# University of Latvia

# Medical Faculty

## DIPLOMA WORK

# Central venous catheter infections in hemodialysis patients

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**Riga 2013**

## ACKNOWLEDGEMENTS

First and foremost, I would like to thank my family for supporting me through the long journey of my medical studies. I am also grateful to Professor Žileviča for guiding me in this process of completing my thesis work, both regarding my work as well as morally.

I would also like to extend my acknowledgements to Dr. Ziediņa for helping me decide my theme as well as providing me with clinical information and Elina Dimiņa for her hand in processing the information in the database.

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## 1. LIST OF ABBREVIATIONS

AVF- Arteriovenous fistula

AVG- Arteriovenous graft

CDC- Center of disease control

CLSI- Clinical and Laboratory Standards Institute

CRBSI- Catheter related blood stream infection

CVC-Central venous catheter

EPS- Extracellular polymeric substance

ERAR- European renal association registry

ESRD-End stage renal disease

HD- Hemodialysis

IDSA- Infectious Diseases Society of America

KDOQI- Kidney Disease Outcomes Quality Initiative

MDR- Multiple drug resistance

MIC- Minimal inhibitory concentration

MR- Methicillin resistant

MRSA- Methicillin resistant staphylococcus aureus

MS-Methicillin sensitive/ Methicillin susceptible

MSSA- Methicillin sensitive staphylococcus aureus

NKF-National Kidney Foundation

PSKUS- Pauls Stradins Clinical University Hospital

TEE- Transesophageal echography

TMP-SMZ- Trimethoprim-sulfamethoxazole

USRDS- United States Renal Disease Society

VRE- Vancomycin resistant enterococci

## 2. ABSTRACT

The study was designed to analyze the spectrum of bacterial agents that cause central venous catheter related infections in hemodialysis patients in Pauls Stradins Clinical University Hospital nephrology department and their sensitivity to antibacterial therapy in order to be able to recommend an optimal empirical therapy.

The study was retrospective and the information was collected using specially designed forms. Interpretation of the data was done using Microsoft excel 2007 program.

Among 33 patients that were found, 38 pathogens were discovered as five cases were polymicrobial. . 94.7% of the bacteria were gram positive and 5.3% were found to be gram-negative. Among the gram-positive, 57.9% were Staphylococcus coagulase-negative, 31.6% were Staphylococcus aureus and 5.3% were Enterococcus spp. with none being vancomycin resistant. All the Staphylococcus aureus strains were methicillin sensitive. 77% of the coagulase-negative Staphylococcus strains were methicillin resistant. Among the gram-negative bacteria 50% was Enterobacter cloacae and 50% was Pseudomonas aeruginosa.

The resistance against β-lactam antibacterial therapy was observed in 84.8% of bacteria and methicillin resistance in 44.7% of bacteria.

After analyzing the results from this study, the recommended empirical therapy for central venous catheter infections among hemodialysis patients in Pauls Stradins Clinical University Hospital nephrology department is combination of vancomycin plus ceftazidime.

## KOPSAVILKUMS

Pētījums tika izstrādāts, lai analizētu dažāda spektra baktērijas, kas izraisa centrālā venozā katetra saistītās infekcijas hemodialīzes pacientiem un to jūtīgumu uz antibakteriālo terapiju, lai varētu rekomendēt optimālu empīrisko terapiju Paula Stradiņa Klīniskās Universitātes slimnīcas nefroloģijas nodaļā.

Pētījums bija retrospektīvs un informācija iegūta, izmantojot speciāli izstrādātas formas. Datu interpretācīja tika veikta, izmantojot Microsoft Excel 2007 programmas.

Medicīnas kartiņu arhīvā bija atrasti 33 pacienti un viņiem tika atklāti 38 patogēni. No visas pacientu kopā 5 bija polimikrobu infekcijas. 94.7% no baktērijām bija gram pozitīvas un 5,3%, gram negatīvas. Starp gram pozitīvām baktērijām 57,9% bija Staphylococcus koagulāzes negatīvās, 31,6% Staphylococcus aureus un 5,3% Enterococcus, no kurām neviena nebija vankomicīna rezistenta. Visi Staphylococcus aureus bija meticilīna jutīgi. 77% no koagulāzes negatīviem stafilokokokiem bija meticilīna rezistenti. No gram-negatīvām baktērijām 50% bija Enterobacter cloacae un 50% Pseudomonas aeruginosa.

Baktēriju rezistence pret antibakteriālo terapiju procentuāli bija šāda: pret β-laktāma antibakteriālo terapiju- 84,8% un pret meticilīna 44.7%.

Analizējot šī pētījuma rezultātus, ieteicamā empīriskā terapija, Paula Stradiņa Klīniskās Universitātes slimnīcas nefroloģijas nodaļā, centrālā venozā katetra inficētiem hemodialīzes pacientiem, ir kombinētā terapija- vankomicīns kopā ar ceftazidīmu.

# 3. AIMS AND OBJECTIVES

The aim of this study is to analyze central venous catheter related infections in hemodialysis patients in the nephrology department of Pauls Stradins Clinical University Hospital.

**Objectives**:

1. To analyze the spectrum of etiological agents that cause the central venous catheter related infections in hemodialysis patients.
2. To observe the choice of empirical antibacterial therapy in this group of patients.
3. To study and suggest optimal antibacterial therapy in this group of patients after antimicrobial susceptibility of the isolated agents is obtained.

# 4. INTRODUCTION

Hemodialysis (HD) is one of the methods of renal function replacement, in which, with the use of a HD machine, creatinine, urea and extra fluid are removed from the blood in conditions when both the kidneys are no longer capable of performing their role in fluid and waste excretion [National Kidney Foundation]. HD is becoming more important and performed more often as there has been a rise in chronic kidney disease. Worldwide, in 2008, 2.3 million patients were registered to have end stage renal disease (ESRD) [Wolfgang et al, 2010]. In Latvia, in 2010, 440.6 patients were registered with ESRD per million population as compared with 391.2 per million population in 2007 [European renal association registry, 2007]. In the United States, the prevalence of ESRD is increasing as well [National Kidney Foundation, 2002] and the number of patients enrolled in the ESRD Medicare program has increased from approximately 10,000 beneficiaries in 1973 to 86,354 in 1983 and to 547,982 as of 2008 [USRDS 2010 Annual Data Report].

