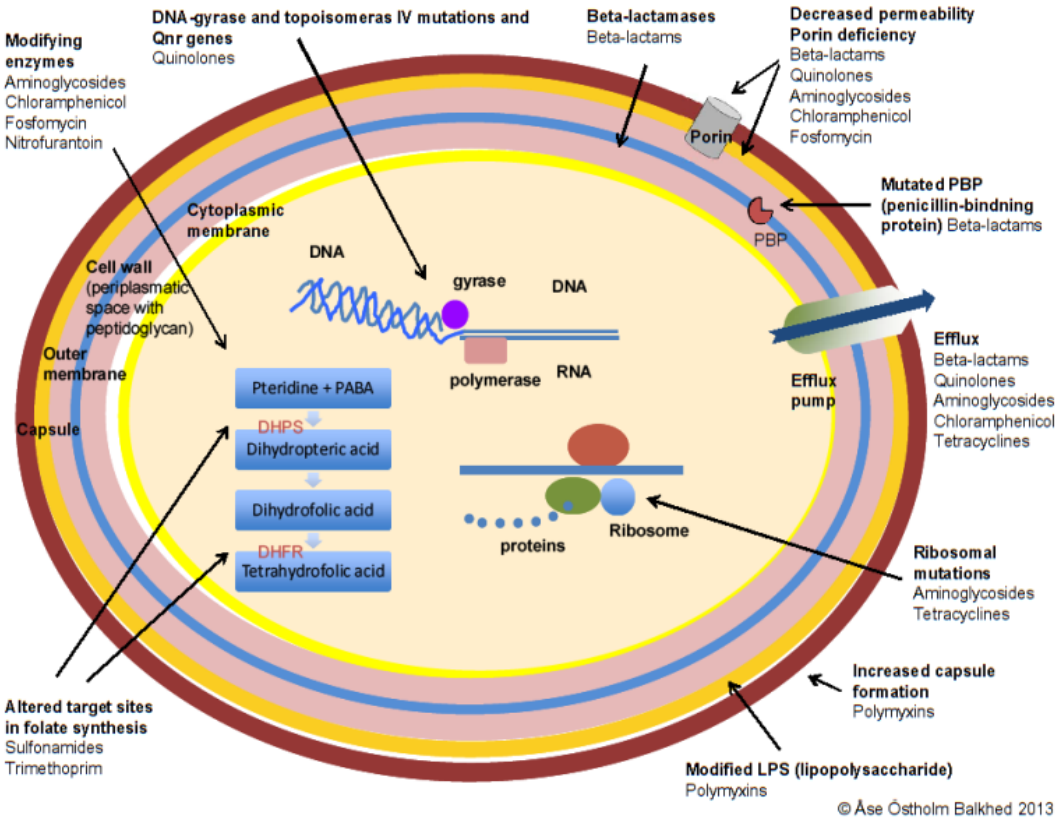
The treatment of Gram-negative BSI is increasingly complicated by the rising prevalence of multidrug-resistant Gram-negative bacilli strains. Susceptible *Enterobacteriaceae* become resistant to antimicrobial agents by acquiring resistance genes from other bacteria or through mutation and selection.

The burden of antimicrobial resistance among bloodstream infections caused by Gram-negative organisms is profound. Between 2009 and 2010 , in the United States alone, among the 27,766 CLABSI reported to the National Healthcare Safety Network, the prevalence of resistance to broad-spectrum antibiotics to be(23):

- *K. pneumoniae* – 29 and 13 percent resistant to third or fourth generation cephalosporins and carbapenems, respectively
- *E. coli* – 42, 19, and 2 percent resistant to fluoroquinolones, third or fourth generation cephalosporins and carbapenems, respectively
- *Enterobacter spp* – 37 percent resistant to third or fourth generation cephalosporins
- *P. aeruginosa* – 31, 26, and 26 percent resistant to fluoroquinolones, third or fourth generation cephalosporins, and carbapenems, respectively
- *A. baumannii* – 67 percent resistant to carbapenems

In addition to these, there has been emergence and dissemination of extended-spectrum beta-lactamases and carbapenemases.

These multidrug-resistant pathogens are no longer limited to an in hospital acquired infection. Patients are frequently infected or colonized with these pathogens in the community and in long term care facilities(41–43).



(44) **Figure 1: resistance mechanisms in Enterobactericeae**

Extended-spectrum beta-lactamases

Extended-spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics - penicillins, cephalosporins, and the monobactam aztreonam. Plasmids that carry ESBLs typically carry other resistance genes as well; thus, these organisms are frequently multidrug-resistant.

The ESBL family is heterogeneous. SHV and TEM-type ESBLs arose by amino acid substitutions that allowed narrower spectrum enzymes to attack the new oxyimino-beta-lactams. Others include members of the CTX-M family, represent plasmid acquisition of broad-spectrum beta-lactamases originally determined by chromosomal genes.

ESBLs vary in activity against different oxyimino-beta-lactam substrates but do not affect the cephamycins (cefoxitin, cefotetan and cefmetazole) and the carbapenems (imipenem, meropenem, doripenem, and ertapenem).

They are also susceptible to beta-lactamase inhibitors, such as clavulanate, sulbactam, and tazobactam, which consequently can be combined with a beta-lactam substrate to test for the presence of this resistance mechanism.

ESBLs have been found exclusively in Gram-negative organisms, primarily in *Klebsiella pneumoniae* and *Escherichia coli* but also in *Acinetobacter*, *Burkholderia*, *Citrobacter*, *Enterobacter*, *Morganella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Serratia*, and *Shigella spp*.

Infection due to ESBL-producing *E. coli* has become widespread in hospitals around the world (45). Community-associated infection due to ESBL has also been recognized as an important clinical problem. A substantial portion of community-onset infection

due to ESBL-producing *E. coli* has been observed among patients with no discernible health care-associated risk factors (46).

TYPES OF ESBL

TEM beta-lactamases — the amino acid substitutions responsible for the ESBL phenotype cluster around the active site of the enzyme and change its configuration, allowing access to oxyimino-beta-lactam substrates. Single amino acid substitutions at positions 104, 164, 238, and 240 produce the ESBL phenotype, but ESBLs with the broadest spectrum usually have more than a single amino acid substitution. Based upon different combinations of changes, currently more than 220 TEM-type enzymes have been described. Not all behave as ESBL, and some, such as TEM-1 and TEM-2, only hydrolyze beta-lactams such as penicillins and narrow spectrum cephalosporins (47). Most are ESBLs, some are resistant to beta-lactamase inhibitors, and a few are both ESBLs and inhibitor-resistant.

SHV beta-lactamases — ESBLs in this family also have amino acid changes around the active site, most commonly at positions 238 or 238 and 240. More than 190 SHV varieties are known, and they are found worldwide. SHV-2, SHV-5, SHV-7, and SHV-12 are among the most common (48). Not all the SHVs are ESBL and some, such as SHV-1, only hydrolyze beta-lactams such as penicillins and narrow spectrum cephalosporins (47).

CTX-M beta-lactamases — these enzymes were named for their greater activity against cefotaxime than other oxyimino-beta-lactam substrates (eg, ceftazidime, ceftriaxone, or cefepime). They represent acquisition of resistance due to plasmid acquisition of beta-lactamase genes normally found on the chromosome of *Kluyvera* species, a group of rarely pathogenic commensal organisms.

More than 160 CTX-M enzymes have been described (49). They have been found in many different Enterobacteriaceae including *Salmonella*, and are the most common ESBL type worldwide (50), and are increasingly prevalent in the United States (51). The proliferation of CTX-M enzymes is due not to being better beta-lactamases than TEM or SHV varieties but to the capture and dissemination of CTX-M genes by mobile genetic elements that mediate rapid and efficient spread between replicons and from cell to cell, especially to highly successful lineages such as *E. coli* ST131 and ST405 and *K. pneumoniae* CC11 and ST147 (52).

OXA beta-lactamases — OXA beta-lactamases are also plasmid-mediated beta-lactamase variety that could hydrolyze oxacillin and related anti-staphylococcal penicillins. Amino acid substitutions in OXA enzymes can also give the ESBL phenotype. OXA-type ESBLs have been found mainly in *Pseudomonas aeruginosa* isolates from Turkey and France. OXA beta-lactamases with carbapenemase activity have also been described.

Others — Other plasmid-mediated ESBL families, such as PER, VEB, and GES, are uncommon and have been found mainly in *P. aeruginosa* and at a limited number of geographic sites (53). In addition to conferring high-level resistance to antipseudomonal

beta-lactams, these ESBLs also degrade cephalosporins, and monobactams. Other rare ESBLs found in Enterobacteriaceae are BES, SFO, and TLA.

Beta-lactamases in Enterobacteriaceae				
Class	**Subgroups**	**Ambler class**	**Phenotypic test**	**Hydrolytic activity against**
Penicillinases	TEM-1, TEM-2 SHV-1	A	Inhibited by clavulanic acid	Penicillins
Cephalosporinases $ESBL_A$	TEM-ESBLs SHV-ESBLs CTX-M			Penicillins Cephalosporins
Cephalosporinases non-ESBL	Chromosomal Amp C	C	Inhibited by cloxacillin	Penicillins Cephalosporins
Cephalosporinases $ESBL_M$	Plasmid-mediated Amp C CIT (CMY variants), MOX, FOX, DHA, ACC, EBC			
	OXA-ESBL	D		
Carbapenemases $ESBL_{CARBA-A}$	KPC	A	Synergy with boric acid	Penicillins Cephalosporins Carbapenems
Carbapenemases $ESBL_{CARBA-B}$	Metallo-beta-lactamases NDM, VIM, IMP	B	Synergy with dipicolinic acid/ EDTA	
Carbapenemases $ESBL_{CARBA-D}$	OXA-48-like	D	Temocillin MIC>32 mg/L	Penicillins Carbapenems

The majority of infections with ESBL-producing organisms in the hospital are caused by *K. pneumoniae*. However, over the past decade, ESBL-producing *E. coli* has emerged as an important cause of both hospital-onset and, in particular, community-onset bacteremia. As a result, *E. coli* is now the most common cause of ESBL infection worldwide. In one series, these resistant organisms accounted for 7.3 percent of cases of community-onset bacteremia (54).

Risk factors for infection with an ESBL-producing organism among patients with bacteremia include admission from a nursing home, the presence of a gastrostomy tube, transplant receipt, chronic renal failure, receipt of antibiotics within the preceding 30 days, and length of hospital stay before infection.

The only proven therapeutic option for severe infections caused by extended-spectrum beta-lactamase (ESBL)-producing organisms is the carbapenem family.

CARBAPENEM:(55)

The term “carbapenem” is conferred to a 4:5 fused ring lactam of penicillins that contain a double bond between C-2 and C-3, along with the substitution of carbon for sulfur at C-1.

Chemistry

Studies from early carbapenems revealed that the carbon atom at the C-1 position played a major role in the potency and spectrum of carbapenems, and in their stability against –lactamases.

Further research has taught us that a hydroxyethyl R2 side chain aids in resistance to hydrolysis by lactamases and a trans configuration of the C-5 C-6 lactam ring leads to greater stability against beta-lactamases. aids in resistance to hydrolysis by lactamases (56). *R* configuration at C-8 also enhances potency.

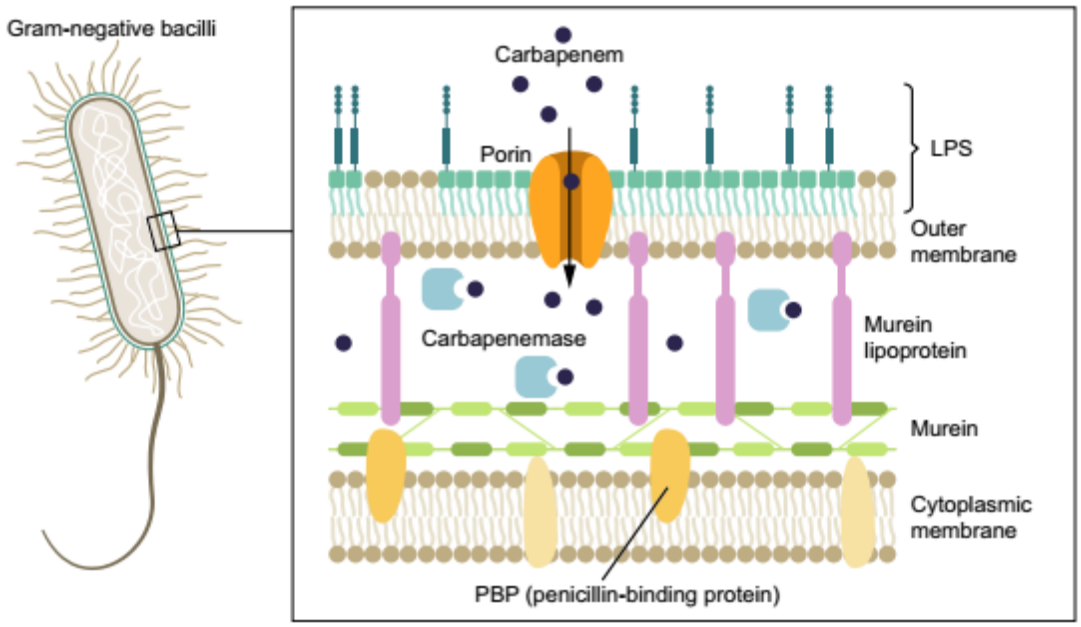
Mechanism of action

Carbapenems enter Gram-negative bacteria through outer membrane proteins (OMPs), known as porins. After traversing the periplasmic space, carbapenems “permanently” acylate the PBPs.(57)

PBPs are enzymes (i.e., transglycolases, transpeptidases, and carboxypeptidases) that catalyze the formation of peptidoglycan in the cell wall of bacteria.

Carbapenems act as mechanism-based inhibitors of the peptidase domain of PBPs and can inhibit peptide crosslinking among other peptidase reactions.

As carbapenems bind to many different PBPs, inhibiting their action, thereby causing autolysis at a more rapid rate than cell wall formation. This thereby weakens the peptidoglycan layer of the cell wall, causing the cell to burst due to osmotic pressure.



(58) **Figure 2:** Schematic view of the cell wall in Gram-negative bacilli showing the outer membrane including a porin where the antibiotic can enter the cell, the periplasmic space where the b-lactamases are located, the cytoplasmic membrane and multidrug efflux pumps that can export antimicrobial agents out of the bacterial cell.

Microbiological activity

Carbapenems demonstrate a broader antimicrobial spectrum *in vitro* than the available penicillins, cephalosporins, and beta-lactam/beta-lactamase inhibitor combinations (59).

Imipenem, panipenem, and doripenem are potent antibiotics against Gram-positive bacteria (59–61). Meropenem, biapenem, ertapenem, and doripenem are slightly more effective against Gram-negative organisms (59).

Carbapenems can also be combined with other antimicrobials to treat serious infections. Combination therapy is a subject of intense interest, since the emergence of MDR pathogens often requires us to treat patients with more than one antibiotic (53,62,63).

It is in this very niche area of infections that we encounter the catastrophic reality of Carbapenem Resistant Enterobactericeae.

CARBAPENEM RESISTANCE

Carbapenem resistance in Enterobacteriaceae is therapeutic challenge with every increasing prevalence, if left unchecked exudes terrifying implications for public health and society (62,63). These bacteria, including *Escherichia coli*, *Klebsiella pneumoniae* and other species, are commensals in the human gut and frequently are the cause of hospital acquired and community acquired infections, ranging from the urinary, gastrointestinal and respiratory tracts as well as bloodstream infections (BSI) (19).

Mediation of resistance to carbapenems among Enterobacteriaceae is by transferable beta-lactamase enzymes (66). Due to the occurrence of more than one resistance gene on the same mobile genetic elements (67), carbapenemase producing strains are normally extensively drug resistant (i.e. susceptible to ≤2 antimicrobial classes) (68).

CLASSIFICATION

Carbapenemases are carbapenem-hydrolyzing beta-lactamases that confer resistance to a broad spectrum of beta-lactam substrates, including carbapenems. This mechanism is distinct from others such as impaired permeability due to porin mutations.

The carbapenemases have been organized based on amino acid homology in the Ambler molecular classification system. Class A, C, and D beta-lactamases all share a serine residue in the active site, while Class B enzymes require the presence of zinc for activity (and hence are referred to as metallo-beta-lactamases). Classes A, B, and D are of greatest clinical importance among nosocomial pathogens.

Class A beta-lactamases

Class A beta-lactamases are characterized by their hydrolytic mechanisms that require an active-site serine at position 70 (69). These include penicillinases and cephalosporinases in the TEM, SHV, and CTX-M-type groups (which do not hydrolyze carbapenems), as well as additional groups that possess beta-lactamase (including carbapenemase) activity (47,69,70).

Class A beta-lactamases with carbapenemase activity may be encoded on chromosomes or plasmids. Chromosomally-encoded enzymes include SME (*Serratia marcescens* enzyme), NMC (non-metalloenzyme carbapenemase) and IMI (imipenem-hydrolyzing) beta-lactamases. Plasmid-encoded enzymes include KPC (*Klebsiella pneumoniae* carbapenemase) and GES (Guiana extended spectrum). GES has been described in *Pseudomonas aeruginosa* and *K. pneumoniae* (71–73).

Klebsiella pneumoniae carbapenemase (KPC)

The most clinically important of the Class A carbapenemases is the *K. pneumoniae* carbapenemase (KPC) group. These enzymes reside on transmissible plasmids and confer resistance to most beta-lactams (71). Several variants of KPC enzymes have been identified. Some hydrolyze beta-lactams at varying rates, which may contribute to different susceptibility profiles in KPC-producing bacteria when tested in vitro(74,75). KPC can be transmitted from *Klebsiella* to other genera, including *E. coli, P. aeruginosa*, *Citrobacter*, *Salmonella*, *Serratia*, and *Enterobacter* spp (76–78). Another

carbapenemase, BKC-1, has been detected in rare clinical isolates of *K. pneumoniae* in Brazil (79).

Class B beta-lactamases

Class B beta-lactamases are also known as the metallo-beta-lactamases (MBLs), because of their dependence upon zinc for efficient hydrolysis of beta-lactams. MBLs can be inhibited by EDTA (an ion chelator); they are not inhibited by beta-lactamase inhibitors such as tazobactam, clavulanate, sulbactam, and avibactam. Additional groups of acquired MBLs have been identified: IMP, VIM, GIM, SPM, and SIM.

There are both naturally occurring and acquired MBLs. Naturally occurring MBLs are chromosomally encoded and have been described in *Aeromonas hydrophilia*, *Chryseobacterium* spp, and *Stenotrophomonas maltophilia* (80). Acquired MBLs consist of genes encoded on integrons residing on large plasmids that are transferable between both species and genera (69,81–83).

New Delhi metallo-beta-lactamase (NDM-1)

Enterobacteriaceae isolates carrying a novel MBL gene, the New Delhi metallo-beta-lactamase (NDM-1), were first described in December 2009 in a Swedish patient hospitalized in India with an infection due to *K. pneumoniae*(84).

The gene encoding this MBL is located in a very mobile genetic element, and the pattern of spread appears to be more complex and more unpredictable than that of the gene encoding KPC (84,85). The large number of resistance determinants in the isolates studied raise concern that this gene is an important emerging resistance trait (86). In

general, bacteria containing NDM-1 have tested susceptible to colistin or tigecycline, though such susceptibility may be short-lived.

In addition to *K. pneumoniae*, NDM-1 has also been identified in other Enterobacteriaceae (including *E. coli* and *Enterobacter cloacae*) (87) as well as non-Enterobacteriaceae (including *Acinetobacter*)(88).