As the use of central venous catheters (CVC)s is increasing to perform HD and one of the possible and frequently occurring complications is HD catheter infection, it is important to not only be aware of such an occurrence but also be able to treat the episode efficiently all the while try to reduce the prevalence.

HD catheter infections can cause sepsis, suppurative thrombophlebitis, endocarditis, septic arthritis, osteomyelitis, and/or abscess [Allon et al, 2004]. To avoid these complications, knowledge of types of pathogens, trends, resistance to antibiotic therapy and success rate of the type of therapy chosen are very important.

As CVC infections in HD patients is a major problem all over the world, this study was designed to understand the spread of microorganisms causing HD catheter infections and their susceptibility to antibacterial therapy, to be able to treat it better with the most effective empirical antibacterial therapy.

# 5. LITERATURE REVIEW

## 5.1. CVC infection

The infections associated with HD catheters include local exit site infection as well as systemic bacteremia. The majority of bacteremia among HD patients are caused by HD catheters. According to Center of Disease Control (CDC) criteria, HD catheter infections can be classified according to the following types: 1) Exit-site infection where in the inflammation is confined to the area surrounding the catheter exit site, not extending superiorly beyond the cuff if the catheter is tunneled, with exudate culture confirmed to be positive. 2) Tunnel infection where the catheter tunnel superior to the cuff is inflamed, painful and may have drainage through the exit site that is culture positive. 3) Catheter related bacteremia where blood cultures are positive for the presence of bacteria with or without the accompanying symptoms of fever. Catheter related infections can further be sub-classified as the following: A) Definite bloodstream infection when the same organism from a semi quantitative culture of the catheter tip (> 15 colony forming units per catheter segment) and a peripheral or catheter blood sample in a symptomatic patient with no other apparent source of infection. B) Probably bloodstream infection when defervescence of symptoms after antibiotic therapy with or without removal of catheter, in the setting in which blood cultures confirm infection, but catheter tip does not (or catheter tip does, but blood cultures do not) in a symptomatic patient with no other apparent source of infection. C) Possible bloodstream infection when defervescence of symptoms after antibiotic treatment or after removal of catheter in the absences of laboratory confirmation of bloodstream infection in a symptomatic patient with no other apparent source of infection [IDSA guidelines, 2009].

## 5.2. Vascular access for HD

There are three methods of vascular access for HD: CVC, AVF and AVG [National Kidney Foundation]. Further, the text is about CVCs. The aim of the CVCs is to achieve access of large veins i.e. V. cava superior or inferior via V. jugularis interna, V. subclavia or V. femoralis, so that large amounts of blood can flow through the catheter. CVCs may be tunnelled, cuffed or non-tunneled non-cuffed [National Kidney Foundation].

Bacteremia generally results from contamination of the catheter lumen or migration of bacteria from skin puncture site [Dahlberg et al, 1986; Nielsen et al, 1998]. This migration usually limits the duration of use of non-tunneled catheters [Dahlberg et al, 1986]. The risk of infection with tunneled catheters is significantly reduced because the cuff, which is usually positioned just proximal to the catheter exit site, serves as a barrier to the migration of bacteria from the skin. The bacteremia rate ranges from 3.8 to 6.6 episodes per 1000 days in non-tunneled catheters where as the range of bacteremia rate using tunneled catheters is 1.6 to 5.5 episodes per 1000 days [Hannah et al, 2002; Zaleski et al, 1999; Saxena et al, 2005; Fernandez-Cean et al, 2002]. Also, catheter-associated bacteremia is associated with a 22 to 38 percent rate of metastatic infectious complications or death [Marr et al, 1997]. The wide range of differences reflects the differences in practice. Rates as low as 1 episode per 1000 days have also been achieved with detailed catheter protocols [Beathard et al, 2003].

For non-tunneled catheters, the development of exit-site infection or bacteremia requires immediate removal of the catheter and appropriate intravenous antibiotic therapy [Ishani et al, 2005; K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations 2006; Oliver et al, 2000]. Exit-site infections associated with tunneled catheters may respond to antibiotics therapy even without the removal of the HD catheter.

### 5.2.1. Non-tunneled catheters

Non-tunneled HD catheters are designed for short-term use and are the preferred catheter for immediate HD vascular access. Various non-tunneled catheters are available which are composed of materials such as polyurethane, polyethylene, polyvinyl chloride, and medical grade silicone. Their luminal diameters range from 1 to 2 mm and pump flow rates are 200 to 300 ml/min [Contreras et al, 2003]

The non-tunneled catheter tips should be in the superior vena cava and confirmed by using chest radiograph or fluoroscopically at the time of placement before initiating dialysis therapy and they should be used only in conditions when the patient is hospitalized for less than one week. There should be a plan either to discontinue or to change to tunneled catheter within a week. [IDSA guidelines, 2009]

The duration of usage of non-tunneled catheters varies with location of insertion. Mechanical malfunction and infectious complications are the primary reasons for removal of

non-tunneled dialysis catheters. The infection rate in non-tunneled catheters inserted in V. jugularis interna suggest that they should be used for no more than one week [Gulati et al, 2003; Butterly et al, 2000] and the infection and dislodgement rates for femoral catheters require that they be left in place for no more than five days and only in bed-bound patients with good exit-site care. According to another study, catheters inserted in V. Jugularis interna and V. Subclavia are generally suitable for two to three weeks of use although longer periods have also been reported [Ponikvar R et al, 2005] and femoral catheters are usually limited to a single dialysis session in ambulatory patients, and three to seven days in bed-bound patients [Cheesbrough et al, 1986; Weijmer et al, 2004; Dugué et al, 2012; Vascular Access 2006 Work Group].

After two weeks of insertion, the rate of infection rises in both the V. femoralis and V. jugularis interna [Oliver et al, 2000]. Infection rates per 1000 days at risk for non-tunneled catheter were found to be more than five times as great as with internal jugular tunneled catheters and almost seven times greater with femoral non-tunneled catheters. The rate of infection also varies according to the site of catheter insertion. Studies show that the highest risk is with femoral catheters, followed by jugular and then subclavian vein catheters. In non-tunneled catheters, femoral catheters are found to have the highest infection rate, averaging 7.6 episodes per 1000 days, with more than 10% being infected by one week [Oliver et al, 2001]. In another study of 105 non-tunneled HD catheters (79 subclavian and 26 jugular), a significantly higher risk of catheter-related bacteremia was associated with internal jugular access as compared with subclavian venous access [Kairaitis et al, 1999]. Another study of 318 new HD catheters, a significantly higher risk of bacteremia was recorded after insertion into the femoral vein compared with internal jugular vein placement [Oliver et al, 2000]. In contrast, a large trial in which 750 dialysis patients were randomly assigned to receive short-term jugular or femoral venous access, no significant differences in infection rates were found for jugular and femoral venous catheterization (2.3 versus 1.5 per 1000 infections per catheter-days, respectively) [Parienti et al, 2008]. Again, the large differences reflect the difference in practice.

### 5.2.2. Tunneled catheters

Tunneled HD catheters are associated with lower rates of infectious complications as compared with non-tunneled catheters [Weijmer et al, 2008]**.** The larger lumen size of tunneled catheters also allows for greater blood flow rates (>400 ml/min) than non-tunneled catheters.

Tunneled catheters are mainly used for intermediate or long-term (>1-2 weeks) HD vascular access [Schwab et al, 1994]. Tunneled HD catheters are generally double lumen catheters with a polyester cuff generally positioned at the skin exit site which allows tissue in growth that seals off the catheter tunnel. They are composed of silicone and other soft flexible polymers like thin polyurethane, which are less thrombogenic than the materials used in non-tunneled catheters. There is no proven advantage of one long-term catheter design over another, although this area is undergoing a great deal of study. Catheter choice should be based on local experience, goals for use and cost.

At the time the tunneled catheter is inserted, it should be in the midatrium, with the arterial lumen facing the mediastinum. It should have their tips within the right atrium confirmed by fluoroscopy for optimal flow and they should not be placed on the same side as a maturing AV access [IDSA recommendations, 2009].

The survival of tunneled HD catheters is highly variable. One-year use of tunneled HD catheters is as low as 9 percent, but with variations [Hodges et al, 1997]. One study found a 74 percent one-year and a 43 percent two-year catheter survival. In another study, one-year patency was 50 percent when the catheter was used as permanent access [Suhocki et al, 1996]. Bacteremia was the main cause of removal of catheters.

The advantages of tunneled HD catheters are that they are universally applicable, they may be inserted into many sites with relative ease, there is no time required for maturation of the site and can be used immediately, they do not have short-term hemodynamic consequences such as changes in cardiac output or myocardial load and they have the ability to provide vascular access during a period of months, allowing for fistula maturation in patients who require immediate HD [Albers et al, 1994]. On the other hand, tunneled venous catheters have high morbidity due to thrombosis and infection, there is a risk for permanent central venous stenosis or occlusion, discomfort and cosmetic complaints are found and

overall they do still have a lower use-life as compared with other methods of vascular access such as AVF or AVGs [Albers et al, 1994].

The preferred site for insertion of tunneled catheters is the right internal jugular vein because it offers a more direct route to the right atrium that the left-sided great veins. This location is also associated with lower risk for complications compared with other potential catheter insertion sites. [Vanholder et al, 1994]. Placement of the catheter in the left internal jugular vein potentially puts the left arm's vasculature in jeopardy for a permanent access on the ipsilateral side. Femoral and translumbar vein placement are associated with the greatest infection rates compared with other sites. Catheters should not be placed in the subclavian vessels on either side due to the high risk of stenosis [Kamran et al, 2003], which can permanently exclude the use of upper extremity vascular access.

Overall, the use of catheters is first choice for long-term vascular access is discouraged because of the risks of infection, thrombosis, stenosis and inconsistent blood flow.

### 5.2.3. Port system catheters

In an effort to surmount many of the infection issues that are related with long-term catheters, port catheter systems which are a special type of catheter based device system in which the catheter tubing is connected to a subcutaneously placed device have been designed. At the moment there is only one port device used for the purpose of HD and according to this, the access to the catheter lumen occurs percutaneously by using a buttonhole technique. The port system has a pinch valve mechanism that required special cannulation needles to open the valves that access the circulation. There is data that supports the use of these port systems as a bridge device until permanent vascular access in maturing or has been placed and also in those who are at a greater risk for fistula maturation failure [Canaud et al, 1999]. It is also used well in patients who have exhausted other access options [Rayanet al, 2003] and in children [Nosher et al, 2001]. The most significant disadvantage of this method is the infection of the implantation pocket. This can be treated, but of course prevention must be the goal.

## 5.3. Pathogenesis

HD catheter infections may occur by either of the following methods: The organism may migrate from the skin along the outside of the catheter into the bloodstream or direct inoculation can also occur from a biofilm containing pathogenic organism that forms on the inner surface of the catheter. (A biofilm is an aggregate of microorganisms in which cells adhere to each other on a surface. These adherent cells are frequently embedded within a self-produced matrix of EPS, also known as slime [Allon et al, 2004]. The vascular catheters are colonized by microorganisms within 24 hours after insertion [Raad et al, 1993]. The formation of the biofilm itself can occur both on the external and internal surface of the catheters. It is produced by a combination of host factors such as fibronectin, fibrinogen, fibrin and extracellular polysaccharides and microbial products such as glycocalyx or slime. It also plays a role in the antibacterial resistance [Lewis et al, 2001]. Although there has been documented by a variety of methods, the relationship of thrombin sheath to infection has not been evaluated clinically. The proteins which are in the fibrin sheath provide adhesion for organisms binding, particularly staphylococcus aureus but whether the intervention using some fibrinolytics would reduce the infection rate in unknown and still needs to be researched [KDOQI guidelines].