Class D beta-lactamases

Class D beta-lactamases are also referred to as OXA-type enzymes because of their preferential ability to hydrolyze oxacillin (rather than penicillin) (89). Enzymes in this group are variably affected by the beta-lactamase inhibitors clavulanate, sulbactam, or tazobactam. OXA carbapenemases have been identified in *Acinetobacter baumannii* (90–92) and Enterobacteriaceae (especially *K. pneumoniae*, *E. coli*, and *E. cloacae*) (93).

Among the heterogeneous OXA group (which includes more than 100 enzymes), six subgroups have been identified with varying degrees of carbapenem-hydrolyzing activity: OXA-23, OXA-24/OXA40, OXA-48, OXA-58, OXA-143, and OXA-51. The first five groups are carried on transmissible plasmids, while the last group, OXA-51, and is chromosomally encoded. Enterobacteriaceae with OXA-48-type enzymes have variable susceptibility to these agents. Expression of a promoter insertion element (ISAba1) in OXA-23 and OXA-51 likely contributes to carbapenem resistance(94).

EPIDEMIOLOGY

Klebsiella pneumoniae carbapenemases

The *K. pneumoniae* carbapenemase (KPC) is the most common carbapenemase in the United States. Following the first description of KPC from a clinical isolate of *K. pneumoniae* in the late 1990s in North Carolina (71,93), KPC-production has been identified in isolates from nearly every state, as of 2015 (95). In a surveillance study from sites in seven states from 2012 to 2013, the incidence of carbapenem-resistant Enterobacteriaceae isolates from urine or a sterile site was 2.93 cases per 100,000 person years; approximately half of the submitted isolates possessed the KPC beta-lactamase (96).

KPC-possessing isolates have also been increasingly recovered from other regions of the world, including Europe (97,98), Asia (99,100), Australia (101), and South America (102).

Class D carbapenemases

While *A. baumannii* carrying OXA-23-, OXA-24/40-, and OXA-58-type carbapenemases are of significance in Europe, they have also been encountered in medical centers in Eastern Asia, the Middle East, Australia, South America, and the United States (89). The first isolate of *K. pneumoniae* with OXA-48 was identified in Turkey (64). Enterobacteriaceae with OXA-48-type enzymes have also identified in the United States, Europe, the Middle East, and Northern Africa.

Of greater importance to our study population is the metallo-beta-lactamases, of which NDM-1 was first identified in patients who had sought treatment in India.

Metallo-beta-lactamases

Metallo-beta-lactamases (MBLs) were initially described in Japan in 1991(103). MBLs have since been described in other parts of Asia, Europe, North America, South America, and Australia (104–106). The transfer of patients between hospitals and the increase in international travel may be important factors in the geographical dissemination of MBL genes (107,108).

The MBL gene, the New Delhi metallo-beta-lactamase (NDM-1), was first described in December 2009 in a *K. pneumoniae* isolate from a Swedish patient who had been hospitalized in India (84). Subsequent reports have included patients who have travelled and undergone procedures (so called "medical tourism") in India and Pakistan (87), as well as cases reported in Asia, Europe, North America, the Caribbean, and Australia (85,87,109).

In the United States, between January 2009 and February 2011, seven Enterobacteriaceae isolates with NDM-1 production were reported to the Centers for Disease Control and Prevention (CDC) (3). These were all identified in patients who had travelled to India or Pakistan, the majority of whom received medical care there.

Isolates of *P. aeruginosa* which co-harbour genes for both KPC and NDM have also been described (110).

A study done in Europe between 2008 and 2010, to assess the prevalence of NDM-1 CRE, had 77 cases in 13 countries, with indications of an increase in the spread of such infections as the years progressed. Most cases gave history of recent travel to or hospitalisation in the Indian Subcontinent(111).

Majority of the clinical isolates had *bla*$_{\text{NDM-1}}$ determinant located on conjugative plasmids. Few isolates has the determinant on the bacterial chromosome, indicating intragenomic recombination. NDM-1 was produced by K. pneumoniae and E.coli isolates from the same patient which suggested in vivo transfer.

These offer a characteristic potential for horizontal dissemination.

Closer home a study done in Aga Khan University in Karachi, revealed that 94% of their isolates (n=104) were positive for bla$_{\text{NDM-1}}$ gene. *Klebsiella pneumoniae* was most frequent isolate followed by E.coli. mortality among patients with bacteremic illness was approximately 57%.(112)

It is these facts and figures that make the development of treatment guidelines imperative in CRE bacteremia.

ANTIBIOTIC THERAPY(7)

There is a lacuna in clinical data on the therapy of CRE BSI, hence treatment choice is often controversial. Results from RCTs, observational studies and case reports on KPC or VIM producing strains are inconsistent, due to differences in patient populations, causative bacteria and severity of illness. Combination of two or more drugs, to which the causative organism is susceptible or resistant have been used, with variations in doing regimens and treatment duration adds to the complexity of analysis.

Treatment options include polymixins, some aminoglycosides and tigecycline which generally retain in vitro activity against CRE.

Other options include high dose prolonged infusions of carbapenem therapy as a part of the combination regimen, when the carbapenem MIC <=4mg/L.

Polymixin:

Polymixins in use are of two types, Polymixin E (colistimethate) and Polymixin B. There are cyclic peptides that differ by 1 amino acid; they possess targeted Gram negative activity. Through an electrostatic interaction between the cationic polypeptide antimicrobial and the anionic lipopolysaccharide of the outer membrane of the bacteria, there is a resultant leakage of cellular contents and bacterial cell lysis. (113)

Tigecycline:

It is a glycycline which is bacteriostatic and binds to the 30S ribisomal subunit and therby inhibits protein synthesis. The FDA has approved it for the treatment of skin infections and complicated abdominal infections and Community acquired pneumonia.

Its plasma concentrations however are relatively low and hence are often deemed to be to be inadequate to treat blood stream infections.(114)

Fosfomycin:

Is a phosphonic acid derivative, which is bactericidal against broad spectrum Gram positive and Gram negative organisms.

Pyruvul transferase is a bacterial enzymes that is inactivated by fosfomycin, causing inhibition of bacterial cell wall synthesis. Fosfomycin has good dstribution into kidneys, bladder wall, prostate, lung, soft tissue, CSF and bone(115).

Aminoglycosides:

They inhibt protein synthesis by binding to the 30S subunit of the ribosome. They exhibit concentration dependant activity against gram negative bacteria and have a prolonged post antibiotic affect.(116)

TREATMENT AND TREATMENT OUTCOMES

Monotherapy:

Colsitin has become the foundation against which treatment of CRE rests. Howver monotherpay With Colistin has been associated with exponentially high mortality rate exceeding 50%.(117)

Monotherapy with Tigecycline has also come into question, due in part to the bacteristatic effect and the inadequate antibiotic concentrations in the serum.

Fosfomycin, has been studied sparsely and possibly has a higher risk of emerging resistance during therapy(9).

Combination therapy:

Multiple in vitro studies have demonstrated that there is increased activity against CRE when antibiotics are given in cobination. Synergistic effects have been observed for double and also triple combinations that could include aminoglycosiders, aztreonam, carbapenem, colistin, rifampicin, tigecycline or fosfomycin.

Colistin is often used as a part of the combination therapy as it acts as a detergent to increase the permeability of other antibiotics through the outer membrane of the bacteria(118).

Clinical observational studies have demonstrated that combination therapy is superior to monotherapy when treating severe infectons due to CRE.

Combinations that are frequently used include, colistin/tigecycline. Colistin/carbapenema, carbaenem/aminoglycoside and colistin/aminoglycoside.

Fosfomycin can be used in strains that show resistance to colistin.(119)

Patients with BSI with CRE are known to be associated with high mortality, than patients with bacteremia due to susceptible organisms. BSI has also been known to have worse outcomes when compared to infections at other sites. 14 day and in-hospital, all cause mortality, of patients with CRKP BSI was deemed to be 42% and 58% respectively in a case series of 60 patients. Risk factores for mortlaity included increased markers of chronic or acute morbidity , such as Pitts bacteremia score and APACHE II(121) .

Optimal therapy still remains a poorly answered question as most treatment decisions are made on observational studies alone.

A recent randomised control trial looked at treatment outcome after comapring colistin monotherapy to combiantion therapy of Colistin + Carbapenem. The primary outcome was all cause mortality at 14 days and secodnary outcome looked at mortality at 24 days. There was no significant difference in outcomes, both at 14 and 24 days between the two groups (120).

Other recent evidence suggets that among CRE BSI, a scoring system for low and high risk can predict mortality, INCREMENT CPE score. From Januray 2004 to December 2013, 480 patients with CRE BSI were recruited for this study. *Klebsiella pneumoniae* was the most frequent organism. Appropriate therapy, which was defined as receipt of at least one antimicrobial with in vitro acivity agaisnt the isloate in queation was associated with lower mortality. Among paitents with a low mortality score (0-7) there was no significant difference in outcome between groups that received monotherpay

and combination therapy. A significant reduction in mortality was ascertained in the high mortality score (8-15), in patients that received combination therapy.(12)

This thesis wishes to address the following questions, and in the course of doing so, shed some light on appropriate antibiotic therapy for this threat to the healthcare system.

1. Prevalence of CRE bacteremia in a tertiary hospital in South India
2. Outcome (mortality) among patients with CRE BSI
3. Factors associated with mortality among patients with CRE BSI (exposure variables: demographic variables, primary source of bacteremia, severity of illness, carbapenem MIC, types of carbapenemases, appropriateness of empiric antibiotic treatment).

RESULTS

This prospective cohort study was done from May 2017 to August 2018.

200 patients with blood stream infection with Carbapenem Resistant Enterobactericeae were initially sought for inclusion in this thesis. After application of the exclusion criteria 163 patients were recruited.

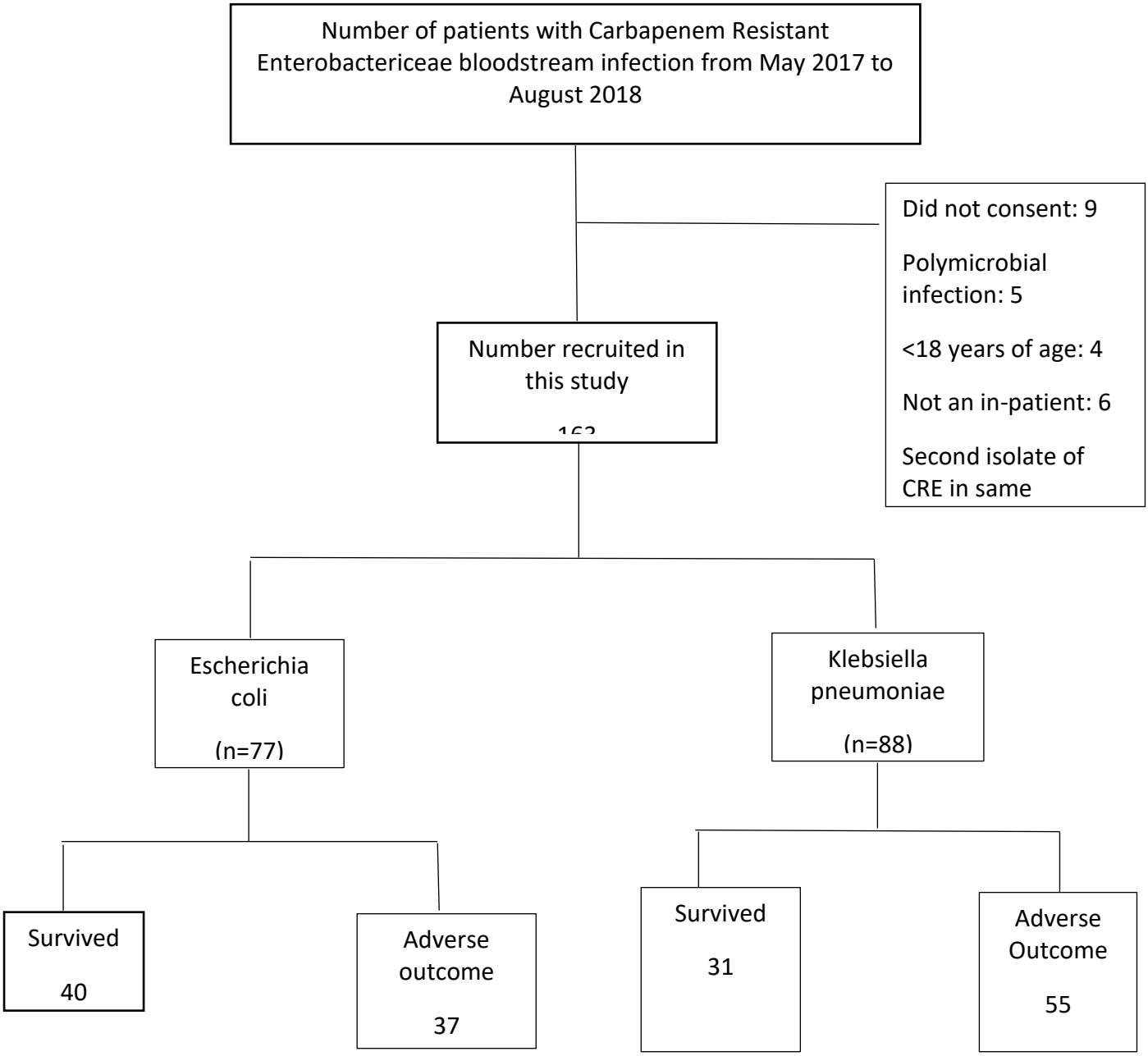


Figure 1: Strobe Diagram

PATIENT CHARACTERISTICS

163 patients were included in this study after obtaining written informed consent.

Of the 163 patients recruited in the study, 60% (n=98) were male and 40 %(n=65) were female.

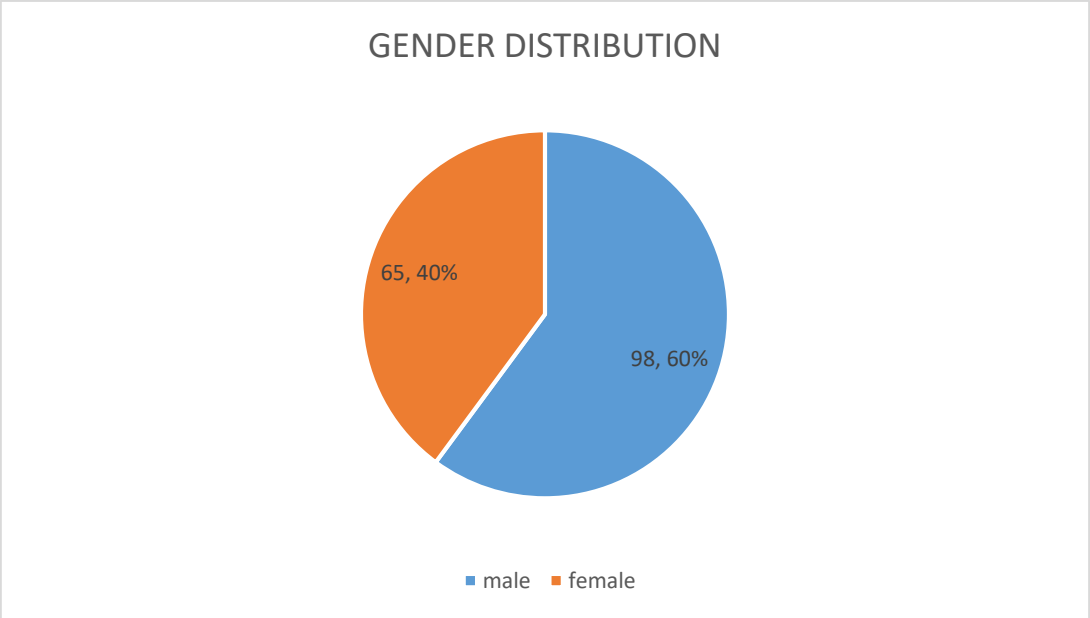


Chart 1: Gender distribution. N=163

The mean age of patients recruited in this study was 47.56 ± 17.48 years.

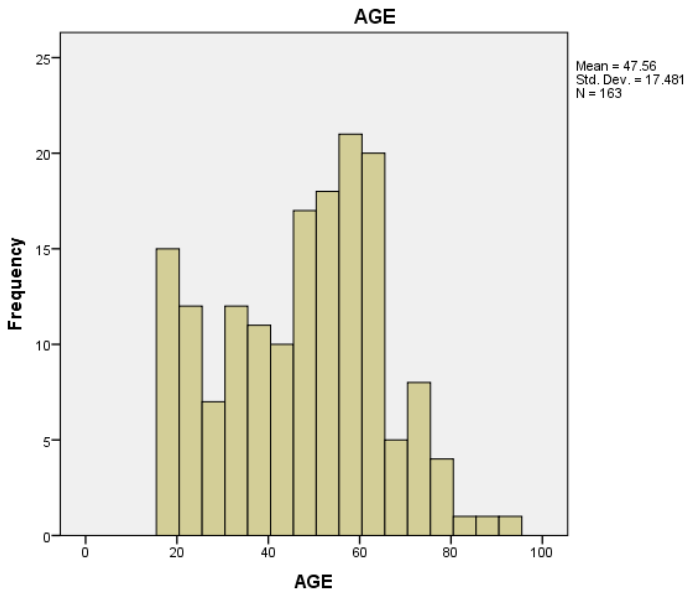


Chart 2: Age Distribution n=163 (x axis: age; y axis: frequency in numbers)

A majority (64%) of the participants were categorised as unemployed, which included students, housewives and retired personnel.

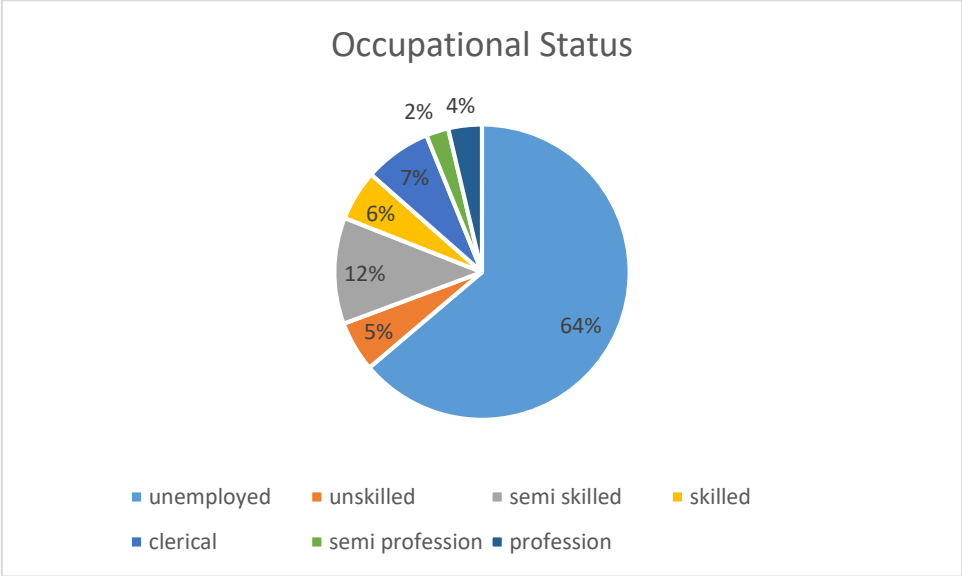


Chart 3: Distribution of occupational status n=163

29.4% (n=48) of the patients had systemic hypertension, and 30.7% (n=50) had diabetes mellitus. 6 patients tested positive for HIV, Hepatitis B and Hepatitis C cumulatively (n=1, n=3, n=6, respectively). 28.8% (n=47) patients had an underlying malignancy, of which 30 were haematological and 17 were non haematological.