## 5.4. Risk factors

The most important risk factor for HD catheter infections is prolonged duration of usage. It has been shown that the likelihood of HD catheter infection is 35 and 48% within 3 and 6 months respectively [Lee et al, 2005].

Other risk factors include previous catheter related infections, recent surgery, diabetes mellitus, iron overload, immunosuppression and hypoalbuminemia [Kozeny et al, 1984; Tanriover et al, 2000]. Interestingly, HIV infection has not been associated with a higher risk of HD catheter infection [Mitchell et al, 2006].

## 5.5. Microbiology

The most common HD catheter infection causative agents are gram-positive organisms. Staphylococcus aureus and coagulase negative Staphylococcus account for 40-80% of all HD catheter infections. Other predominant gram-positive agent is Enterococcus spp. Gram-negative organisms account for 30-40% of all HD catheter infections. MRSA infection has also become an important causative agent of HD catheter infections [Allon et al, 2004; Marr et al, 1997; Jacobsson et al, 2007; Swartz et al, 1994; Beathard et al, 1999; Dryden et al, 1991].

### 5.5.1. Coagulase-negative Staphylococcus

The most common causes of catheter-related infections are coagulase-negative Staphylococci. In most cases the infection has a benign course. It is often a problem to interpret positive blood cultures for coagulase-negative Staphylococci are they are the most common contaminants, while also being the most common agents that cause CRBSI. If a catheterized patient is found to have a single positive blood culture that grows coagulase-negative Staphylococci, then additional blood cultures should be obtained through the suspected catheter and from a peripheral vein before the initiation of antibiotics in order to verify a true CRBSI [Bouza et al, 2007]. For uncomplicated CRBSI caused by coagulase-negative Staphylococci, 5-7 days of antibiotic therapy should be used if the catheter is removed and 10-14 days in combination with antibiotic lock therapy, if the catheter is retained. Exception to this treatment is Staphylococcus lugdunensis which should be approached similarly to Staphylococcus aureus [Zinkernagel et al, 2008]. The choices of antibiotics for MS coagulase-negative Staphylococcus are penicillinase-resistant penicillin (e.g. nafcillin or oxacillin 2g q24h or alternatively first generation cephalosporins, vancomycin or TMP-SMZ if sensitive. Although vancomycin should be avoided if possible due to concerns of increasing vancomycin resistance. For MR coagulase-negative Staphylococci vancomycin is the choice of antibiotics at 15mg/kg iv q12h or alternatively daptomycin at 6mg/kg per day or linezolid. [IDSA recommendations, 2009]

### 5.5.2. Staphylococcus aureus

Patients that have CRBSI due to Staphylococcus aureus should have the catheter removed and receive 4-6 weeks of antibiotics due to the risk of infective endocarditis [Rosen et al, 1999; Pigrau et al, 2003] unless the patient is not diabetic, immunosuppressed, if the patient has no prosthetic intravascular device, if there is no evidence of endocarditis, thrombophlebitic or TEE and ultrasound and in these situations, a minimum of 14 days antibacterial therapy is a must. Patients that are considered for a shorter duration of therapy must have a TEE done 5-7 days after the initiation of bacteremia to minimize the possibility of false-negative results. Also additional TEE should be obtained for patients with persistent fever or bloodstream infection greater than 72 hours after catheter withdrawal and initiation of targeted antibacterial therapy if a previous TEE did not have previous signs of endocarditis or metastatic infection. Short term catheters should be removed immediately whereas long term catheters should be removed unless there are specific contraindications such as lack of another venous access. The recommended antibacterial therapy for MS staphylococcus aureus is penicillinase-resistant penicillin such as nafcillin or oxacillin 2g q24h or alternatively, cefazolin 2g q8h or vancomycin 15mg/kg q12h. In case of MR cases, vancomycin should be used at 15mg/kg q12h or alternatively daptomycin 6-8mg/ķg per day or linezolid [IDSA recommendations, 2009].

### 5.5.3. Enterococcus spp.

Enterococci account for 10% of all nosocomial blood stream infections [Wisplinghoff et al, 2004], many of which are caused by intravascular catheters. Enterococcal bacteremia that persists for greater than 4 days is associated with mortality. [DiazGranados et al, 2005; Bhavnani et al, 2000]. A 7-14 day course of antibacterial therapy is recommended for uncomplicated enterococcal CRBSI in which long term catheter is retained and antibiotic lock solution is used or when short term catheter is removed. The choice of antibiotic therapy in ampicillin susceptible enterococcus is ampicillin 2g q4h or q6h with or without aminoglycoside 1mg/kg q8h or alternatively vancomycin. If the enterococcus is ampicillin resistant but vancomycin sensitive, then vancomycin with or without aminoglycoside and finally if the enterococcus is resistant to vancomycin, then linezolid 600mg q12h or daptomycin 6mg/kg per day should be used [IDSA recommendations, 2009].

### 5.5.4. Gram-negative bacilli

Risk factors for infection due to gram negative bacilli are being critically ill, neutropenic, having received prior antibiotic therapy and having a femoral catheter. Over the past two decades the rate of gram negative infection due to intravascular catheter has decreased [Seifert et al, 1997]. Unfortunately, the resistance to third and fourth generation cephalosporins has increased [Jacoby et al, 2005; NNIS System Report, 2004; Safdar et al, 2002]. E. coli and klebsiella species that are ESBL negative are best treated with a third generation cephalosporin (e.g. ceftriaxone 1-2g per day) or alternatively ciprofloxacin or aztreonam and ESBL positive specially are best treated with carbapenem (e.g. ertapenem 1g per day, imipenem 500 mg q6h, meropenem 1h q8h or alternatively ciprofloxacin or azteonam. Enterobacter species and Serratia marcescens are best treated with carbapenems or alternatively cefepine or ciprofloxacin. Acinetobacter species are recommended to be treated with ampicillin/sulbactam 3g q6h or carbapenem. Pseudomonas aeruginosa is best treated with a fourth generation cephalosporin (cefepime 2g q8h) or carbapenem (imipenem 500mg q6h) or piperacillin and tazobactam 4.5g q6h with or without aminoglycoside. Finally burkholderia cepacia is recommended to be treated with TMP-SMZ 3-5 mg/kg q8h or carbapenem. [IDSA recommendations, 2009]

### 5.5.5. Candida spp.

In cases of CRBSI due to candida species, the catheters should be removed. For patients with candidemia and a short term CVC for whom candidemia is obvious, the catheter should be removed and the catheter tip should be sent for culture. Alternatively for patients with limited venous access, exchange over a guidewire is done and if the catheter is colonised with the same species of candida are found in the percutaneous blood culture, the CVC must be removed. Anti-fungal therapy is recommended for all cases of CRBSI, including those in which the clinical picture improves once the catheter has been removed. Echinocandin or fluconazole are the main choice of anti fungal medication. [IDSA recommendations, 2009]

## 5.6. Clinical Manifestation

The symptoms of HD catheter infections are quite non-specific, with fever and/or chills being the most sensitive feature. Other clinical manifestations may include catheter dysfunction, hemodynamic instability, and altered mental status along with other symptoms and/or signs of sepsis such as hypothermia, acidosis and hypotension. Also oedema, pain, increased sensitivity, hyperaemia, chills and bad odour from the site are signs of the possibility of an infection [KDOQI guidelines]

According to three prospective clinical studies, the presence of fever or chills in catheter dependent HD patients was associated with positive blood cultures in 60-80% of patients [Krishnasami et al, 2002; Vardhan et al, 2002]. A large number of HD catheter infections occur in the absence of evidence of an exit site infection. In a series of 1436 episodes of tunneled dialysis catheter related bacteremia, a definite purulent exit site infection was observed in only 4.6% of cases [Sychev et al, 2011].

## 5.7. Diagnosis

The definitive diagnosis of HD catheter infection requires one of the following:

- Concurrent positive blood cultures of the same organism from the catheter and a peripheral vein.
- Culture of the same organism from both the catheter tip and at least one percutaneous blood culture.
- Culture of the same organism from two peripherally drawn blood cultures and an absence of an alternate focus of infection.

[Chatzinikolaou et al, 2004]

In HD patients in whom a peripheral blood sample cannot be obtained, HD catheter infection can be diagnosed if two cultures drawn at separate times (10-15 minutes apart) are positive with a credible pathogen in a patient with signs and symptoms of bacteremia, but without evidence of an alternate source of infection.

There are certain limitations of the diagnostic criteria in HD patients such as obtaining peripheral blood cultures may not be possible in up to 40% of dialysis patients, either because their peripheral veins cannot be accessed or because an existing vein needs to be preserved for future fistula or graft creation [Allon et al, 2009; Mermel et al, 2009] or if the symptoms occur during a dialysis session, there is no meaningful difference between samples drawn from peripheral veins and those drawn from catheters or dialysis tubing since systolic blood is circulating through the dialysis system. Also, handling of blood cultures in outpatient setting is frequently less than ideal. Variable periods before culture bottles are eventually placed in an incubator and differences in temperature during transport to a microbiology laboratory are some of the limitations [Allon et al, 2009].

## 5.8. Treatment

The treatment of HD catheter infection is based on antibacterial therapy and possible removal of the catheter. Antibiotic therapy is administered to all HD patients suspected to have catheter infection. First as empiric therapy after cultures are taken and submitted, followed by tailored therapy once the result of the culture and antibiotic sensitivity tests are available.

### 5.8.1. Empiric Therapy

Antibacterial therapy is initiated very often in catheter-related infections empirically. As mentioned earlier, HD catheter infections can be caused by both gram-positive and gram-negative organisms. Therefore, the empiric therapy administered should cover both gram-positive and gram-negative organisms. Also, the severity of the patient's clinical disease, the risk factors for infection, the likely pathogen associated with the specific catheter or device and the general microbial epidemiology should be taken into consideration while prescribing empirical antibacterial therapy.

Coagulase-negative Staphylococci are the most common cause of catheter-related infection and most of them exhibit methicillin resistance, so that should be taken into

consideration while prescribing empirical therapy [Miragaia et al, 2002; Pottumarthy et al, 2005]. Vancomycin is associated with a low clinical success rate in treating MRSA bacteremia when the MIC is greater than or equal to 2µg/mL [Moise et al, 2007; Sakoulas et al, 2004].

According to the recommendations by the IDSA, vancomycin should be used for empirical therapy in health care settings with an increased prevalence of methicillin-resistant Staphylococci. If the prevalence of vancomycin MIC is greater than or equal to 2µg/mL, then alternative agents such as daptomycin should be used. Linezolid should not be used as empirical therapy. It should be reserved for specific conditions only, due to the fear of resistance. Empirical therapy should also have coverage for gram-negative bacilli based on the local antimicrobial susceptibility data and the severity of the disease (e.g. fourth generation cephalosporin, carbapenem or a β-lactam/β-lactamase combination, with or without an aminoglycoside). Since the frequency of aminoglycoside ototoxicity may be quite high, some experts prefer the use of ceftazidime over gentamicin. Others believe that is it better to use gentamicin as empiric therapy and a less toxic non-aminoglycoside when the culture result and sensitivity results are available [Feldman et al, 2007].

Empirical combination antibacterial coverage for MDR gram-negative bacilli, such as Pseudomonas aeruginosa should be used when CRBSI is suspected in patients with neutropenia, severely ill patients with sepsis, or patients known to be colonized with such pathogens, until the culture and susceptibility data are available. Also, in patients suspected to have CRBSI if femoral catheters have been used, gram-negative coverage should be added to the gram-positive coverage as well [IDSA recommendations, 2009]

Empiric therapy can be stopped if the initial blood cultures have negative results or if there is no identified source of infection and signs and symptoms of the infection have resolved [IDSA recommendations, 2009]

### 5.8.2. Targeted therapy

Once the organism and sensitivity have been identified, the antibiotic regimen should be modified accordingly.