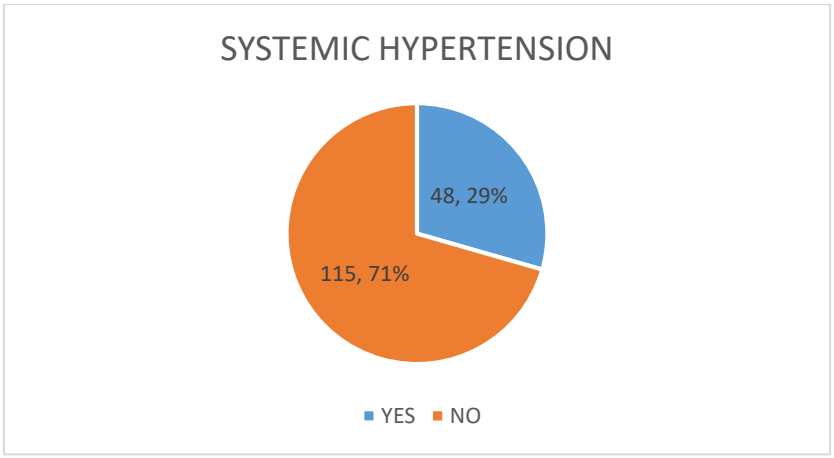


Chart 4: Distribution of Systemic Hypertension, n=163

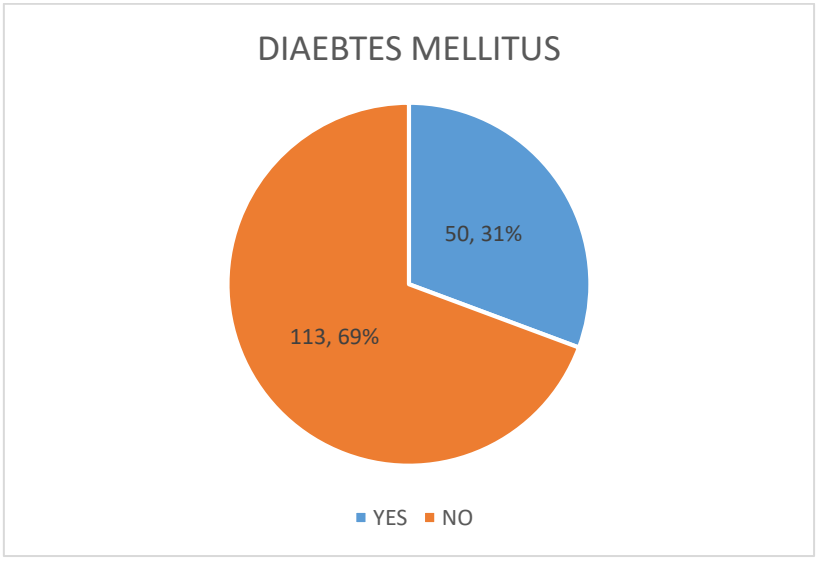


Chart 5: Distribution of Diabetes Mellitus, n=163

Table 1: Demographic Characteristics, n=163

Characteristic		Number(%) n=163
Gender	**Male**	98 (60.1)
	Female	65 (39.9)
Mean Age(years)		47.56 ± 17.58
Systemic Hypertension		48 (29.4)
Diabetes Mellitus		50 (30.7)
Malignancy		47 (28.8)
Haematological		30 (18.8)
Non-Haematological		17 (10.4)
HIV Infection		1 (0.6)
Hepatitis B Infection		3 (1.8)
Hepatitis C Infection		2 (1.2)

CLINICAL CHARACTERISTICS

Of the patients who had Carbapenem-resistant isolates of *Klebsiella spp*. or *Escherichia coli*, 109 (66.9%) has history of previous hospitalisation. 162 of these were febrile on day 1 (day of blood culture being taken).

On the day of taking the blood culture that grew the isolate of interest, 125 (76.7%) were hypotensive (systolic blood pressure <90 mm Hg) and 84 (51.5%) had an acute kidney injury.

63 (38.7%) needed mechanical ventilation, and 54 (33.1%) suffered a cardiac arrest.

In order to objectively evaluate the severity of their illness APACHE II score was calculated at the time of recruitment, and the mean APCHE II score was 24.90 ± 10.86.

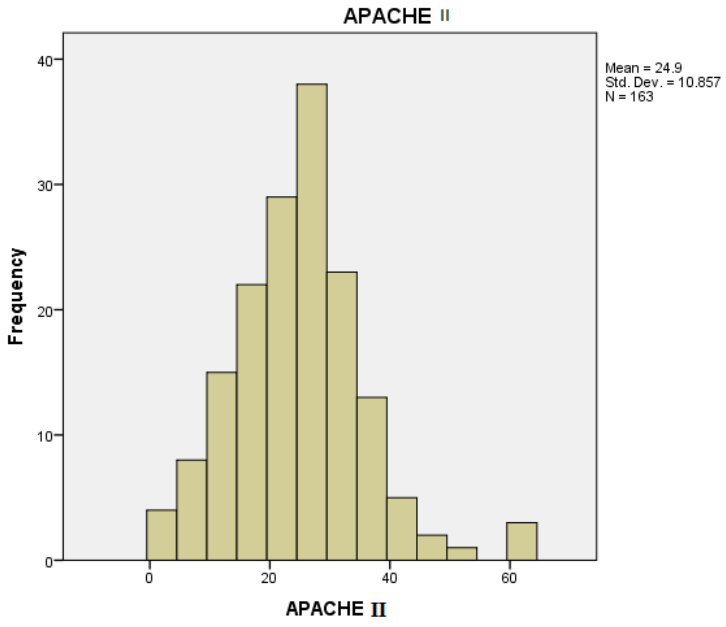


Chart 6: Distribution of APACHE II score in the cohort (x axis: APACHE II score, y axis: frequency in numbers)

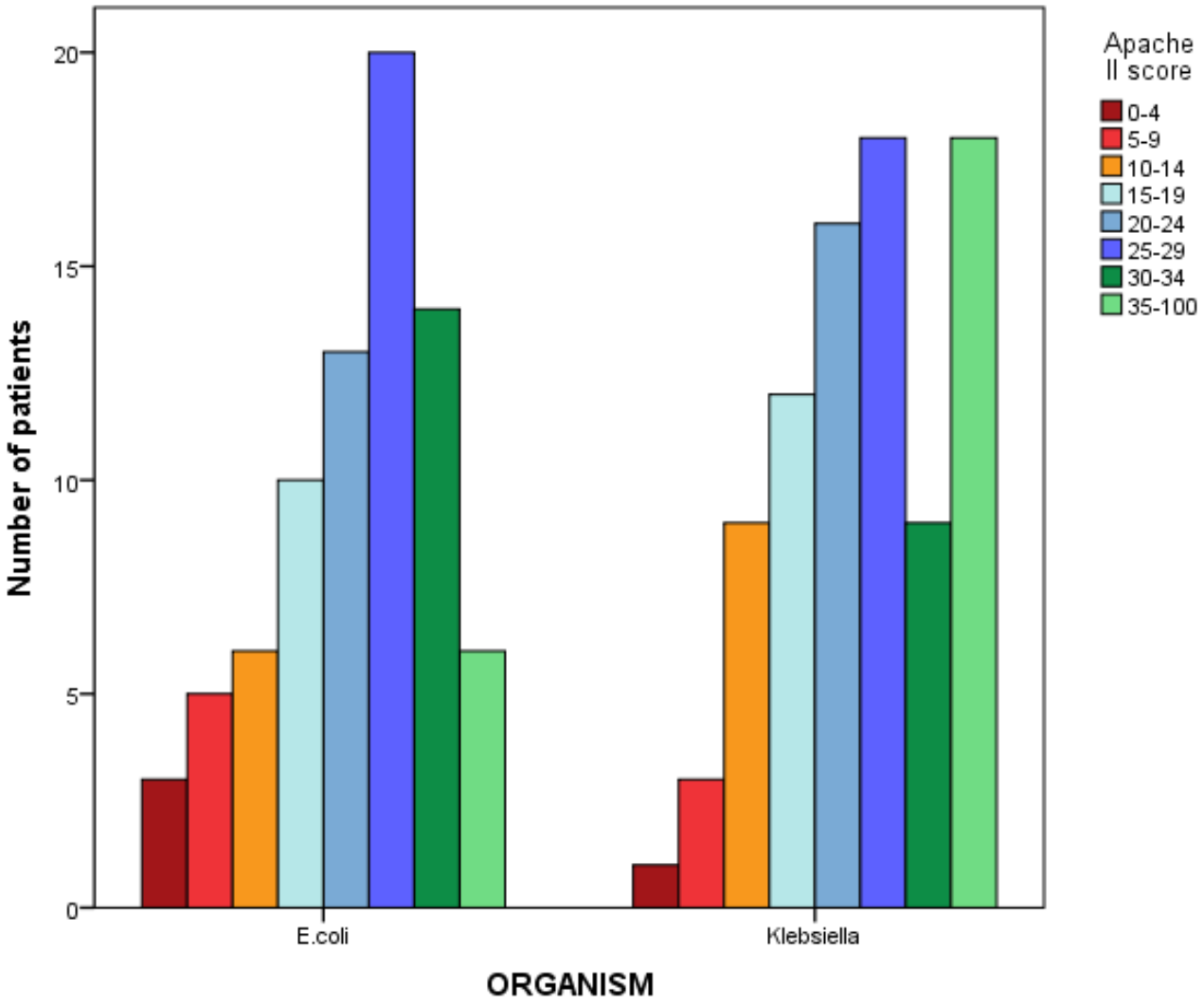


Chart 7: Distribution of APACHE II score stratified based on organism grown (x axis: APACHE II scores, y axis: frequency in numbers)

Pitt’s Bacteremia Score was also calculated with a mean value of 8 ± 4.6.

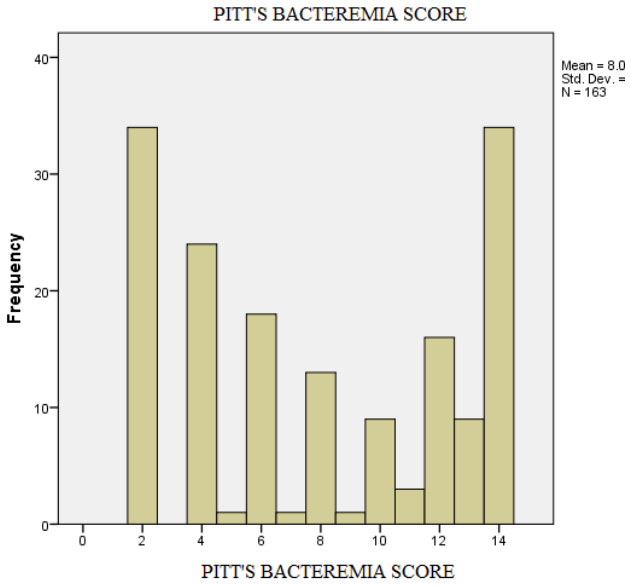


Chart 8: Distribution of Pitt’s Bacteremia Score in the cohort, n=163 (x axis: Pitt’s Bacteremia score, y axis: frequency in numbers)

Patients had a mean oral temperature of 102.1 ± 1.766 °F, with a mean MAP of 66 ± 13.89 mm Hg.

Mean GCS (Glasgow Coma Scale) was 11.2± 3.60.

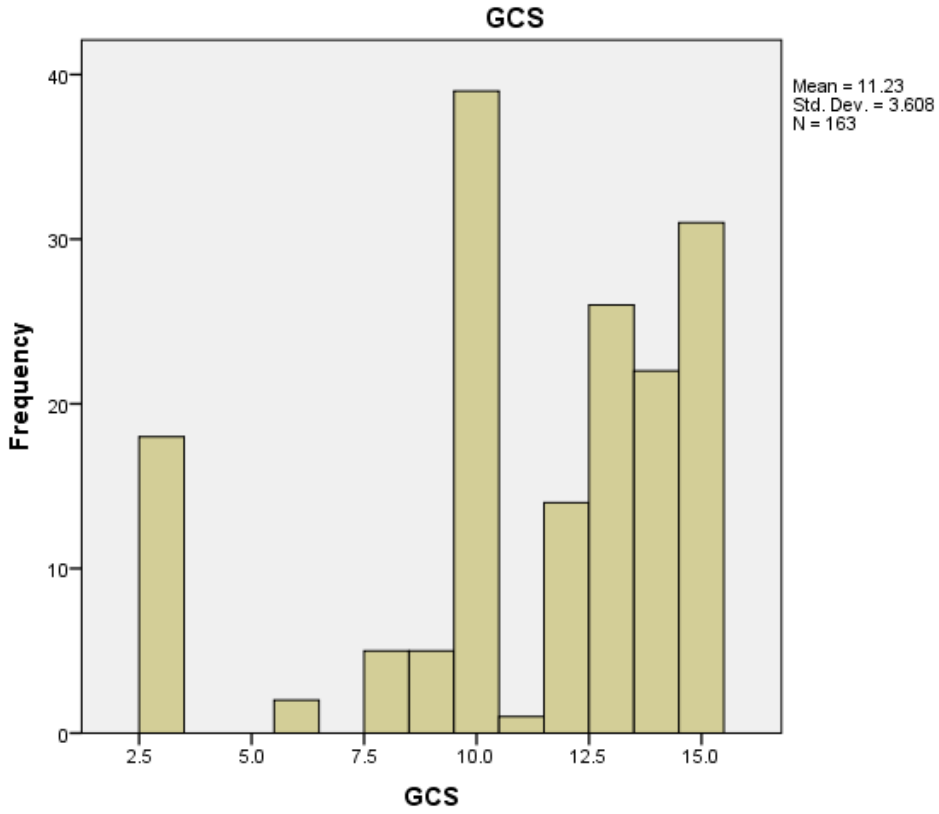


Chart 9: Distribution of GCS in the cohort, n=163 (x axis: GCS, y axis: frequency in numbers)

Table 2: Clinical Characteristics (n=163)

Characteristic	Number (%)	Median	IQR (25^{th} centile, 75^{th} centile)
Previous Hospitalisation	109 (66.9)		
Hypotension Systolic Blood Pressure <90mmHg	125 (76.7)		
Mechanical Ventilation	63 (38.7)		
Cardiac Arrest	54 (33.1)		
Mental Status			
Alert	21 (12.9)		
Disoriented	37 (22.7)		
Stuporous	61 (31.4)		
Comatose	44 (27)		
Acute Kidney Injury	84 (51.5)		

Temperature(°F)	102.12 ± 1.766	103	101,103
Mean Arterial Pressure (mmHg)	66 ± 13.89	65	60,73
APACHE II	24.90	26	18,31
Pitt's Bacteremia Score	8 ± 4.6	8.01	4,13

LABORATORY CHARACTERISTICS

The mean total counts for patients in this study were 11,694 ± 11008 cells/mm, which represents the wide range of leukopenia and leukocytosis that can be seen in sepsis.

Mean values for creatinine were 2.09 ± 2.2 mg/dl, with haematocrit being 25.16 ± 5.56 on an average.

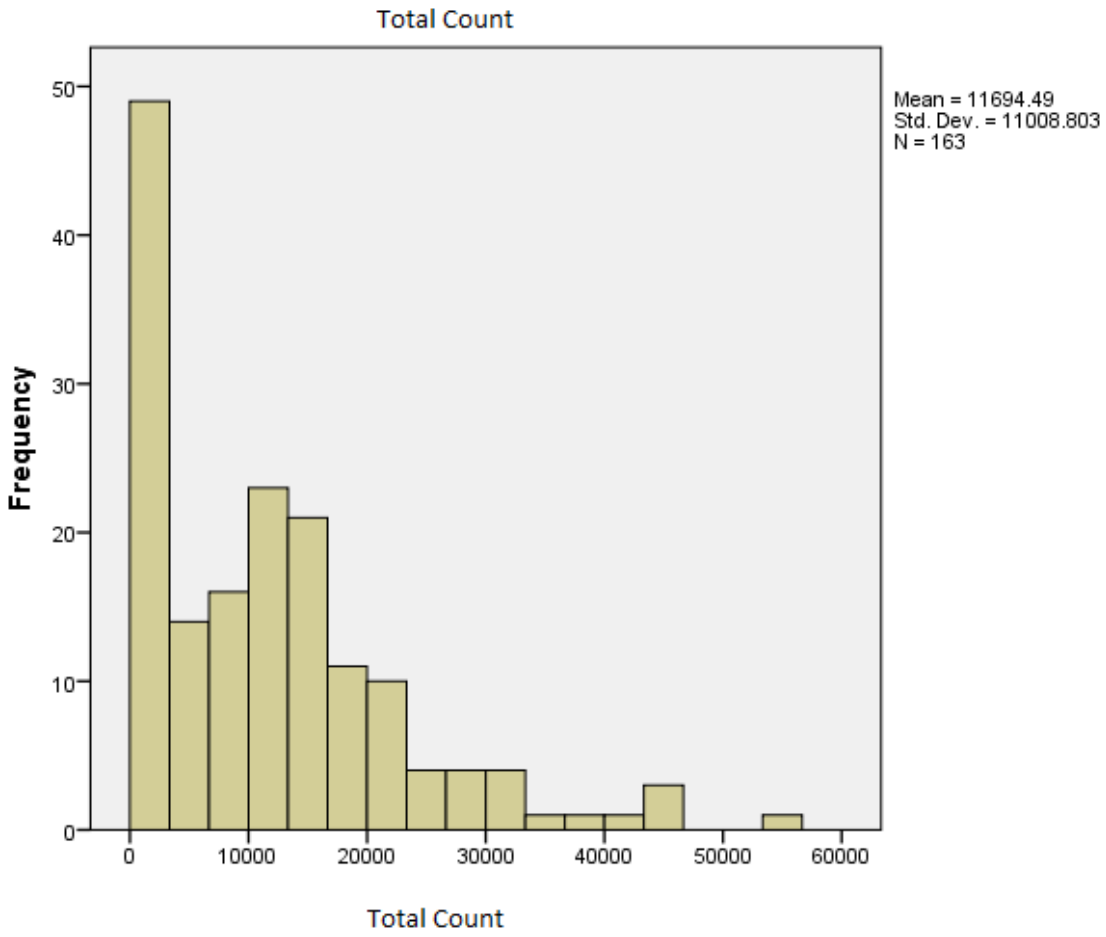


Chart 10: Distribution of total WBC count the cohort, n=163 (x axis: total WBC count in cells/ccmm; y axis: frequency in numbers)

Of the 163 Carbapenem-resistant Enterobactericeae isolates, 77 (47.2%) were *Escherichia coli* and 86 (52.8%) were *Klebsiella* spp.