- Methicillin-resistant Staphylococcus- Continue to administer vancomycin. If allergic to it, then daptomycin should be administered.
- Methicillin-sensitive Staphylococcus- Once the Staphylococcus organism is established to be methicillin-sensitive, vancomycin should be substituted with cefazolin (a first generation cephalosporin) in patients who are not allergic to it. The preference of use of cefazolin in this setting is due in part due to the observation that the widespread use of vancomycin has been associated with an increasing incidence of infections due to vancomycin-resistant enterococci [Tokars et al, 1998]. In addition, cefazolin is as or more effective than vancomycin for treatment of methicillin-sensitive Staphylococcal infection [Stryjewski et al, 2007; Marx et al, 1998; Fogel et al, 1998; Chan et al, 2012].
- Vancomycin-resistant enterococcus- Vancomycin-resistant enterococcus should be treated with daptomycin.
- Gram-negative organisms- 95% of gram-negative bacteria isolated in HD catheter infection are sensitive to both aminoglycosides and third- generation cephalosporins [Poole et al, 2004; Krishnasami et al, 2002].

The dose-related details for tailored therapy have been mentions in an earlier section ‘Microbiology’ for the various causative agents in catheter related infections.

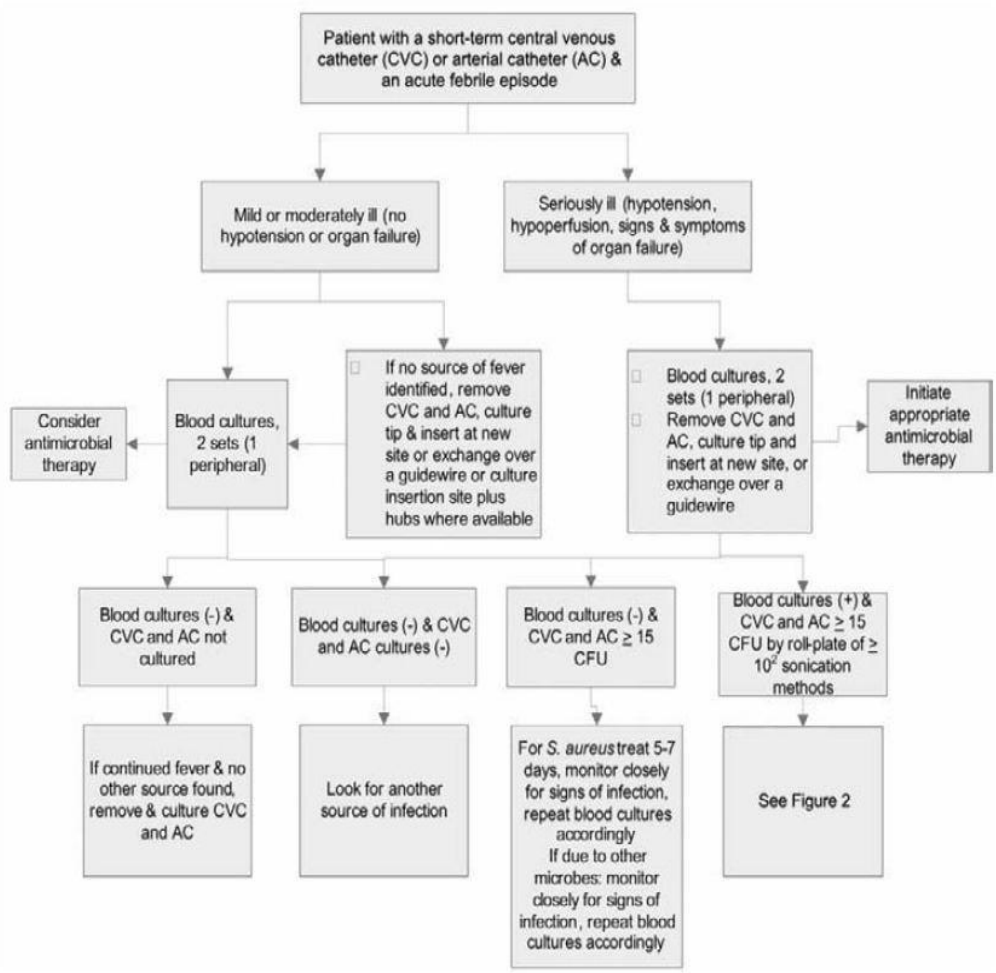


Figure 1: Methods for the diagnosis of acute fever for patients suspected of having short- term CVC according to the IDSA guidelines 2009.

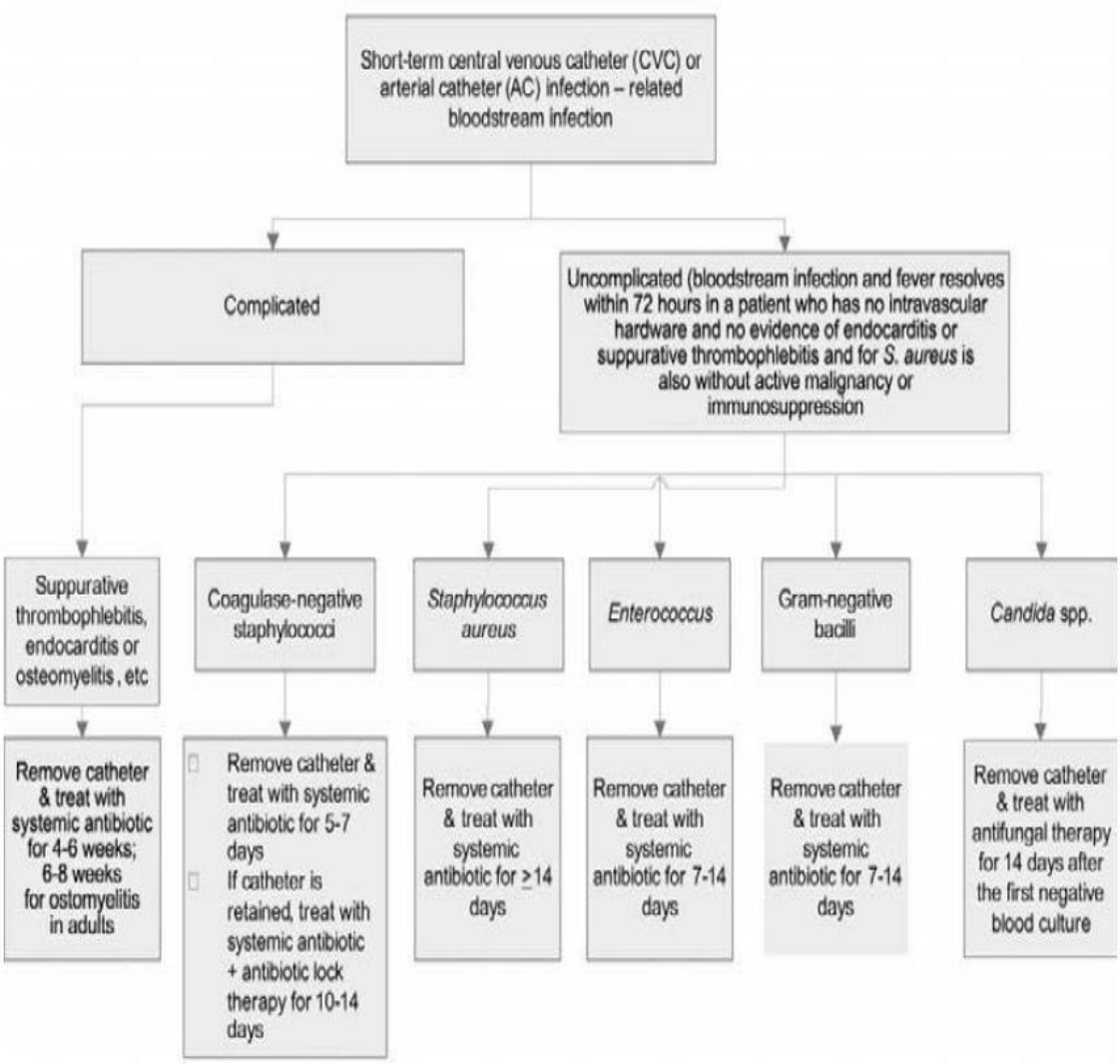


Figure 2: Approach to the management of patients with short-term CVC related bloodstream infection according to the IDSA guidelines 2009.

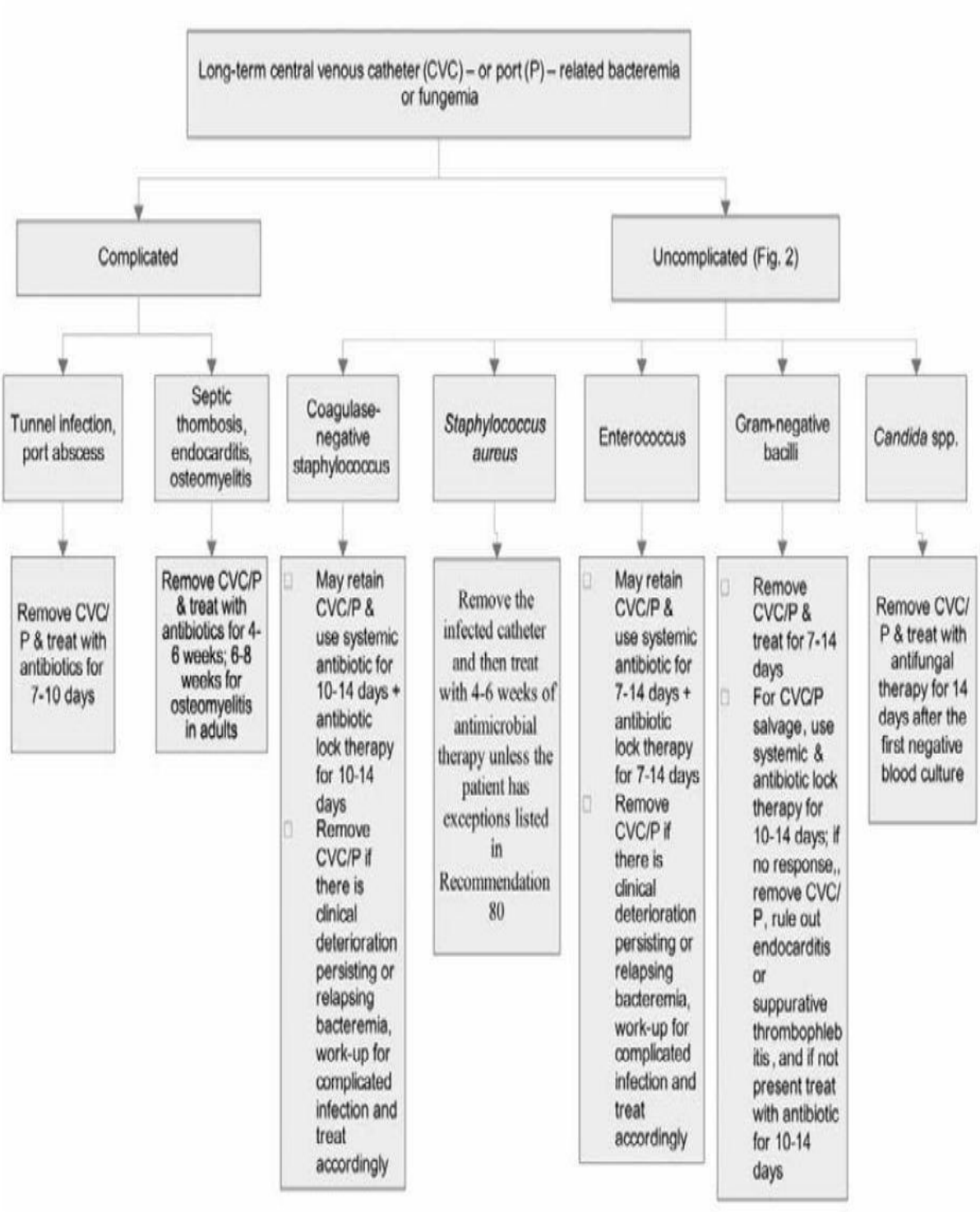


Figure 3: Approach to the treatment of patients with long-term CVC or port-related bloodstream infection according to IDSA guidelines 2009.