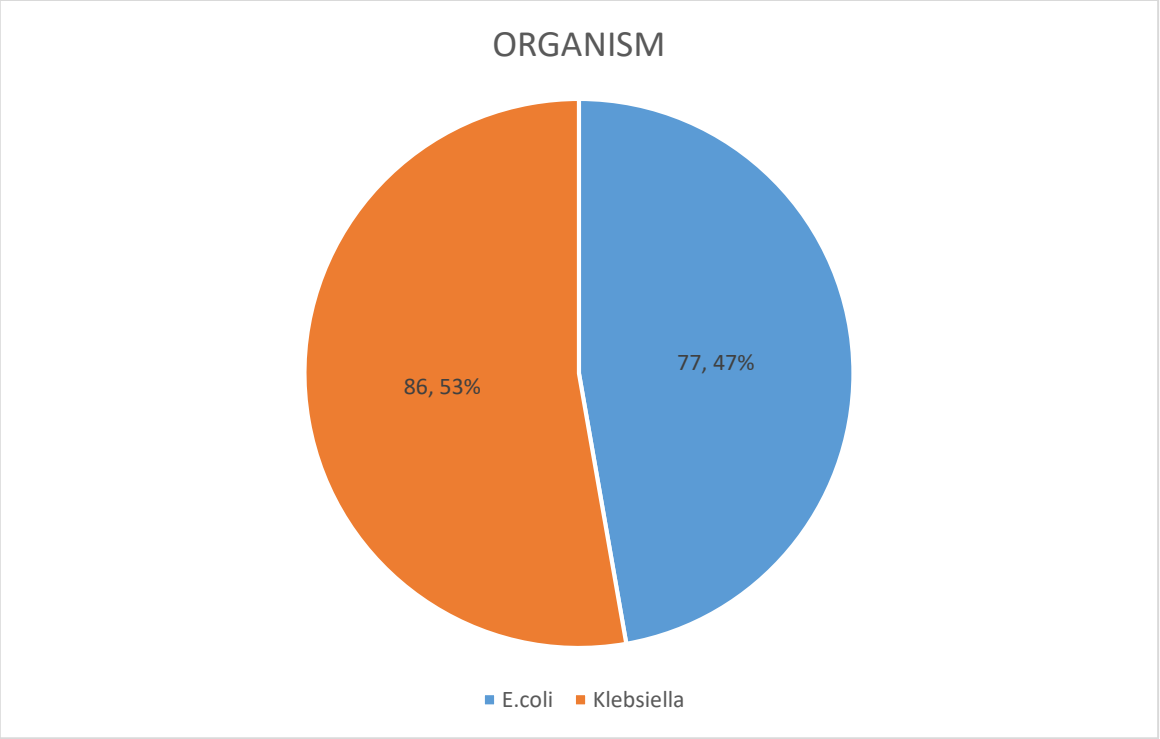


Chart 11: Distribution of CRE organism in the cohort, n=163

Primary source of infection: The source of bacteremia was determined to be primary BSI, which included 12 CLABSI, in 104 (63.8%), pneumonia (lung) in 16 (9.8%), urinary tract in 21 (12.9%), gastrointestinal tract in 10 (6.1%) and soft tissue infections in 22 (7.4%).

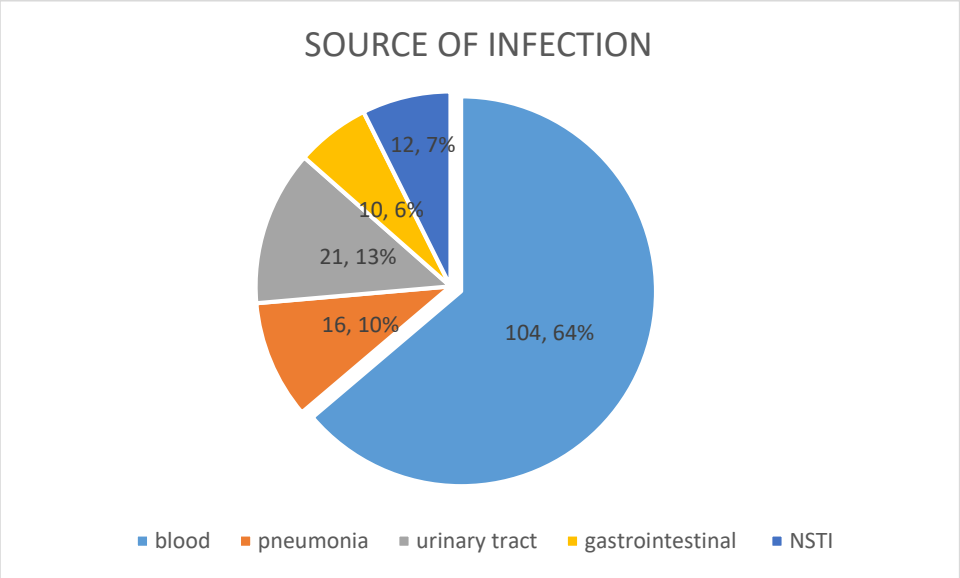


Chart 12: Distribution of primary source of infection, n=163

15 (9.2%) had features of other infections during the course of their hospital admission, this was predominantly seen in patients with haematological malignancies, with profound neutropenia, who had developed concomitant fungal infections.

Of the empiric antibiotics used, Cefoperazone-Sulbactam was used in 31 (19.01%), Piperacillin-Tazobactam in 19 (11.7%) and Meropenem in 113 (69.3%).

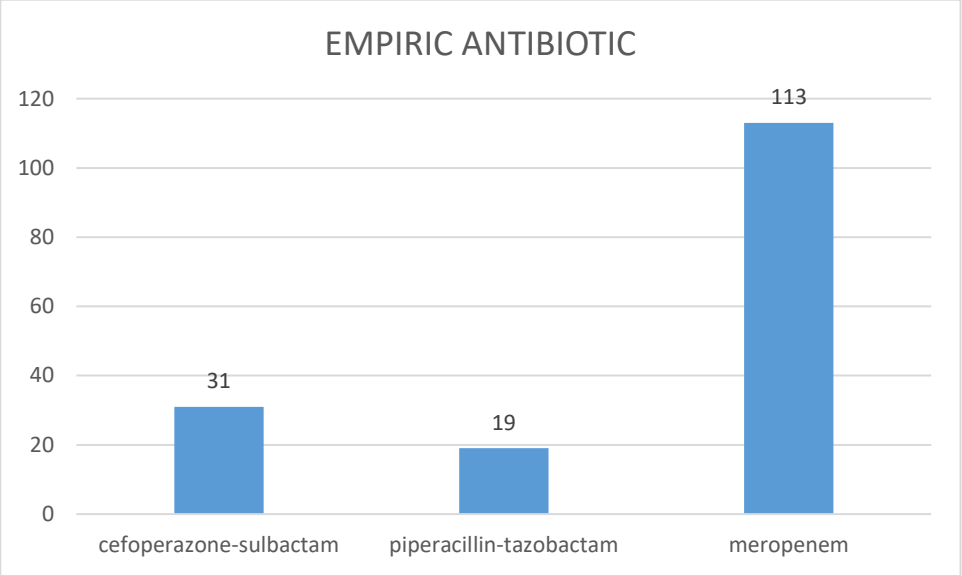


Chart 13: Empiric antibiotic use in the cohort, n=163 (x axis: empiric antibiotics used; y axis: frequency in numbers)

Table 3: Laboratory Parameters

Laboratory Parameters	**Number (%)**
Mean Total WBC count (cells/ccmm)	11694 ± 11008
Mean Serum Creatinine (mg/dl)	2.6 ± 2.2
Mean Haemoglobin (G/dl)	25.16 ± 5.56
CRE Organism	
E. coli	77 (47.2)
***Klebsiella* spp**	86 (52.8)
Source of Bacteremia	
Primary Blood Stream	104 (63.8)
Pneumonia (lung)	16 (9.8)
Urinary Tract Infection	21 (12.9)
Gastrointestinal	10 (6.1)
SSTI	12 (7.4)
Other Infections	15 (9.2)

Empiric Antibiotics	
Cefoperazone-Sulbactam	31 (19)
Piperacillin-Tazobactam	19 (11.7)
Meropenem	113 (69.3)

OUTCOME

Cumulative all-cause mortality at day 14 (from the date of positive blood culture was obtained) was the primary outcome of interest for the purpose of this study. Discharge against medical advice was also considered an adverse outcome. In this regard, of the 163 patients, 73 (44.8%) died during the 14 day follow up period of this thesis, while 19 (11.7%) were discharged against medical advice. Revised adverse outcome is 92 (56.4%).

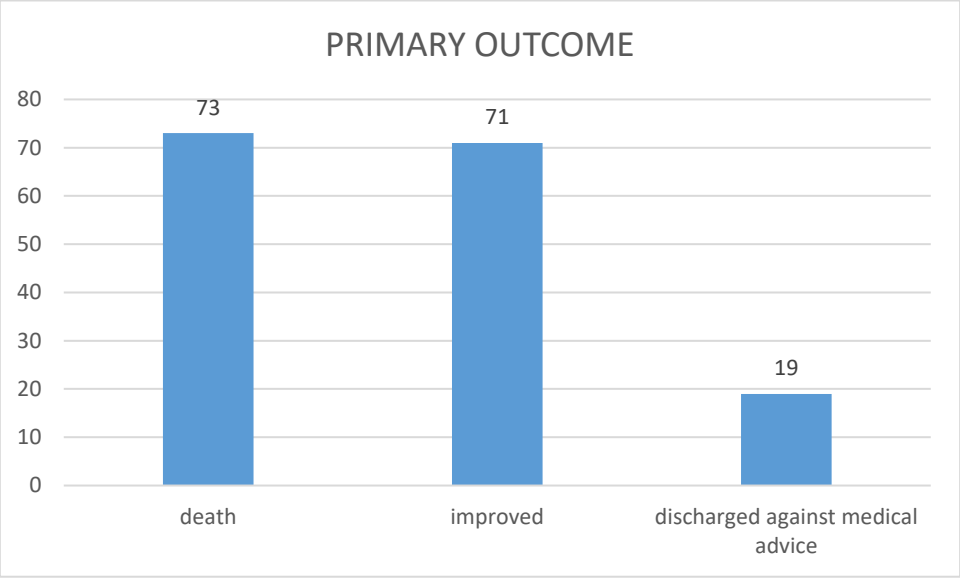


Chart 14: Primary outcome, n=163 (x axis: outcome of interest, y axis frequency of outcome in numbers)

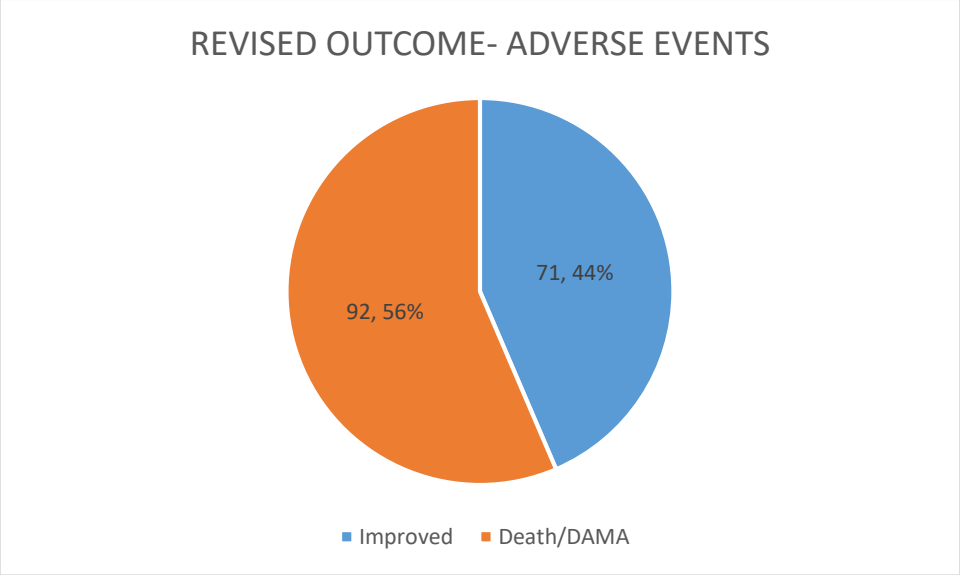


Chart 15: Distribution of revised outcome (Death+DAMA), n=163

Among the two isolates of interest, patients with *Escherichia coli* in the blood stream 37 of 77 had an adverse outcome (48.1%) and 55 of 86 (64%) patients with *Klebsiella* spp had an adverse outcome, in univariate analysis, this was found to be statistically significant with an OR 0.52 (95% CI 0.27-0.9760) p = 0.042 .

Overall survival probability in this cohort was 79% at 3 days, 69% at 7 days and 44% at 14 days. Mean estimate for survival is 10.15 days with standard error of 0.04 (95% CI 9.37-10.93). This is represented in the following Kaplan Meier graph.

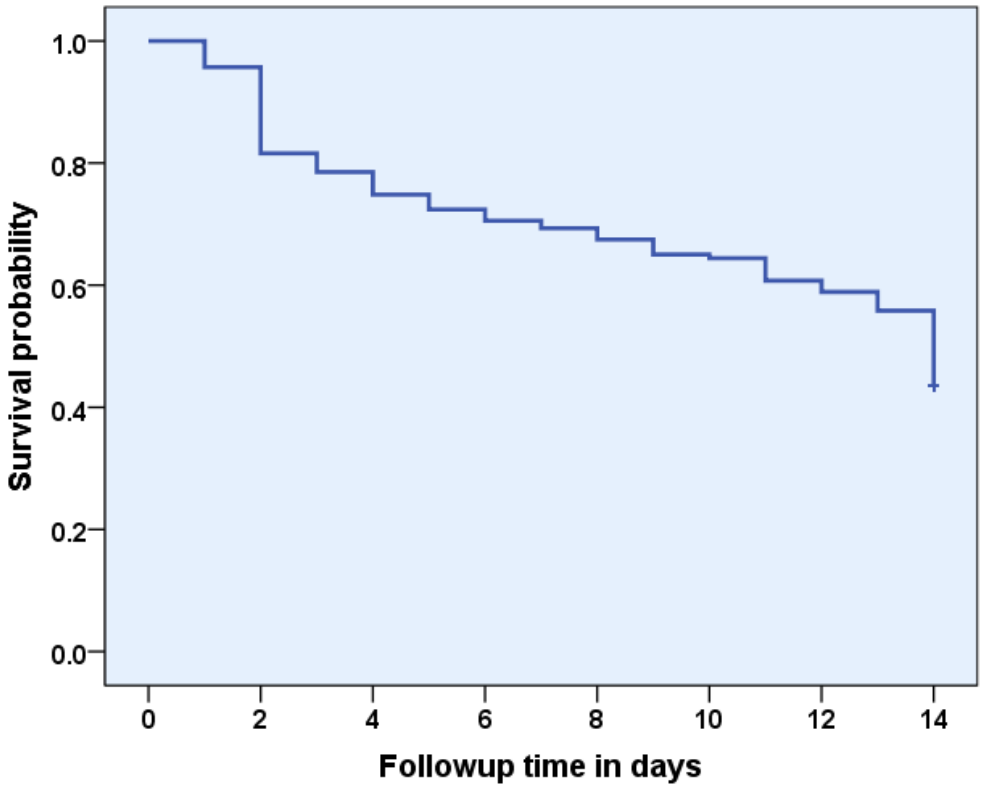


Chart 16: Survival Analysis, in percentage on the y axis and follow up time on the x axis. (Mean estimate for survival is 10.15 days with standard error of 0.04 (95% CI 9.37-10.93) while median was 14).

Mean survival time for *E.coli* was 10.78 with standard error of 0.55 (95% CI of 9.69-11.86), while for *Klebsiella* spp it was 9.53 with standard error of 0.573 (95% CI 9.37-10.93). Survival analysis revealed Hazard ratio of 1.48 (95%CI 0.97 -2.24) p=0.068 with a greater risk of death in patients with *Klebsiella* spp than with *Escherichia coli.*

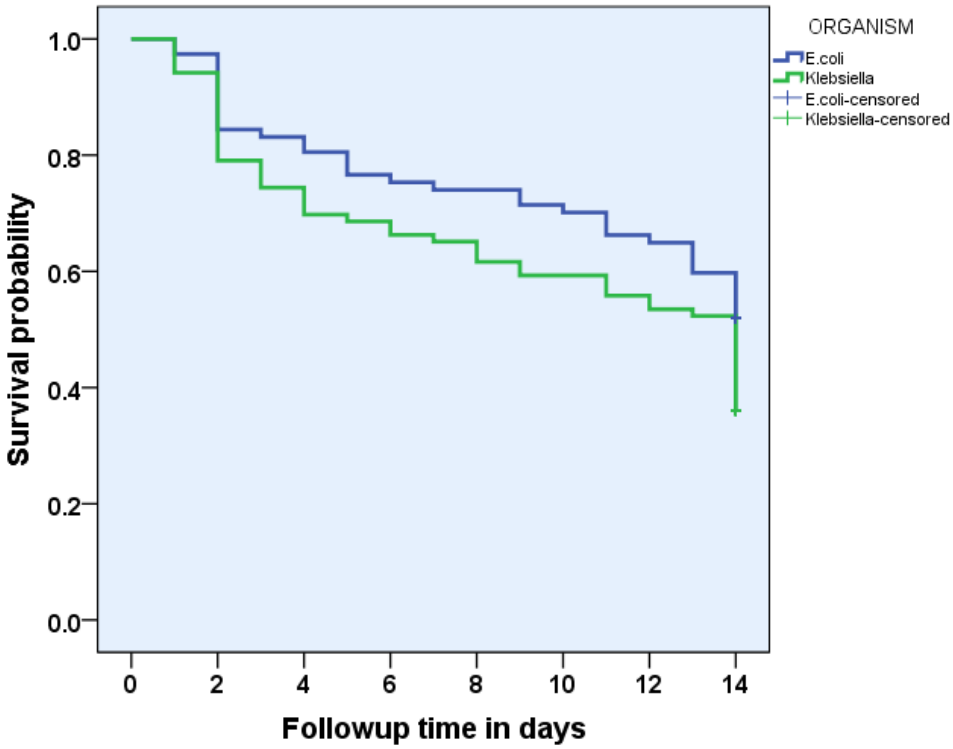


Chart 17: Survival analysis categorised by organism, y axis: survival probability in percentages, x axis: survival in days. (Estimates for survival in Mean: 10.779 for *E.coli*, 9.593 for *Klebsiella* spp)

Predictors for an adverse outcome considered were, comorbid illnesses like diabetes mellitus, systemic hypertension, presence of an underlying malignancy and Charlson Comorbidity Index, severity of illness as measured by validated scores like APACHE II, Pitts Bacteremia score and INCREMENT CPE score.

Table 4: 14 day treatment outcomes

Treatment Outcome	**Number (%)**
Death	73 (44.8)
Discharged Against Medical Advice (DAMA)	19 (11.7)
Improved	71 (43.6)
Adverse Outcome (Death + DAMA)	92 (56.4)

Table 5: Treatment outcomes stratified according to organism

Organism	**Outcome**	**Number (%)**
Escherichia coli	Survived	40 (48.1)
	Adverse Outcome	37 (51.9)
***Klebsiella* spp**	Survived	31 (36)
	Adverse Outcome	55 (64)

Table 6: Univariate and multivariate Cox regression analysis for adverse outcomes of patients with Carbapenem-resistant Enterobactericeae bloodstream infection. (n=163)

Characteristic	**Univariate Analysis**		**Multivariate Analysis**	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Age (years)				
<45*				
45-70	1.2 (0.63-2.35)	0.556		
>70	0.75 (0.23-2.23)	0.576		
Male gender	0.75 (0.416-1.45)	0.456		
Escherichia coli*				
***Klebsiella* spp.**	0.52 (0.27-0.9760)	0.042		
Source				
Primary BSI	2.20 (1.15-4.26)	0.017	2.44 (1.05-5.921)	.049
Charlson Comorbidity Index	0.827 (.393-1.738)	0.616		
Mechanical Ventilation	12.4 (4.1-37.2)	<0.001	22.5 (8.26-61)	<0.001

Septic Shock	7.63 (3.23-18.24)	<0.001		
Mental Status: not alert	2.92 (1.34-7.84)	0.027	2.4 (1.05-5.92)	0.049
Malignancy	0.831 (0.42-1.64)	0.594		
CPE increment Score (high mortality score 8-15)	10.23 (4.75-22)	<0.001	4.29 (1.13-14)	0.017
Pitt's Bacteremia Score (>4)	9.33 (3.59-24)	<0.001	4.42 (0.8-23)	0.079

* Reference index

Age and gender were not found to be significant predictors of mortality. Significant difference in mortality was seen among the isolates, with 55 of 86 (64%) patients with *Klebsiella spp*. in blood having an adverse outcome (OR 0.52, 95% CI 0.27-0.976, p=0.042) compared to *E.coli* bacteremia.

In univariate analysis we found that, primary blood stream infections, which included catheter related blood stream infections were also associated with a significant increase in mortality when compared to other sources of bacteremia (OR 2.44, 95% CI 1.5-5.921,p =0.049). Other variables that were significantly associated with mortality in multivariate analysis were, hypotension at presentation (OR 7.63, 95% CI 3.23-18.24, p=<.001), mechanical ventilation (OR 12.4, 95% CI 4.1-37.2,p =<0.01), altered mental status (OR 2.92, 95%CI 1.34-7.84, p=0.027), Pitt's Bacteremia Score of >4 (OR 9.33,

95% CI 3.59-24, p=<0.001) and INCREMENT CPE score between 8-15 (OR 10.23, 95%CI 4.75-14, p=<0.001). There was no significance in mortality based on Charlson Comorbidity Index presence of underlying malignancy or the Urinary Tract as primary source on infection.

During this study the antibiotics prescribed were left to the discretion of the treating physician.

All patients received an appropriate targeted therapy, which by the definition used was at least 1 antimicrobial with in-vitro sensitivity to the isolate of interest. Monotherapy was used in only 7 out of 163 patients (4.29%). Combination therapy used comprised of Colistin, Tigecycline and Teicoplanin containing regimens.

The combination of Meropenem with Colistin, 99 (60.7%) was used maximally in the Medicine Wards and Medical ICU in out institution , while a trend towards preferring Tigecycline with Colistin +/- Meropenem, 25(15.3%) was seen among the surgical wards and the Surgical ICU.

There was no significant difference observed in mortality between combination therapy regimens, however combination therapy had better outcomes than monotherapy.

Antibiotic sensitivity was not available for all isolates. Much of the unavailable data is from patients who succumbed to their illness prior to attainment of the sensitivity pattern. Data on amikacin, colistin, tigecycline, fosfomycin and minocycline have been analysed. These are the antimicrobials that are available to treat CRE infections.

Data on susceptibility is available on, 130/163 for amikacin, 97/163 for colistin, 1/163 minocycline, 18/163 for fosfomycin and 82/163 for tigecycline.

Out of the data available, valid percentages of susceptibility extrapolated to 163 is as follows:

19% susceptible to amikacin,

83% susceptible to colistin,

67% susceptible to fosfomycin

77% susceptible to tigecycline.

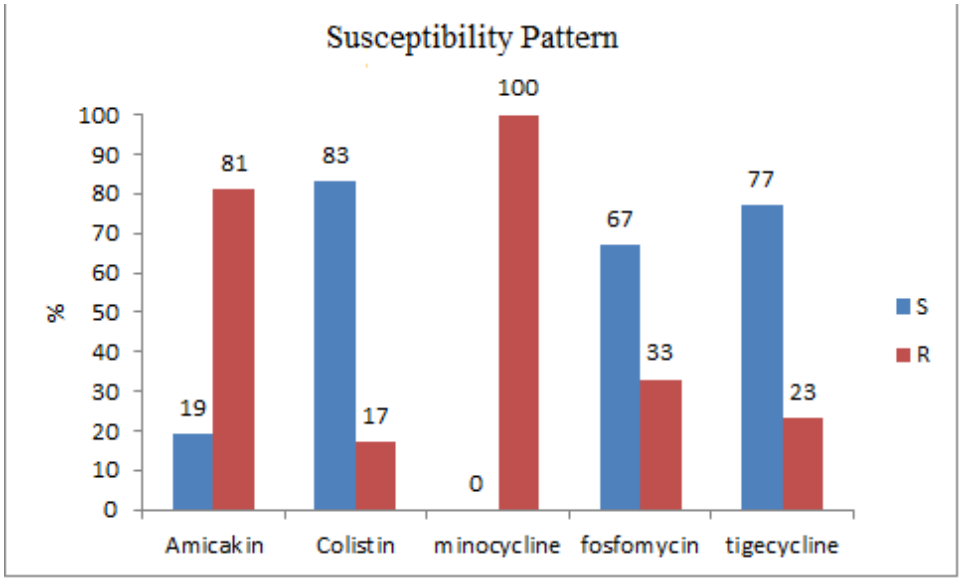


Chart 18: Distribution of antimicrobial susceptibility, x axis: antimicrobials, y axis: validated susceptibility in percentages (S: susceptible; R: resistant)

Table 7: Mortality of patients receiving appropriate therapy according to antimicrobials administered and the INCREMENT CPE mortality score strata.

Antimicrobial	**All Patients N=163 (%)**	**Low Mortality Score(0-7)**	**High Mortality Score (8-15)**	**Adverse Outcome (%)**
Colistin	1 (0.6)	1(100)	0	1(100)
Tigecycline	1 (0.6)	1 (100)	0	1 (100)
Teicoplanin	5 (3)	1 (20)	4 (80)	5 (100)
Colistin + Meropenem	99 (60.7)	40 (40.4)	59 (59.6)	49 (49.5)
Colistin + Rifampicin	6 (3.7)	3 (50)	3 (50)	3 (50)
Tigecycline + Meropenem	4 (2.5)	0	4 (100)	2 (50)
Tigecycline + Colistin	7 (4.3)	2 (28.6)	5 (71.4)	3 (42.9)
Colistin + Teicoplanin	12 (17.2)	2 (16.7)	10 (83.3)	9(75)

Tigecycline + Meropenem + Colistin	28 (17.26)	5 (17.9)	23 (82.1)	20 (71.4)

DISCUSSION

This study was designed as a prospective cohort, to assess treatment outcomes in patients with Carbapenem Resistant Enterobactericeae blood stream infections which is an ever increasing threat in medical practice today.

Over the period of May 2017 to August 2018, 200 patients were documented to have CRE bacteremia, of which 163 were included in this study. These numbers corroborate the increasing prevalence of CRE bacteremia, a study done in the Aga Khan University had 104 isolates (112) while a large study done across 13 centres in Europe has 77 CRE isolates . A large study done over 10 centres from January 2004 to December 2013 had 480 isolates.

Among the 163 isolates, 86 (52.7%) were *Klebsiella spp* and 77 were *Escherichia coli.* Most other studies find a significantly larger percentage of *Klebsiella spp* when compared to *Escherichia coli.* This is included 86% preponderance in the INCREMENT trial(119) and 57% in the study from Aga Khan University(112).

Our primary objective was to look at treatment outcomes, where a 14 day all-cause mortality was the primary end point. Death and discharges against medical advice were considered as a composite adverse outcome. 92 of 163 (56.4%) had an adverse outcome in our study, which is comparable to all other studies done on CRE bacteremia.

Survival analysis revealed Hazard ratio of 1.48 (95%CI 0.97 -2.24) p=0.068 with a greater risk of death in patients with *Klebsiella* spp than with *Escherichia coli.*

Predictors of mortality that were looked at included a range of features, from demographic profile, to comorbid illnesses, severity of illness , primary source of infection and the organism cultured.

Demographic characteristics

60% of the participants in this study were male with a majority of the participants being categorised as unemployed.

Mean age was 47.56 with 85(51.5%) of the participants within the 45-70 age group. A similar population distribution has been seen in most other studies on CRE bacteremia.

Both sex and age were not significant predictors of mortality, this was not in corroboration with other studies where an increasing age was found to be associated with higher risk of mortality.

One reason for this difference could be the very small number of people above the age of 70 recruited in this study (15 out of 163).

Most of the women were housewives and the majority of the men were unemployed or retired personnel.

Clinical Characteristics

162 of the patients were febrile on day 1, deemed as the day the blood culture was drawn. Mean temperature ascertained during the course of this study was 102.12 degree Fahrenheit.

Majority of the patients were tachycardic and tachypnoeic, with the mean pulse rate being 110/min and mean respiratory rate was 29/min.

Hypotension was noted in 125 of 163 patients (76.6%), with a mean Mean Arterial Pressure being 66mmHg and was associated with a significant risk of adverse outcome (OR7.63, 95% CI 3.23-18, p=<0.001).

Patients who needed mechanical ventilation, during the course of their admission, were also found to have significantly higher risk for adverse outcomes (OR12.4, 95%CI 4.1-37.2, p=<0.001). Similar observations were made in INCREMENT trial and the study from the Aga Khan University.

Other clinical feature that had significant correlation with an adverse outcome was an altered mental status (OR 2.92, 85% CI 1.34-7.84, p=0.027).

Among the comorbidities studied, 30.7 % had diabetes mellitus and 29.4% has systemic hypertension. 28.8% had an associated malignancy.

In order to subjectively evaluate the patient's condition at presentation, various validated scores were used, such as the APACHE II score, mean value calculated during this study was 24.90 which has a mortality of 40% associated with it.

Other index that was calculated was the Charlson Comorbidity Index, of which the mean value attained was 2.24 for *Escherichia coli* and 2.86 for *Klebsiella* spp which is comparable to other studies like the INCREMENT trial(119).

In terms of assessing the severity of illness, the Pitt's bacteremia score and Increment CPE score were calculated for all participants.

A Pitt's Bacteremia Score of more than 4 is suggestive of a severe infection, in our study the mean value was 8.01 which was much higher that the values that were attained in the INCREMENT trial. A Pitt's bacteremia score of more than 4 was also a significant predictor of mortality in this study (OR 9.33, 95% CI 3.59-24, p=<0.001).

The INCREMENT CPE score which was validated in the INCREMENT trial, has cut off values for low and high mortality scores. 0-7 is associated with low mortality and 8-15 is associated with high mortality, in this study the mean CPE score was 7.88 for patients with *Escherichia coli* isolates and 8.88 for *Klebsiella spp.* The CPE score was also a significant predictor of mortality (OR 1.23, 95% CI 4.75-22, p=<0.001).

Our study had a preponderance of primary blood stream infections, where another source could not be delineated, and 104 of 163 (63.8%). Other similar studies have shown a 47.1% (25 of 53) (115) and 35.7% (20 of 58) (120) primary bloodstream infections.

Antibiotic Regimens

During the course of this study, there was no input by the investigators on the choice of antibiotics. Treatment decisions were left to the discretion of the treating physicians.

Empiric Antibiotics that were used were Cefaperazone-Sulbactam, Piperacillin-Tazobactam and Carbapenem (Meropenem). 113 of 163 (69.3%) used Meropenem as the empiric antibiotic of choice.

Antibiotic sensitivity tests were reported within 48 hours and definitive therapy was initiated based on its report.

Susceptibility pattern that has been ascertained through this study suggests that up to 81% of our isolates are resistant to amikacin. Colistin has a susceptibility rate of 83% when extrapolated for the number of isolates we have information for, and tigecycline has a susceptibility rate of 77%.

Among the definitive antimicrobials used, monotherapy was used in a very small proportion of patients, 7 of 163 (4.2%) all of whom has an adverse outcome.

Among the combination therapies used, Colistin with Carbapenem, was used most frequently 99 of 163 (60.7%), with a mortality rate of 49.5%.

28 of 163 had triple antibiotic with Tigecycline + Meropenem + Colistin, with 71.4% mortality, reflecting that patients who were sicker from the onset required a much more aggressive antibiotic regimen.

CONCLUSIONS

This prospective cohort study, aimed to look at treatment outcomes of patient's with Carbapenem Resistant Enterobactericeae bloodstream infections. The overall 14 day all-cause mortality in patients with CRE BSI was 56.4%, being higher in with *Klebsiella spp* than with *Escherichia coli* infections. Primary blood stream infections place the patients at higher risk for an adverse outcome.

Other significant predictors of mortality included both clinical and indicial parameters.

Hypotension at presentation, requirement of mechanical ventilation and altered mental status were predictors of adverse outcomes. As were elevated INCREMENT CPE score (8-15, indicating high mortality score) and Pitts' Bacteremia score of more than 4.

Therapeutic options are limited, and among the available options combination therapy appears to be associated with better outcomes. Meropenem with Colistin is the most widely used combination of choice, especially in the Medical wars, while Tigecycline containing regimens are preferred in the surgical setting.

LIMITATIONS

1. Short term follow up of 14 days does not give information on long term outcomes
2. Carbapenem MIC were not available for most patients and hence correlation of low or high MIC with adverse outcomes could not be studied.
3. Type of Carbapenemases was not evaluated in this study, hence its effect on the outcome could not be ascertained.

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ANNEXURE

ANNEXURE 1: IRB APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

November 24, 2017

Dr. Nalini Sarah Newbigging,
PG Registrar,
Department of Medicine,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Treatment outcomes in patients with Carbapenem Resistant Enterobactericeaeo bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India.
Dr. Nalini Sarah Newbigging, Employment Number: 29569, PG Registrar, General Medicine, Dr. O.C. Abraham, Employment Number : 05638, Dr Alice Mathuram, Associate Professor , Dr Vignesh Kumar, Assistant Professor, Dr Ronald Carey, Associate professor, Dr Karthik G , Assistant Professor. Department of Medicine. Ms. Tunny Sebastian Lecturer Dept. of Biostatistics.

Ref: IRB Min. No. 10566 (OBSERVE) dated 08.03.2017

Dear Dr. Nalini Sarah Newbigging,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

SECRETARY (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr O C Abraham, Dept. of Medicine, CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Ref: IRB Min. No. 10566 (OBSERVE) dated 08.03.2017

Dear Dr. Nalini Sarah Newbigging,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Treatment outcomes in patients with Carbapenem Resistant Enterobactericeaeo bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India" on March 08th 2017.

The Committee reviewed the following documents:

1. IRB Application format
2. Consent forms and Case report form,
3. Cvs of Drs. Alice Mathur, Tunny Sebastian, O C Abraham, Ronald Carey, Nalini, Vignesh.
4. No. of documents 1 – 3..

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on March 08th 2017 in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Rekha Pai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal, Basic Medical Scientist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor,Endocrinology, CMC, Vellore	Internal, Clinician
Dr Sneha Varkki	MBBS, DCH, DNB	Professor, Paediatrics, CMC, Vellore	Internal, Clinician
Dr. Sathish Kumar	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician

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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Treatment outcomes in patients with Carbapenem Resistant Enterobactericeaeo bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 40,000/- INR (Rupees Forty thousand Only) will be granted for 24 months.

Yours sincerely,

Dr. BIJU GEORGE
MBBS, MD, DM,
SECRETARY (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

ANNEXURE 2: CONSENT FORM

Treatment outcomes in patients with Carbapenem Resistant Enterobactericeae bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India.

Subject ID: _____

Subject's Name: _____

Date of Birth (if available):

Age (in completed years): _____

(i) I confirm that I have read and understood the information sheet dated February 1st 2017 for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the study, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative

Date: _____/_____/_____

Witness: _____

Signatory's Name: _____ Signature:

ANNEXURE 3: PATIENT INFORMATION FORM

Treatment outcomes in patients with Carbapenem Resistant Enterobactericeae bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India.

Date: February 1st 2017

Gram negative bacilli like E.coli and Klebsiella are common pathogens that are encountered in hospital setting. However the over the past few decades there has been an increasing emergence of resistance to common antibiotics being used to treat these infections. After the emergence of ESBL and their subsequent treatment with carbapenems, there has now emerged resistance to carbapenems. This poses a novel threat to the treatment of these serious often life threatening infections. There it is imperative to study both treatment outcomes to be able to analyse appropriate antibiotic therapy for these infections. Any publications arising from the study will not have any patient identifiable data. You can opt out of the study if you wish to do so at any time.

By enrolling yourself into this study you subject yourself to no added tests or investigations. This study will not influence the treatment that you are currently receiving. Your treatment will not be altered in any form as a consequence of your participation in this study. You will also be required to answer some questions regarding your health status at the beginning of this study. All information provided by you will be kept confidential and your identity will not be revealed to a third party under any circumstances.

By participating in this study, you will go a long way in helping the health care community better understand the mechanisms of the illness so that diagnosis can be made early and correct treatment be instituted in time to prevent the many complications of the disease.

Thank you

Nalini Sarah Newbigging

ANNEXURE 4: CASE REPORT FORM

Treatment outcomes in patients with Carbapenem Resistant Enterobactericeae bacteremia and factors affecting mortality, a study done in a tertiary care hospital in South India.

1. Serial no: ☐☐☐

2. Name: _____

3. Hospital number: ☐☐☐☐☐☐☐

4. Address: _____
_____

_____

_____

5. Phone no:

6. Occupation:

7. Age: in years: ☐☐

8. Gender: ☐ male (1) female (2)

9. Height: in cms ☐☐☐

10. Weight: in kgs ☐☐

11. BMI: ☐☐.☐☐

Comorbidities and baseline evaluation

12. HTN: ☐ Yes (1) no (2)

13. DM: ☐ yes (1) no (2)

14. Malignancy: ☐ (1) yes (2) no

15. BBVS:

a. Hiv: ☐ (1) yes (2) no

b. HepB: ☐ (1) yes (2) no

c.HebC: ☐ (1) yes (2) no

16. Smoking: ☐ yes (1) no (2)

17. Alcohol: ☐ yes (1) no (2)

18. Previous hospitalization: ☐ yes (1) no (2)

19. APACHE II SCORE: ☐☐

A.Chronic organ insufficiency: ☐ yes (1) no (2) if yes, then

☐ (5 emergency surgery, 2 elective surgery, 5 not post op)

B. temperature: _____

C.Acute renal failure: ☐ (1) yes (2) no

D.Mean Arterial pressure: _____

E.Pulse rate:

F.Respiratory rate:

g.Sodium:

h.Potassium:

i. Creat: ☐ <1.4(1) 1.4-2 (2) >2(3)

j.Hematocrit:

K.Total WBC:

l.GCS:

m.PaO2:

20. Pitts bacteremia index: ☐

a.Temperature:_____

b.Hypotension: ☐ yes (1) no (2)

C.Mechanical ventilation: ☐ yes (1) no (2)

D.Cardiac arrest: ☐ yes (1) no (2)

E.Mental status: ☐ (1) alert (2) disoriented (3) Stuporous (4) comatose

TREATMENT

21. CRE in blood: ☐ yes (1) no (2)

22. Organism: ☐ (1) E.coli (2) Klebsiella

23. Primary source: ☐ blood (1), lung (2), urine (3), other (9)

24. Choice of antibiotic: ☐ meropenem (1) colistin (2) colistin+mero (3) tigecycline (4)

OUTCOMES

25. Febrile on day 1: ☐ yes (1) no (2) TEMP: _____

26. Febrile on day 7: ☐ yes (1) no (2) TEMP: _____

27. Febrile on day 14: ☐ yes (1) no (2) TEMP: _____

28. Other infections: ☐ yes (1) no (2)

29. Outcome: ☐ death (1)

Improved (2)

Discharged (3)

30. Direct cost of treatment:

31. 1 month survival: yes (1) no (2)

32.3 month survival: yes (1) no (2)

ANNEXURE 5: DATA SHEET

SNO	Ami	Coli	mi	fos	tige	date of c/s	day c	OCCUF	AGE	SEX	HEIGHT	WEIGH	HTN
1.00	S	S			S			2.00	38.00	2.00	150.00	67.00	2.00
2.00	R	R			S	9/6/217	11	1.00	33.00	2.00	150.00	55.00	2.00
3.00	R	R			R	2/6/217	14	1.00	70.00	2.00	155.00	70.00	1.00
4.00	S	S			S			7.00	62.00	1.00	160.00	73.00	2.00
5.00	R	S			R			1.00	18.00	1.00	163.00	59.00	2.00
6.00	R				S	01/06/2017	10	1.00	45.00	2.00	152.00	45.00	1.00
7.00						05/06/2017	2	2.00	57.00	1.00	161.00	51.00	1.00
8.00						08/06/2017	2	3.00	49.00	1.00	160.00	70.00	2.00
9.00	R	S			S	08/06/2017	6	1.00	54.00	2.00	154.00	60.00	2.00
10.00						13/06/2017	2	1.00	59.00	2.00	156.00	60.00	1.00
11.00	R	S				14/06/2017	6	1.00	75.00	2.00	152.00	50.00	2.00
12.00	R	S						1.00	22.00	1.00	165.00	70.00	2.00
13.00	R	S				20/06/2017	14	1.00	64.00	2.00	157.00	60.00	1.00
14.00	R	S			S			1.00	21.00	1.00	167.00	60.00	2.00
15.00	R	R			S	22/06/2017	4	1.00	49.00	2.00	156.00	65.00	2.00
16.00	S	S		S	S	25/06/2017	13	7.00	27.00	1.00	170.00	70.00	2.00
17.00	S	S		R	S	28/06/2017	14	3.00	35.00	1.00	170.00	70.00	2.00
18.00	R					28/06/2017	3	1.00	19.00	1.00	168.00	70.00	2.00
19.00	R	S			S			1.00	36.00	2.00	154.00	60.00	1.00
20.00						11/07/2017	1	3.00	23.00	1.00	165.00	70.00	2.00
21.00	R	R		S	S	12/07/2017	1	3.00	22.00	1.00	175.00	65.00	2.00
22.00						13/07/2017	1	1.00	62.00	1.00	167.00	75.00	2.00
23.00	R	S		R	S	16/07/2017	11	1.00	21.00	1.00	167.00	65.00	2.00
24.00						17/07/2017	2	1.00	25.00	2.00	160.00	50.00	2.00
25.00	R	S				27/07/2017	11	1.00	45.00	2.00	156.00	50.00	2.00
26.00	S	S			S	30/7/2017`	14	7.00	34.00	1.00	168.00	60.00	2.00
27.00	R	S		S	S			1.00	52.00	2.00	154.00	45.00	2.00
28.00	R	S			R			3.00	59.00	1.00	169.00	65.00	1.00
29.00	R	S			S	07/11/2017	3	5.00	58.00	1.00	170.00	60.00	1.00
30.00	S	R			R	08/11/2017	14	1.00	76.00	1.00	167.00	60.00	1.00
31.00	R	R		S	R			1.00	34.00	2.00	160.00	76.00	2.00
32.00	S	S			S	17/11/2017	9	1.00	64.00	2.00	156.00	70.00	2.00
33.00	S	S						1.00	74.00	2.00	160.00	54.00	2.00
34.00	S	S		R	R			1.00	61.00	1.00	170.00	70.00	2.00
35.00	S	S			S	21/11/2017	13	3.00	59.00	1.00	165.00	60.00	2.00
36.00	R	R			S			1.00	44.00	2.00	160.00	50.00	2.00
37.00	S	R			S	28/11/2017	2	1.00	18.00	1.00	165.00	56.00	2.00
38.00	R	S			S	29/11/2017	1	3.00	54.00	1.00	170.00	65.00	2.00
39.00	R	R		S	S			4.00	52.00	1.00	173.00	60.00	1.00
40.00	S	S			S			1.00	62.00	2.00	165.00	66.00	2.00
41.00	R	S		R	R	16/12/2017	nine	1.00	18.00	2.00	156.00	40.00	2.00
42.00						17/12/2017	1	1.00	51.00	2.00	160.00	54.00	2.00
43.00	S	S			S	12/10/2017	13	1.00	45.00	2.00	160.00	50.00	1.00
44.00	R	S			S	11/10/2017	9	1.00	59.00	2.00	156.00	50.00	1.00
45.00	R	S			S	17/10/2017	13	1.00	59.00	2.00	160.00	40.00	1.00
46.00	R	S			S			4.00	49.00	1.00	163.00	60.00	1.00
47.00						16/10/2017	2	2.00	49.00	1.00	170.00	65.00	2.00
48.00	S	S			S			5.00	58.00	1.00	169.00	70.00	2.00
49.00	S				S	23/10/2107	4	1.00	67.00	1.00	160.00	60.00	2.00

50.00	R	R		S	25/10/2017	14	7.00	54.00	1.00	168.00	70.00	2.00
51.00	R				26/10/2017	two	1.00	55.00	1.00	160.00	66.00	1.00
52.00	R	S		S			1.00	18.00	2.00	156.00	65.00	2.00
53.00							1.00	19.00	2.00	158.00	####	1.00
54.00					09/11/2017	4	3.00	44.00	1.00	170.00	60.00	2.00
56.00	R			S	22/12/2017	4	1.00	56.00	2.00	160.00	45.00	2.00
57.00	R	S	R	R			1.00	18.00	1.00	156.00	46.00	2.00
58.00	R	S					6.00	23.00	2.00	160.00	40.00	2.00
59.00	R	S			28/12/2017	14	1.00	62.00	1.00	168.00	60.00	1.00
60.00	S	S					1.00	93.00	1.00	156.00	55.00	1.00
61.00	R			S			4.00	39.00	1.00	170.00	70.00	1.00
62.00					30/12/2017	1	7.00	37.00	2.00	160.00	56.00	2.00
63.00	R		R	R	30/12/2017	5	5.00	37.00	1.00	160.00	70.00	2.00
64.00					09/01/2018	11	1.00	49.00	2.00	146.00	40.00	2.00
65.00	R	S		R			5.00	54.00	1.00	160.00	56.00	2.00
66.00							1.00	60.00	2.00	160.00	70.00	2.00
67.00	R	S		S			1.00	62.00	1.00	160.00	63.00	1.00
68.00	R	S			18/01/2018	14	1.00	65.00	1.00	168.00	77.00	1.00
69.00	S	S	S				1.00	61.00	1.00	168.00	70.00	1.00
70.00	R						1.00	56.00	2.00	150.00	60.00	1.00
71.00	R	S					1.00	22.00	2.00	150.00	47.00	2.00
72.00	R	S		S			1.00	31.00	1.00	160.00	70.00	2.00
73.00	R	R		S	29/01/2018	nine	1.00	51.00	2.00	156.00	65.00	2.00
74.00	R	S		R	09/02/2018	7	1.00	23.00	2.00	160.00	56.00	2.00
75.00	R				22/02/2018	6	1.00	35.00	1.00	168.00	65.00	2.00
76.00					23/02/2018	2	1.00	63.00	2.00	160.00	89.00	1.00
77.00	R	S			23/02/2018	14	1.00	31.00	2.00	158.00	54.00	2.00
78.00	R	R		S	01/03/2018	14	5.00	36.00	1.00	168.00	66.00	2.00
79.00	R				02/03/2018	14	5.00	39.00	1.00	165.00	68.00	2.00
80.00	R				02/03/2018	14	1.00	18.00	1.00	165.00	50.00	2.00
81.00					27/09/2017	2	5.00	44.00	1.00	165.00	70.00	1.00
82.00					29/07/2018	2	1.00	80.00	1.00	163.00	45.00	2.00
83.00	R			S	01/10/2017	2	5.00	47.00	1.00	160.00	65.00	2.00
84.00					02/10/2017	2	1.00	71.00	1.00	160.00	56.00	1.00
85.00					05/10/2017	2	3.00	30.00	2.00	156.00	45.00	2.00
86.00	R						6.00	39.00	1.00	168.00	65.00	2.00
87.00	R	S		S			1.00	35.00	2.00	160.00	56.00	2.00
88.00	R			S			5.00	51.00	1.00	167.00	70.00	2.00
89.00	R						1.00	40.00	2.00	160.00	54.00	2.00
90.00	R	S		S			4.00	25.00	1.00	170.00	60.00	2.00
91.00	S			S	23/10/2017	5	1.00	68.00	1.00	160.00	70.00	1.00
92.00	R			R	24/10/2017	14	4.00	35.00	1.00	160.00	56.00	2.00
93.00	R	S	S	S			1.00	41.00	2.00	150.00	65.00	2.00
94.00					08/08/2018	2	3.00	57.00	1.00	168.00	66.00	2.00
95.00					10/08/2018	2	1.00	46.00	2.00	151.00	55.00	2.00
96.00	R	S		R	09/08/2018	13	1.00	68.00	2.00	156.00	70.00	1.00
97.00	R	S		S	27/08/2018	14	1.00	65.00	1.00	160.00	75.00	1.00
98.00	S			S	29/08/2018	5	1.00	30.00	1.00	150.00	60.00	2.00
99.00	R						3.00	31.00	1.00	170.00	63.00	2.00
100.00	R	S					1.00	27.00	2.00	153.00	40.00	2.00

101.00	R	S			01/09/2017	12	1.00	63.00	1.00	160.00	56.00	2.00
102.00	R	S		R	07/09/2017	1	7.00	51.00	1.00	160.00	75.00	2.00
103.00	R	S		R	11/09/2017	14	3.00	47.00	1.00	165.00	67.00	2.00
104.00							1.00	72.00	1.00	166.00	76.00	2.00
105.00							1.00	60.00	1.00	163.00	75.00	1.00
106.00	R	S		S			1.00	20.00	2.00	157.00	63.00	2.00
107.00	R	S		R			5.00	49.00	1.00	167.00	56.00	2.00
108.00	R	R		R	08/03/2018	3	1.00	52.00	2.00	148.00	61.00	2.00
109.00	R	S					4.00	47.00	1.00	160.00	50.00	2.00
110.00	R	S					3.00	56.00	1.00	166.00	75.00	2.00
111.00	S	R	R	R	12/03/2018	14	1.00	87.00	1.00	166.00	73.00	1.00
112.00					27/02/2018	11	3.00	47.00	1.00	170.00	66.00	2.00
113.00	R						1.00	75.00	1.00	165.00	76.00	2.00
114.00	R	S		S			4.00	55.00	1.00	166.00	76.00	1.00
115.00	R	S		S	22/03/2018	12	1.00	61.00	1.00	170.00	60.00	1.00
116.00					23/03/2018	2	1.00	46.00	2.00	160.00	60.00	2.00
117.00	R	S			23/03/2018	4	2.00	25.00	1.00	165.00	60.00	2.00
118.00					26/03/2018	8	2.00	36.00	2.00	169.00	66.00	2.00
119.00	R	S					1.00	79.00	1.00	168.00	60.00	1.00
120.00					27/02/2018	2	5.00	57.00	1.00	160.00	70.00	2.00
121.00	R						1.00	57.00	2.00	154.00	46.00	1.00
122.00	R						3.00	55.00	1.00	160.00	70.00	2.00
123.00	S						1.00	53.00	2.00	160.00	65.00	2.00
124.00	S				21/03/2018	2	1.00	63.00	2.00	150.00	65.00	1.00
125.00	R	S					2.00	55.00	1.00	165.00	70.00	1.00
126.00	R						1.00	56.00	2.00	156.00	59.00	1.00
127.00	R	S		S			1.00	56.00	2.00	160.00	70.00	2.00
128.00	R	S					3.00	58.00	1.00	167.00	70.00	2.00
129.00					30/04/2018	2	2.00	34.00	1.00	167.00	60.00	2.00
130.00					30/04/2018	14	1.00	44.00	2.00	156.00	40.00	2.00
131.00	R	S	S	S	02/05/2018	7	6.00	39.00	2.00	160.00	50.00	2.00
132.00	R	R	S	S			1.00	73.00	1.00	163.00	60.00	1.00
133.00	R			S			1.00	65.00	2.00	157.00	80.00	1.00
134.00					06/05/2018	12	1.00	75.00	1.00	160.00	70.00	1.00
135.00	R	S					1.00	54.00	2.00	156.00	65.00	1.00
136.00	R	S	S	S	12/05/2018	4	1.00	30.00	2.00	157.00	40.00	2.00
137.00	R	S					1.00	24.00	2.00	155.00	73.00	2.00
138.00							4.00	81.00	2.00	156.00	65.00	1.00
139.00	R			S			1.00	62.00	1.00	160.00	65.00	2.00
140.00	R			S			1.00	63.00	1.00	163.00	72.00	2.00
141.00	R	S					1.00	20.00	2.00	156.00	50.00	1.00
142.00					22/05/2018	3	1.00	60.00	1.00	160.00	70.00	2.00
143.00	S	S					5.00	42.00	1.00	160.00	59.00	2.00
144.00	R				14/06/2018	3	1.00	18.00	1.00	163.00	55.00	2.00
145.00					14/06/2018	2	1.00	28.00	2.00	150.00	32.00	2.00
146.00	R				15/06/2018	2	1.00	48.00	2.00	156.00	70.00	2.00
147.00	R	S	S	S			1.00	18.00	1.00	160.00	60.00	2.00
148.00	R						1.00	68.00	1.00	160.00	70.00	2.00
149.00					23/06/2018	2	1.00	18.00	2.00	154.00	45.00	2.00
150.00	R	S		S			1.00	30.00	1.00	155.00	56.00	2.00

151.00		R	S		S	26/06/2018	8	2.00	59.00	1.00	170.00	69.00	2.00
152.00		R			S			1.00	73.00	1.00	163.00	70.00	1.00
153.00		R	S		S			3.00	34.00	1.00	159.00	63.00	2.00
154.00		R				20/07/2017	2	1.00	20.00	1.00	160.00	55.00	2.00
155.00		R	S					1.00	46.00	2.00	156.00	62.00	2.00
156.00		R	R	S	R	30/07/2017	11	3.00	48.00	1.00	165.00	75.00	1.00
157.00		R	S					2.00	44.00	1.00	165.00	60.00	2.00
158.00		R	S			07/08/2018	8	6.00	47.00	1.00	163.00	70.00	1.00
159.00		R	S		S	12/08/2018	5	1.00	63.00	2.00	156.00	60.00	2.00
160.00		R	S			12/08/2018	14	3.00	55.00	1.00			2.00
161.00		R	R		S			1.00	19.00	1.00	166.00	60.00	2.00
162.00		R	S					4.00	46.00	1.00	160.00	66.00	2.00
163.00		R	S		S			1.00	77.00	1.00	166.00	70.00	1.00
164.00		S	S		S			1.00	62.00	1.00	166.00	70.00	2.00

DM	MALIG	HIV	HEPE	HEPC	SMOI	ALCOI	PREVI	APACH	COI	MXCC	ARF	TEMPEI	MAP	PR	RR
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	8.00	2.00		2.00	102.00	73.00	84.00	34.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	31.00	2.00		1.00	104.00	70.00	110.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	19.00	2.00		2.00	100.00	#####	112.00	32.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	14.00	2.00		2.00	102.00	87.00	80.00	20.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	11.00	2.00		2.00	102.00	90.00	110.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	62.00	2.00		2.00	102.00	97.00	84.00	16.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	36.00	1.00	3.00	1.00	102.00	73.00	100.00	24.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	29.00	1.00	3.00	1.00	100.00	80.00	100.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	27.00	2.00		2.00	99.00	63.00	100.00	24.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	10.00	2.00		2.00	99.00	90.00	110.00	16.00
1.00	2.00	2.00	1.00	2.00	2.00	2.00	2.00	29.00	2.00		2.00	100.00	77.00	110.00	42.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	4.00	2.00		2.00	100.00	70.00	84.00	20.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	49.00	1.00	3.00	1.00	103.00	67.00	120.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	30.00	2.00		1.00	100.00	#####	103.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	36.00	2.00		2.00	103.00	67.00	110.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	27.00	2.00		2.00	101.00	73.00	90.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	33.00	2.00		2.00	104.00	57.00	120.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	26.00	2.00		2.00	102.00	37.00	107.00	38.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	34.00	1.00	3.00	1.00	104.50	57.00	116.00	34.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	27.00	2.00		2.00	100.00	73.00	100.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	32.00	1.00	3.00	1.00	102.00	57.00	112.00	34.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	37.00	2.00		2.00	104.00	60.00	124.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	8.00	2.00		2.00	98.00	83.00	110.00	20.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	24.00	2.00		1.00	98.00	73.00	110.00	26.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	12.00	2.00		2.00	98.00	93.00	100.00	24.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	18.00	2.00		1.00	103.00	97.00	88.00	28.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	10.00	2.00		2.00	98.00	83.00	110.00	24.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	12.00	1.00	3.00	1.00	98.00	#####	80.00	24.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	2.00		2.00	102.00	70.00	110.00	36.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	37.00	1.00	3.00	2.00	103.00	70.00	120.00	34.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	15.00	1.00	3.00	1.00	100.00	75.00	88.00	24.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	29.00	2.00		1.00	101.00	73.00	112.00	24.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	17.00	2.00		1.00	102.00	90.00	80.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	13.00	2.00		2.00	100.00	90.00	80.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	15.00	2.00		2.00	98.00	83.00	90.00	26.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	8.00	2.00		2.00	98.20	80.00	80.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	15.00	1.00	3.00	2.00	102.00	70.00	110.00	32.00
2.00	1.00	2.00	2.00	2.00	1.00	1.00	1.00	42.00	2.00		1.00	104.00	75.00	112.00	36.00
1.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	15.00	1.00	2.00	2.00	100.00	90.00	80.00	36.00
2.00	1.00	1.00	2.00	2.00	2.00	2.00	1.00	7.00	2.00		2.00	98.00	90.00	84.00	20.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	19.00	2.00		2.00	104.00	60.00	112.00	32.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	27.00	2.00		2.00	104.00	60.00	112.00	36.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	30.00	1.00	1.00	1.00	100.00	70.00	84.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	24.00	1.00	3.00	1.00	100.00	90.00	84.00	21.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	30.00	1.00	3.00	2.00	103.00	60.00	120.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	30.00	1.00	2.00	1.00	104.00	60.00	120.00	28.00
1.00	2.00	2.00	2.00	2.00	1.00	1.00	2.00	44.00	1.00	1.00	1.00	104.00	60.00	113.00	25.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	32.00	1.00	3.00	1.00	102.00	70.00	100.00	28.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	32.00	1.00	3.00	2.00	104.00	80.00	130.00	30.00

1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	17.00	1.00	3.00	2.00	100.00	80.00	90.00	30.00
2.00	2.00	2.00	2.00	2.00	1.00	2.00	1.00	15.00	2.00		1.00	98.00	73.00	80.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	20.00	2.00		2.00	104.00	70.00	112.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	9.00	2.00		2.00	101.00	73.00	88.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	28.00	2.00		1.00	104.00	60.00	120.00	34.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	2.00		2.00	102.00	73.00	126.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	19.00	2.00		2.00	104.00	50.00	120.00	44.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	6.00	2.00		2.00	104.00	70.00	130.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	40.00	1.00	3.00	1.00	104.00	54.00	100.00	24.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	17.00	1.00	3.00	2.00	101.00	60.00	88.00	28.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	14.00	1.00	1.00	1.00	102.00	73.00	84.00	24.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	28.00	2.00		1.00	104.00	80.00	110.00	34.00
2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	20.00	2.00		2.00	102.00	60.00	90.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	29.00	2.00		2.00	103.00	50.00	146.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	26.00	1.00	1.00	1.00	102.00	73.00	108.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	23.00	2.00		1.00	102.00	73.00	114.00	34.00
2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	34.00	1.00	3.00	1.00	102.00	50.00	116.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	32.00	1.00	3.00	1.00	103.00	60.00	110.00	20.00
2.00	2.00	2.00	2.00	2.00	1.00	2.00	1.00	26.00	2.00		1.00	101.00	60.00	118.00	26.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	21.00	1.00	3.00	2.00	102.00	60.00	110.00	24.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	21.00	2.00		2.00	104.00	60.00	114.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00		2.00	100.00	70.00	100.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	1.00	1.00	2.00	103.00	60.00	112.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	23.00	2.00		1.00	104.00	56.00	120.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	29.00	2.00		1.00	103.00	56.00	120.00	36.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	32.00	2.00		1.00	104.00	46.00	140.00	46.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	34.00	2.00		1.00	103.00	60.00	130.00	46.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	18.00	2.00		2.00	102.00	60.00	140.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	22.00	2.00		1.00	103.00	50.00	120.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	36.00	2.00		1.00	103.00	60.00	120.00	40.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	20.00	2.00		2.00	102.00	73.00	120.00	32.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	33.00	2.00		1.00	103.00	50.00	130.00	14.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	28.00	1.00	1.00	2.00	103.00	40.00	140.00	20.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	39.00	2.00		1.00	102.00	60.00	134.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	33.00	2.00		1.00	103.00	60.00	120.00	40.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	16.00	2.00		1.00	100.00	73.00	84.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	12.00	2.00		2.00	100.00	60.00	110.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	26.00	1.00	3.00	1.00	103.00	70.00	110.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	4.00	2.00		2.00	98.00	75.00	100.00	24.00
2.00	2.00	2.00	2.00	2.00	1.00	2.00	1.00	14.00	2.00		2.00	103.00	65.00	120.00	30.00
2.00	2.00	2.00	2.00	2.00	1.00	2.00	1.00	16.00	1.00	3.00	2.00	103.00	80.00	130.00	14.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	38.00	1.00	3.00	1.00	103.00	60.00	110.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	25.00	2.00		2.00	104.00	50.00	140.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	28.00	2.00		1.00	104.00	50.00	146.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	2.00		2.00	103.00	50.00	140.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	24.00	2.00		2.00	103.00	60.00	80.00	30.00
2.00	2.00	2.00	2.00	1.00	1.00	2.00	1.00	31.00	1.00	1.00	1.00	102.00	60.00	114.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	31.00	2.00		1.00	104.00	50.00	130.00	30.00
2.00	2.00	2.00	2.00	2.00	1.00	2.00	2.00	19.00	2.00		1.00	98.00	90.00	100.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	62.00	2.00		1.00	103.00	50.00	130.00	36.00

1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	39.00	1.00	3.00	1.00	100.00	70.00	120.00	48.00
1.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	29.00	1.00	3.00	1.00	103.00	60.00	140.00	36.00
2.00	1.00	2.00	2.00	2.00	1.00	2.00	1.00	13.00	3.00	3.00	1.00	102.00	73.00	90.00	20.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	27.00	2.00		2.00	103.00	60.00	110.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	23.00	1.00	3.00	1.00	103.00	70.00	98.00	24.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	2.00		1.00	102.00	74.00	122.00	26.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	25.00	3.00	1.00	1.00	104.00	70.00	126.00	24.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	31.00	2.00		2.00	104.00	60.00	140.00	36.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	28.00	2.00		1.00	103.00	73.00	110.00	36.00
2.00	2.00	2.00	2.00	2.00	1.00	1.00	2.00	22.00	2.00		2.00	103.00	66.00	120.00	36.00
1.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	30.00	2.00		2.00	103.00	60.00	120.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	44.00	2.00		1.00	104.00	50.00	140.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	19.00	2.00		2.00	103.00	70.00	90.00	24.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	32.00	1.00	3.00	1.00	103.00	73.00	110.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	27.00	2.00		1.00	103.00	76.00	110.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	27.00	2.00		2.00	103.00	50.00	140.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	21.00	2.00		1.00	103.00	60.00	140.00	30.00
2.00	2.00	2.00	1.00	2.00	2.00	2.00	1.00	30.00	1.00	3.00	1.00	103.00	50.00	130.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	36.00	1.00	3.00	1.00	102.00	65.00	110.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	27.00	1.00	3.00	2.00	102.00	50.00	110.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	27.00	2.00		1.00	103.00	60.00	112.00	30.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	26.00	2.00		1.00	103.00	63.00	90.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	10.00	2.00		1.00	98.00	73.00	98.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	39.00	1.00	3.00	1.00	102.00	60.00	126.00	30.00
1.00	2.00	2.00	2.00	1.00	1.00	1.00	1.00	14.00	2.00		1.00	100.00	70.00	98.00	20.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	16.00	2.00		2.00	100.00	80.00	100.00	24.00
1.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	9.00	2.00		2.00	100.00	70.00	76.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	18.00	2.00		1.00	102.00	70.00	102.00	32.00
2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	45.00	1.00	2.00	1.00	103.00	50.00	120.00	32.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	2.00	35.00	2.00		1.00	104.00	54.00	126.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	26.00	2.00		2.00	104.00	40.00	130.00	36.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	2.00		2.00	104.00	60.00	96.00	32.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	29.00	2.00		2.00	104.00	30.00	130.00	32.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	27.00	2.00	1.00	1.00	104.00	70.00	100.00	36.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	103.00	30.00	140.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	52.00	2.00		1.00	103.00	50.00	116.00	36.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	23.00	2.00		2.00	103.00	60.00	120.00	36.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	35.00	2.00		1.00	103.00	60.00	120.00	30.00
2.00	2.00	2.00	2.00	2.00	1.00	1.00	2.00	23.00	2.00		2.00	104.00	60.00	112.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	29.00	2.00		1.00	104.00	60.00	120.00	28.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	26.00	2.00		1.00	104.00	50.00	130.00	30.00
2.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	42.00	1.00	3.00	1.00	102.00	60.00	110.00	32.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	2.00	29.00	1.00	2.00	1.00	102.00	73.00	110.00	28.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	15.00	1.00	1.00	1.00	104.00	60.00	88.00	24.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	16.00	2.00		2.00	103.00	60.00	112.00	23.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	28.00	2.00		1.00	104.00	60.00	120.00	30.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	26.00	2.00		2.00	103.00	30.00	120.00	32.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	20.00	2.00		2.00	102.00	60.00	112.00	24.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	29.00	2.00		1.00	104.00	57.00	60.00	40.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	22.00	2.00		2.00	102.00	60.00	120.00	24.00

2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	37.00	1.00	1.00	1.00	102.00	60.00	112.00	32.00
2.00	1.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	2.00		2.00	100.00	70.00	116.00	20.00
2.00	2.00	2.00	2.00	2.00	2.00	1.00	1.00	62.00	2.00		1.00	103.00	60.00	112.00	23.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	27.00	2.00		2.00	104.00	70.00	112.00	32.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	7.00	2.00		2.00	100.00	70.00	112.00	24.00
1.00	2.00	2.00	2.00	2.00	1.00	1.00	2.00	31.00	1.00	3.00	2.00	104.00	60.00	130.00	30.00
2.00	2.00	2.00	2.00	2.00	1.00	2.00	1.00	23.00	2.00		1.00	102.00	60.00	180.00	48.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	22.00	1.00	3.00	2.00	103.00	40.00	55.00	18.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	20.00	2.00		1.00	102.00	78.00	110.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	20.00	2.00		1.00	100.00	50.00	96.00	18.00
2.00	2.00	2.00	2.00	2.00	2.00	2.00	1.00	13.00	2.00		2.00	103.00	70.00	76.00	20.00
1.00	2.00	2.00	1.00	2.00	2.00	2.00	1.00	18.00	2.00		2.00	103.00	66.00	78.00	30.00
1.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	14.00	2.00		2.00	100.00	76.00	110.00	20.00
1.00	2.00	2.00	2.00	2.00	1.00	2.00	2.00	27.00	1.00	3.00	1.00	103.00	70.00	110.00	20.00

NA	K	CREAT	PCV	TC	GCS	PAO2	PITTSII	HYPOT	MECH\	CARDI	MEN	H/NH	CRE
132.00	3.80	0.61	27.00	200.00	15.00	98.00	13.00	2.00	2.00	2.00	4.00	H	1.00
140.00	3.80	1.90	26.00	27900.00	12.00	95.00	10.00	1.00	1.00	2.00	2.00		1.00
141.00	2.60	0.40	33.00	22500.00	15.00	80.00	2.00	2.00	2.00	2.00	1.00		1.00
128.00	3.60	0.65	18.00	100.00	15.00	10.00	2.00	2.00	2.00	2.00	1.00	H	1.00
128.00	3.60	0.49	21.00	100.00	15.00	80.00	2.00	2.00	2.00	2.00	1.00	H	1.00
133.00	4.80	1.18	26.40	19900.00	15.00	80.00	2.00	2.00	2.00	2.00	1.00		1.00
133.00	4.30	2.54	27.00	8400.00	3.00	54.00	11.00	1.00	1.00	1.00	4.00		1.00
146.00	4.60	2.04	24.60	100.00	10.00	80.00	13.00	1.00	1.00	1.00	4.00	H	1.00
134.00	3.40	0.45	24.20	200.00	8.00	55.00	5.00	1.00	2.00	2.00	3.00		1.00
130.00	3.60	0.60	20.00	19800.00	15.00	70.00	2.00	2.00	2.00	2.00	1.00	NH	1.00
142.00	3.60	0.67	26.00	10100.00	3.00	60.00	12.00	1.00	1.00	1.00	4.00		1.00
140.00	3.50	0.46	30.80	8000.00	15.00	89.00	2.00	2.00	2.00	2.00	2.00		1.00
138.00	5.30	3.75	22.00	12600.00	3.00	87.00	12.00	1.00	1.00	1.00	3.00	H	1.00
134.00	4.00	10.40	27.00	1600.00	15.00	54.00	4.00	2.00	1.00	2.00	3.00		1.00
132.00	3.90	0.50	26.00	400.00	10.00	90.00	14.00	1.00	1.00	2.00	3.00	H	1.00
136.00	3.40	0.80	30.00	300.00	10.00	70.00	14.00	1.00	1.00	2.00	4.00	H	1.00
135.00	2.80	1.28	15.00	100.00	10.00	65.00	13.00	1.00	1.00	2.00	4.00		1.00
136.00	4.90	0.93	21.00	11001.00	12.00	59.00	14.00	1.00	2.00	1.00	4.00		1.00
122.00	2.10	5.48	14.70	16300.00	9.00	80.00	12.00	1.00	2.00	2.00	3.00		1.00
124.00	5.00	0.64	21.00	100.00	13.00	60.00	14.00	1.00	2.00	1.00	4.00		1.00
155.00	4.50	1.71	21.00	4700.00	12.00	50.00	14.00	1.00	2.00	1.00	3.00	H	1.00
140.00	2.60	0.54	24.00	36100.00	9.00	60.00	14.00	1.00	2.00	1.00	3.00		1.00
135.00	3.60	0.74	21.60	1400.00	15.00	80.00	2.00	2.00	2.00	2.00	1.00		1.00
138.00	4.30	2.37	26.40	500.00	8.00	60.00	13.00	2.00	2.00	2.00	4.00	H	1.00
135.00	4.20	1.44	28.20	2200.00	12.00	80.00	12.00	1.00	1.00	1.00	2.00	NH	1.00
124.00	3.80	2.90	30.00	19500.00	15.00	90.00	11.00	1.00	2.00	2.00	2.00		1.00
140.00	3.60	0.70	24.60	100.00	15.00	70.00	2.00	2.00	2.00	2.00	3.00	H	1.00
141.00	3.50	2.12	44.00	9900.00	15.00	80.00	2.00	2.00	2.00	2.00	2.00		1.00
140.00	3.70	1.57	26.70	100.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00	H	1.00
135.00	3.20	0.45	22.80	37800.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
126.00	3.50	4.17	21.60	8600.00	15.00	80.00	2.00	2.00	2.00	2.00	3.00		1.00
135.00	2.10	2.07	21.60	13000.00	10.00	67.00	12.00	1.00	2.00	1.00	4.00		1.00
120.00	4.90	2.07	30.00	23200.00	15.00	68.00	2.00	2.00	2.00	2.00	3.00		1.00
130.00	4.50	0.32	30.00	700.00	13.00	77.00	2.00	2.00	2.00	2.00	3.00	H	1.00
115.00	4.00	1.33	7.70	500.00	15.00	60.00	2.00	2.00	2.00	2.00	2.00		1.00
132.00	3.40	0.95	26.00	300.00	15.00	80.00	2.00	2.00	2.00	2.00	1.00	H	1.00
138.00	4.60	0.58	24.00	1600.00	13.00	80.00	6.00	1.00	2.00	2.00	2.00	H	1.00
139.00	5.90	2.06	20.00	100.00	3.00	50.00	14.00	1.00	1.00	1.00	4.00	H	1.00
133.00	4.10	1.10	26.10	10600.00	10.00	67.00	4.00	1.00	2.00	2.00	2.00		1.00
140.00	2.90	0.92	21.00	13200.00	15.00	80.00	2.00	2.00	2.00	2.00	1.00	NH	1.00
131.00	3.50	0.51	24.00	100.00	12.00	80.00	6.00	1.00	2.00	2.00	2.00	H	1.00
125.00	2.50	0.54	26.00	33000.00	14.00	80.00	8.00	1.00	2.00	2.00	3.00		1.00
126.00	4.20	2.24	26.00	13100.00	3.00	60.00	13.00	1.00	1.00	1.00	4.00		1.00
123.00	3.20	4.20	22.00	3500.00	10.00	75.00	4.00	2.00	2.00	2.00	3.00		1.00
138.00	3.80	0.48	26.00	15400.00	3.00	60.00	14.00	1.00	1.00	1.00	1.00		1.00
137.00	4.50	6.98	24.10	13500.00	14.00	77.00	2.00	1.00	1.00	1.00	2.00		1.00
118.00	2.80	1.55	20.00	100.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
136.00	5.10	5.00	22.00	14300.00	13.00	60.00	4.00	1.00	2.00	2.00	2.00	H	1.00
133.00	3.80	1.25	15.00	13200.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00

131.00	4.00	1.51	30.00	4100.00	13.00	80.00	4.00	1.00	2.00	2.00	2.00		1.00
143.00	3.50	3.25	30.00	22700.00	14.00	70.00	6.00	1.00	2.00	2.00	4.00		1.00
147.00	3.10	0.75	30.00	45300.00	10.00	76.00	6.00	1.00	2.00	2.00	3.00		1.00
133.00	3.10	0.97	33.00	11600.00	14.00	80.00	4.00	1.00	2.00	2.00	2.00		1.00
129.00	2.40	7.34	29.00	15700.00	12.00	76.00	9.00	1.00	2.00	1.00	4.00		1.00
126.00	3.90	0.37	29.00	700.00	10.00	96.00	14.00	1.00	1.00	1.00	4.00	NH	1.00
136.00	3.90	0.57	22.00	100.00	14.00	60.00	6.00	1.00	2.00	2.00	3.00	H	1.00
131.00	3.90	0.36	30.00	14400.00	15.00	80.00	4.00	1.00	2.00	2.00	2.00		1.00
128.00	5.20	8.68	30.30	32400.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
127.00	4.60	1.09	36.00	18500.00	14.00	60.00	4.00	1.00	2.00	2.00	2.00	H	1.00
135.00	5.20	4.39	9.00	6800.00	14.00	60.00	6.00	1.00	2.00	2.00	3.00		1.00
129.00	4.90	1.50	36.00	700.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
148.00	2.90	0.56	27.00	300.00	10.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
141.00	3.80	0.79	30.00	29400.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
130.00	3.50	2.53	21.00	11100.00	10.00	70.00	6.00	1.00	2.00	2.00	3.00		1.00
137.00	4.40	5.70	27.00	27600.00	10.00	70.00	8.00	1.00	2.00	2.00	3.00		1.00
143.00	3.90	1.93	27.00	32000.00	3.00	60.00	12.00	1.00	1.00	1.00	3.00		1.00
138.00	2.50	2.49	27.00	9500.00	10.00	70.00	8.00	1.00	2.00	2.00	3.00		1.00
127.00	5.90	4.21	30.00	45700.00	14.00	60.00	6.00	2.00	2.00	2.00	4.00		1.00
130.00	3.30	1.50	24.00	21600.00	15.00	80.00	4.00	2.00	2.00	2.00	3.00		1.00
119.00	2.70	0.41	22.00	700.00	14.00	70.00	6.00	1.00	2.00	2.00	1.00	NH	1.00
134.00	3.70	0.66	30.00	31800.00	15.00	90.00	2.00	2.00	2.00	2.00	1.00		1.00
136.00	4.70	0.93	29.00	56200.00	13.00	70.00	13.00	1.00	2.00	1.00	4.00		1.00
137.00	3.80	0.43	26.20	200.00	10.00	70.00	8.00	1.00	2.00	2.00	4.00	H	1.00
132.00	3.60	2.70	29.00	27700.00	10.00	60.00	13.00	1.00	1.00	1.00	4.00		1.00
144.00	3.50	1.54	18.00	8800.00	13.00	71.00	14.00	1.00	1.00	1.00	4.00		1.00
169.00	3.90	1.94	26.00	40800.00	10.00	60.00	14.00	1.00	1.00	1.00	3.00		1.00
138.00	3.80	0.82	30.00	5900.00	3.00	60.00	10.00	1.00	1.00	2.00	4.00		1.00
138.00	3.50	1.59	26.00	20800.00	13.00	70.00	12.00	1.00	1.00	1.00	4.00		1.00
121.00	3.50	1.83	22.00	100.00	3.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
123.00	6.00	1.13	15.00	900.00	8.00	60.00	4.00	1.00	2.00	2.00	3.00		1.00
143.00	3.70	1.21	33.00	22400.00	8.00	60.00	14.00	1.00	1.00	1.00	3.00	NH	1.00
134.00	3.30	0.13	30.00	10100.00	10.00	70.00	14.00	1.00	1.00	1.00	4.00		1.00
139.00	6.40	2.34	21.00	2000.00	8.00	60.00	14.00	1.00	1.00	1.00	4.00		1.00
156.00	3.30	2.17	26.00	1000.00	13.00	70.00	14.00	1.00	1.00	1.00	4.00	H	1.00
120.00	4.50	0.45	30.00	3700.00	13.00	70.00	2.00	2.00	2.00	2.00	1.00		1.00
144.00	4.30	0.37	26.00	5800.00	13.00	60.00	4.00	2.00	2.00	2.00	3.00		1.00
133.00	4.90	9.24	22.00	6300.00	12.00	70.00	2.00	2.00	2.00	2.00	1.00		1.00
137.00	3.70	0.64	33.00	19200.00	14.00	70.00	2.00	2.00	2.00	2.00	2.00		1.00
132.00	3.30	0.67	26.00	9800.00	14.00	70.00	6.00	1.00	2.00	2.00	2.00		1.00
130.00	4.30	1.33	36.00	11700.00	13.00	70.00	12.00	1.00	2.00	1.00	4.00		1.00
133.00	6.90	8.14	16.00	8600.00	10.00	60.00	12.00	1.00	2.00	1.00	4.00		1.00
135.00	3.80	0.97	24.00	600.00	13.00	70.00	6.00	1.00	2.00	2.00	3.00	H	1.00
135.00	3.40	1.44	30.00	300.00	14.00	70.00	14.00	1.00	1.00	1.00	4.00	NH	1.00
145.00	2.80	0.64	20.00	3000.00	14.00	70.00	14.00	1.00	1.00	1.00	3.00	H	1.00
135.00	3.50	0.92	30.00	17900.00	6.00	70.00	12.00	1.00	1.00	1.00	3.00		1.00
126.00	4.90	4.71	21.00	14500.00	10.00	65.00	12.00	1.00	1.00	2.00	3.00		1.00
135.00	5.10	2.62	36.00	10500.00	6.00	65.00	12.00	1.00	1.00	2.00	3.00		1.00
126.00	3.20	0.70	24.00	3100.00	14.00	70.00	4.00	1.00	2.00	2.00	3.00		1.00
143.00	3.70	1.34	30.00	24200.00	14.00	80.00	8.00	1.00	2.00	2.00	3.00		1.00

137.00	3.20	2.28	18.00	8200.00	3.00	60.00	10.00	1.00	1.00	2.00	3.00		1.00
146.00	4.00	3.36	30.50	500.00	10.00	70.00	10.00	1.00	1.00	1.00	4.00		1.00
135.00	4.70	0.90	30.00	22700.00	13.00	60.00	4.00	2.00	2.00	2.00	2.00	NH	1.00
126.00	3.00	0.78	21.00	14600.00	12.00	70.00	6.00	1.00	2.00	2.00	3.00	NH	1.00
133.00	4.50	1.67	36.00	19200.00	13.00	70.00	2.00	2.00	2.00	2.00	2.00		1.00
121.00	2.80	2.51	24.00	10200.00	15.00	80.00	4.00	1.00	2.00	2.00	2.00	NH	1.00
133.00	3.50	2.51	30.00	16200.00	12.00	70.00	8.00	1.00	2.00	2.00	3.00	H	1.00
139.00	3.10	0.63	22.00	100.00	13.00	60.00	14.00	1.00	1.00	1.00	3.00	H	1.00
134.00	3.50	2.01	24.00	15800.00	9.00	75.00	8.00	1.00	2.00	2.00	2.00		1.00
126.00	3.10	0.67	30.00	26200.00	13.00	86.00	8.00	1.00	2.00	2.00	3.00		1.00
140.00	3.50	0.57	18.00	6500.00	10.00	70.00	6.00	1.00	2.00	2.00	3.00	NH	1.00
141.00	5.30	11.21	24.00	100.00	11.00	70.00	14.00	1.00	1.00	1.00	4.00		1.00
128.00	4.70	0.64	33.00	16700.00	13.00	60.00	2.00	2.00	2.00	2.00	1.00	NH	1.00
141.00	4.10	3.51	36.00	12400.00	10.00	60.00	2.00	2.00	2.00	2.00	2.00	NH	1.00
131.00	3.70	1.09	22.00	11001.00	12.00	60.00	12.00	1.00	1.00	1.00	2.00		1.00
141.00	2.70	1.09	30.00	9000.00	10.00	60.00	14.00	1.00	1.00	1.00	3.00		1.00
133.00	4.40	5.75	20.00	13700.00	13.00	70.00	10.00	1.00	1.00	2.00	3.00		1.00
146.00	3.60	2.85	18.00	9900.00	12.00	65.00	6.00	1.00	2.00	2.00	3.00		1.00
128.00	4.90	5.91	26.00	2000.00	12.00	60.00	2.00	2.00	2.00	2.00	2.00		1.00
126.00	3.20	0.73	21.00	11600.00	10.00	78.00	4.00	1.00	2.00	2.00	2.00		1.00
128.00	4.40	2.30	24.00	13400.00	13.00	70.00	6.00	1.00	2.00	2.00	2.00		1.00
130.00	3.40	4.91	30.00	9000.00	15.00	80.00	2.00	1.00	2.00	2.00	1.00		1.00
134.00	3.50	0.58	24.00	16500.00	14.00	80.00	2.00	2.00	2.00	2.00	1.00	NH	1.00
127.00	5.30	3.97	18.00	5500.00	10.00	70.00	14.00	1.00	1.00	1.00	4.00		1.00
130.00	4.10	1.69	16.00	4900.00	15.00	80.00	6.00	1.00	2.00	2.00	3.00		1.00
126.00	2.90	0.29	24.00	9100.00	15.00	70.00	2.00	2.00	2.00	2.00	2.00	NH	1.00
141.00	3.20	0.47	30.00	6300.00	15.00	70.00	2.00	2.00	2.00	2.00	1.00	H	1.00
128.00	4.60	1.76	26.00	13900.00	13.00	70.00	14.00	1.00	1.00	1.00	3.00		1.00
150.00	6.40	2.73	19.00	15300.00	3.00	60.00	11.00	1.00	1.00	2.00	4.00		1.00
131.00	5.10	12.95	30.00	24500.00	13.00	70.00	8.00	1.00	2.00	2.00	3.00	NH	1.00
140.00	3.10	0.59	22.00	100.00	13.00	65.00	8.00	1.00	2.00	2.00	3.00	H	1.00
131.00	3.90	8.00	30.00	16200.00	13.00	70.00	4.00	1.00	2.00	2.00	2.00		1.00
145.00	2.60	0.34	30.20	26000.00	10.00	70.00	12.00	1.00	1.00	2.00	3.00		1.00
156.00	3.50	1.62	22.00	16000.00	9.00	70.00	13.00	1.00	1.00	1.00	3.00		1.00
130.00	3.20	2.58	19.00	18000.00	13.00	70.00	8.00	1.00	2.00	2.00	3.00		1.00
142.00	3.00	1.30	23.00	100.00	10.00	70.00	12.00	1.00	1.00	2.00	3.00		1.00
138.00	3.70	0.52	24.00	200.00	10.00	70.00	4.00	1.00	2.00	2.00	2.00	H	1.00
137.00	3.00	4.44	24.00	19700.00	14.00	70.00	4.00	1.00	2.00	2.00	2.00		1.00
133.00	4.10	0.84	27.00	22500.00	10.00	60.00	6.00	1.00	2.00	2.00	3.00		1.00
138.00	4.70	4.25	24.00	22900.00	15.00	70.00	2.00	1.00	2.00	2.00	2.00		1.00
142.00	5.50	2.27	27.00	11900.00	12.00	70.00	4.00	1.00	2.00	2.00	2.00		1.00
140.00	6.70	4.00	19.00	10700.00	9.00	60.00	14.00	1.00	1.00	1.00	3.00		1.00
144.00	2.90	1.07	22.00	4300.00	14.00	70.00	2.00	2.00	2.00	2.00	2.00		1.00
135.00	4.90	3.38	33.10	18100.00	15.00	90.00	2.00	2.00	2.00	2.00	1.00		1.00
125.00	3.50	0.37	21.00	5000.00	15.00	80.00	4.00	1.00	2.00	2.00	1.00	H	1.00
152.00	4.30	3.53	22.00	12500.00	14.00	70.00	10.00	1.00	1.00	2.00	3.00		1.00
152.00	3.50	1.44	21.00	44400.00	14.00	80.00	10.00	1.00	2.00	2.00	3.00	H	1.00
133.00	3.90	1.04	24.00	2600.00	14.00	70.00	4.00	1.00	2.00	2.00	2.00		1.00
150.00	3.70	1.94	25.00	1600.00	10.00	70.00	14.00	1.00	1.00	1.00	4.00		1.00
129.00	6.10	0.01	22.00	12800.00	10.00	60.00	10.00	1.00	2.00	2.00	3.00		1.00

141.00	3.10	4.53	26.00	22000.00	10.00	70.00	8.00	1.00	1.00	2.00	3.00		1.00
134.00	3.90	0.73	11.70	10100.00	10.00	68.00	2.00	1.00	2.00	2.00	1.00	NH	1.00
134.00	3.60	1.57	12.40	13100.00	15.00	70.00	2.00	1.00	2.00	2.00	2.00		1.00
148.00	3.80	1.30	28.00	200.00	14.00	70.00	14.00	1.00	1.00	1.00	4.00		1.00
132.00	4.30	0.53	30.00	7700.00	13.00	60.00	2.00	1.00	2.00	2.00	2.00		1.00
143.00	3.00	3.42	25.20	14000.00	10.00	40.00	7.00	1.00	1.00	2.00	3.00		1.00
140.00	2.20	1.01	24.00	8500.00	10.00	78.00	6.00	1.00	1.00	2.00	2.00		1.00
140.00	3.70	0.89	36.00	13500.00	10.00	60.00	12.00	1.00	1.00	1.00	3.00		1.00
141.00	4.20	2.62	23.00	1250.00	10.00	60.00	13.00	1.00	1.00	1.00	4.00		1.00
148.00	2.80	1.09	26.00	5400.00	10.00	70.00	10.00	1.00	1.00	1.00	3.00		1.00
124.00	4.30	0.69	22.00	800.00	15.00	70.00	4.00	1.00	2.00	2.00	1.00		1.00
130.00	3.20	0.36	17.00	13500.00	12.00	60.00	8.00	1.00	1.00	2.00	3.00		1.00
137.00	3.30	0.57	33.00	1350.00	10.00	60.00	4.00	2.00	2.00	2.00	3.00		1.00
144.00	3.20	3.12	24.00	15400.00	15.00	60.00	4.00	2.00	2.00	2.00	3.00		1.00

ORGAI	SOUR	EMP/	DEFAB	FEBRI	FEBRI	FEBR	OTHE	OUT(	outcome_r	CMI	MIC C	MIC ⁻	MIC	MIC F	CPE IN(
1.00	5.00	1.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	1.00				10
2.00	4.00	2.00	1.00	1.00	2.00	2.00	2.00	1.00	1.00	0.00	8.00				12
2.00	2.00	3.00	3.00	1.00	1.00	2.00	1.00	1.00	1.00	5.00			>32		6
1.00	2.00	3.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	4.00	1.00				6
2.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	0.00	2.00	0.50	>8			6
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	2.00					3
2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	4.00					10
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	4.00					10
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	1.00					8
1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	3.00	1.00	4.00					6
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	6.00	1.00				15
1.00	4.00	2.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00	0.50				0
2.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	3.00	1.00	8.00	1.00				15
1.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	2.00	0.00	0.00	2.00				3
2.00	1.00	1.00	9.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00					15
1.00	1.00	3.00	8.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00			2	10
1.00	1.00	3.00	9.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00	1.00			>1024	12
2.00	1.00	3.00	1.00	1.00	2.00	2.00	1.00	1.00	1.00	0.00					7
1.00	2.00	3.00	1.00	1.00	1.00	2.00	1.00	2.00	0.00	0.00	1.00				12
2.00	1.00	3.00	7.00	1.00	2.00	2.00	1.00	1.00	1.00	0.00					7
2.00	2.00	3.00	7.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00	4.00	2.00		8	15.00
1.00	4.00	3.00	1.00	1.00	2.00	2.00	2.00	1.00	1.00	4.00					15
1.00	1.00	1.00	3.00	1.00	1.00	1.00	2.00	3.00	1.00	0.00	0.50	0.25			3.00
2.00	1.00	3.00	7.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00					10
1.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	1.00				10.00
1.00	3.00	3.00	3.00	1.00	1.00	2.00	2.00	3.00	1.00	1.00	0.60				4
1.00	1.00	3.00	6.00	1.00	1.00	2.00	2.00	2.00	0.00	3.00	1.00	3.00		####	6.00
2.00	3.00	3.00	1.00	1.00	1.00	1.00	1.00	2.00	0.00	5.00	0.50	>256			3
2.00	1.00	3.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	6.00	1.00				10.00
2.00	2.00	1.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	8.00	####		>32		10
2.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	1.00	>32	4.00		64	0.00
1.00	3.00	2.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	4.00	0.25				7
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00					3.00
2.00	1.00	3.00	9.00	1.00	1.00	1.00	2.00	2.00	0.00	4.00	1.00			>1024	6
1.00	1.00	1.00	7.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	0.50		32		3.00
2.00	1.00	1.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	####			128	6
2.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00	8.00				10.00
2.00	1.00	1.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	3.00	0.50				10
2.00	2.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	2.00	####	2.00		####	6.00
1.00	3.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	####		0.25			3
2.00	1.00	3.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	2.00		>32	1024	11.00
1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	3.00	1.00	1.00					12
1.00	5.00	3.00	6.00	1.00	2.00	2.00	2.00	1.00	1.00	4.00	0.50		>32		10.00
1.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	5.00	0.50				6
1.00	1.00	3.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	5.00					10.00
1.00	3.00	1.00	3.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	1.00				8
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	4.00					10.00
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00	1.00	8.00			10.00
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	3.00					3.00

2.00	1.00	3.00	1.00	1.00	2.00	2.00	2.00	1.00	1.00	6.00		1.50		7.00
2.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	3.00	1.00	1.00				7.00
1.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	2.00			3.00
1.00	5.00	2.00	3.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00	0.50		>32	12.00
1.00	5.00	2.00	1.00	1.00	2.00	2.00	2.00	1.00	1.00	0.00				10.00
2.00	1.00	1.00	6.00	1.00	1.00	1.00	2.00	1.00	1.00	3.00				15.00
2.00	1.00	1.00	4.00	1.00	1.00	1.00	2.00	2.00	0.00	2.00	####		1024	3.00
2.00	5.00	3.00	5.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	2.00	4.00		10.00
2.00	2.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	6.00	1.00			8.00
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	8.00	1.00			10.00
2.00	5.00	3.00	6.00	1.00	1.00	1.00	2.00	2.00	0.00	4.00	2.00			10.00
2.00	5.00	1.00	9.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00				10.00
2.00	2.00	3.00	6.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00				7.00
1.00	2.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	0.00	0.50			12.00
1.00	1.00	3.00	6.00	1.00	1.00	2.00	2.00	2.00	0.00	4.00	0.50			10.00
1.00	3.00	2.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00				7.00
2.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	6.00	2.00	2.00		7.00
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	6.00	4.00	4.00	>16	15.00
1.00	5.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	1.00			7.00
2.00	4.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	3.00				10.00
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	1.00		>32	6.00
1.00	1.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00	1.00		>32	4.00
2.00	4.00	3.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	3.00				6.00
2.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	2.00		>256	10.00
1.00	2.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00				9.00
1.00	5.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	4.00				15.00
1.00	1.00	3.00	8.00	1.00	2.00	2.00	2.00	1.00	1.00	0.00				7.00
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	0.00	####			7.00
1.00	2.00	3.00	1.00	1.00	1.00	1.00	2.00	3.00	1.00	0.00				12.00
1.00	1.00	1.00	8.00	1.00	1.00	2.00	1.00	1.00	1.00	0.00				7.00
1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00				6.00
1.00	1.00	1.00	7.00	1.00	1.00	1.00	2.00	1.00	1.00	6.00				15.00
1.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00				12.00
2.00	5.00	1.00	9.00	1.00	1.00	1.00	2.00	1.00	1.00	7.00				10.00
1.00	1.00	3.00	9.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00				10.00
2.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	2.00	0.00	0.00	0.50			3.00
2.00	2.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00				3.00
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	4.00				3.00
2.00	2.00	1.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00				3.00
2.00	4.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00	1.00			3.00
1.00	3.00	3.00	1.00	1.00	2.00	2.00	2.00	1.00	1.00	4.00				7.00
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	0.00				7.00
1.00	1.00	1.00	1.00	2.00	2.00	2.00	1.00	2.00	0.00	2.00	0.50			12.00
2.00	1.00	1.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	7.00				15.00
2.00	1.00	1.00	9.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00				15.00
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00	2.00	8.00		10.00
2.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	6.00	2.00	2.00		7.00
1.00	4.00	3.00	9.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00				12.00
1.00	5.00	2.00	9.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	0.25			3.00
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	2.00			12.00

2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	6.00	2.00				10.00
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	5.00					10.00
2.00	4.00	1.00	6.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	0.50				6.00
2.00	1.00	3.00	1.00	1.00	2.00	2.00	2.00	3.00	1.00	7.00					10.00
1.00	1.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	5.00	0.50				6.00
1.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	0.25				6.00
1.00	1.00	3.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	1.00	4.00	>32		10.00
2.00	1.00	3.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	3.00	####	8.00			10.00
2.00	3.00	3.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	0.50	4.00			7.00
1.00	2.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	1.00	0.50				7
2.00	1.00	2.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	####	####	8.00			10.00
2.00	1.00	3.00	9.00	1.00	1.00	2.00	2.00	1.00	1.00	0.00					12
2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00					6
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	7.00	0.50	0.50			6.00
2.00	1.00	1.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	1.00	1.00	>32		15.00
2.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00					15
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	0.00	0.50				7
2.00	1.00	3.00	8.00	1.00	1.00	1.00	2.00	3.00	1.00	3.00	2.00	2.00			12.00
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	7.00	1.00		>16		6
1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	3.00					11
1.00	3.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	3.00					7
1.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	1.00					3
1.00	1.00	2.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	3.00					6
1.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	4.00					10
1.00	1.00	2.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	3.00	0.25				10
1.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00					6
1.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00	1.00				6
1.00	4.00	2.00	1.00	1.00	1.00	1.00	2.00	2.00	0.00	1.00	1.00				7
1.00	4.00	3.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00					12
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	2.00					15
1.00	1.00	1.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	0.25			0.19	15
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00	####		>32		6
2.00	1.00	3.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	4.00	0.50				15
1.00	1.00	3.00	8.00	1.00	1.00	2.00	2.00	1.00	1.00	7.00					10
1.00	2.00	3.00	3.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00	1.00				15
2.00	2.00	3.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	2.00	2.00			32	15
1.00	1.00	1.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	0.75				6
1.00	1.00	3.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	0.00					3
1.00	1.00	3.00	9.00	1.00	1.00	1.00	2.00	2.00	0.00	2.00	0.50				10
1.00	3.00	1.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	4.00					3
1.00	1.00	3.00	1.00	1.00	1.00	1.00	2.00	3.00	1.00	0.00	####	4.00			8.00
2.00	1.00	3.00	8.00	1.00	1.00	1.00	2.00	1.00	1.00	4.00					10
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	2.00				3
1.00	3.00	2.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	0.00					0
1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00	3.00	1.00	2.00					6
2.00	1.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00					7
2.00	1.00	1.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00	1.00			48	10
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	2.00					6
2.00	1.00	2.00	1.00	1.00	1.00	1.00	2.00	1.00	1.00	0.00					12
1.00	1.00	3.00	5.00	1.00	1.00	1.00	2.00	2.00	0.00	0.00	0.50		>32		7

2.00	1.00	3.00	8.00	1.00	1.00	1.00	2.00	3.00	1.00	3.00	0.50				10
2.00	1.00	2.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	5.00		2.00			6
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	1.00				3
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	1.00	1.00	0.00	0.50				7
2.00	1.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	1.00		256		7
2.00	1.00	3.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	4.00	8.00	8.00			10.00
2.00	1.00	3.00	8.00	1.00	1.00	2.00	2.00	2.00	0.00	0.00	1.00	8.00			7.00
2.00	1.00	3.00	9.00	1.00	1.00	2.00	1.00	1.00	1.00	4.00	1.00		>32		15
1.00	1.00	3.00	5.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	0.25		###		10.00
2.00	1.00	3.00	5.00	1.00	1.00	2.00	2.00	3.00	1.00	3.00	0.25				15
2.00	1.00	3.00	8.00	1.00	1.00	2.00	1.00	2.00	0.00	0.00	####			128	3
2.00	5.00	3.00	1.00	1.00	1.00	2.00	2.00	2.00	0.00	3.00					10
2.00	1.00	2.00	1.00	1.00	2.00	2.00	2.00	2.00	0.00	5.00					6
1.00	1.00	3.00	1.00	1.00	1.00	2.00	1.00	2.00	0.00	5.00					6