## 5.9. Catheter management

The optimal management of patients with HD catheter infection is difficult as the catheter is the source of the infection as well as the vascular access necessary for the HD.

Systemic antibiotic therapy is provided for all patients with HD catheter infections. Non-tunneled HD catheters should be removed immediately where as tunneled HD catheters may be managed by the following methods:

- The catheter can be removed immediately with placement of a temporary non-tunneled catheter for vascular access. After the infection is cured, a new permanent HD catheter can be inserted. This is generally the best option for achieving cure of the infection. Severe mortality and morbidity may occur in some patients with certain signs and/or symptoms in whom the infected catheter has not been removed. Hence, immediate removal of the HD catheter is recommended in circumstances such as severe sepsis, hemodynamic instability, evidence of metastatic infection, signs of accompanying exit-site infection, persistence of fever after 48-72 hours after initiation of antibiotics to which the organism is susceptible or if the infection is due to Staphylococcus aureus, Pseudomonas spp. or multiply-resistant bacterial pathogens [IDSA recommendations, 2009]
- Replacement of the infected catheter via exchange over a guide wire can be done in cases when patients are initially bacteremic but lack the above mentioned indications for immediate catheter removal. Also in cases when the removal of the catheter is not feasible or practical. It can be done before the next scheduled dialysis session.
- The use of antibiotic lock solution in the infected catheter is a method of treatment of HD catheter infection used together with systemic antibacterial therapy. It can be used as an alternative to HD catheter removal. The goal of the antibiotic lock solution is to kill the bacteria present in biofilm that frequently adhere to the catheter lumen and to try to achieve successful treatment of the infection while leaving the vascular access for dialysis. It is important to know that both antibiotic lock solution and systemic antibiotic therapy should be administered together [Allon et al, 2009].

### 5.9.1. Antibiotic lock solution

The antibiotic lock solution typically consists of an anticoagulant (heparin or citrate) and high concentrations of an antibiotic. This solution is administered after every dialysis session instead of the standard heparin locks. The duration of the antibiotic lock is as long as the systemic antibiotic therapy. Following are the various antibiotic lock solutions and their constituents [Allon et al, 2009]:

- Vancomycin/ceftazidime/heparin- Vancomycin (1ml of 5mg/mL in saline) plus ceftazidime (0.5mL of 10mg/mL in saline) plus heparin (0.5mL of 1000 U/mL solution)
- Vancomycin/heparin- Vancomycin (1mL of 5mg/mL in saline) plus heparin (1mL of 1000U/mL solution)
- Ceftazidime/heparin- Ceftazidime (1mL of 10mg/mL in saline) plus heparin (1mL of 1000U/mL solution)
- Cefazolin/heparin- Cefazolin (1mL of 10mg/mL in saline) plus heparin (1mL of 1000U/mL solution)

Antibiotic lock solution typically consists of the same type of antibacterial drug used for empiric therapy and adjusted accordingly once the culture and sensitivity results are available. The success rate of an antibiotic lock depends on the infecting organism. The success rate was highest 87-100% in patients with gram negative infections, 75-84% in patients with Staphylococcus epidermidis infections, 61% for Enterococcus infections but only 40-55% in patients with Staphylococcus aureus infections [Maya et al, 2007; Poole et al, 2004; Vardhan et al, 2002; Fernandez-Hidalgo et al, 2006; Peterson et al, 2009].

If fever persists 48-72 hours after initiation of systemic antibacterial therapy and antibiotic lock solution, the infected catheter should be removed. Leaving the infected catheter in HD patients has no role in the treatment of catheter infection unless antibiotic lock solution is used. The biofilm forms rapidly on the inner surface of the catheter and the systemic antibiotic therapy cannot eradicate bacteria in the catheter.

Five large observational studies found that clinical cure occurred in only 22-37% of patients whose catheter related infection was treated with systemic antibiotics alone, when the catheter was not removed. [Marr et al1997; Swartz et al, 1994; Saad et al, 2001; Lund et al, 1996; Pourchez et al, 1989].

## 5.10. Preventing HD catheter infections

According to the CDC guidelines for the prevention of CRBSI update 2011, all relevant health care personnel regarding IV catheter use should be educated for the proper procedures for insertion, maintenance and control measures. Dialysis units should develop a written protocol describing the proper use of aseptic techniques when catheters are manipulated and dressings are applied. All personnel should be adequately trained about the importance of hand hygiene before and after patient contact. It is also recommended that personnel use non sterile gloves and masks when accessing the catheters. Chlorhexidine gluconate-impregnated sponges should be used in intravenous catheter dressings, which may decrease catheter related infections. Also proper records of the trends of types of infection, incidence and antibiotic resistance should be kept, to know the situation of the trend and to be prepared to provide the appropriate treatment [Saad et al, 1999]. Various other methods have been used to prevent catheter infections. These are the use of topical antibiotic exit-site application, lock solutions and elimination of nasal staphylococcus nasal carriage. These methods are shown to decrease the number of HD infections all the while increasing the resistance to the antibiotic therapy [Farr et al, 2002; Deshpande et al, 2002; James et al, 2008; O'Grady et al, 2011; Rabindranath et al, 2009; Yu et al, 1986].

# 6. MATERIALS AND METHODS

The study was performed by collecting data retrospectively from the PSKUS archive, specifically the nephrology department, from 01 January 2012 to 31 December 2012. All patient histories were reviewed and those with CVC infections due to HD were found and the necessary data was collected. The data was filled out in two forms, prepared specifically for this study (appendix 1).

All the data collected was then put in Microsoft excel 2007 and a database was created. Interpretation of the data was done using pivot table function on Microsoft excel 2007 and also manually.

Information about the catheters was collected from the procedure protocol and in certain cases also from the anamnesis and discharge papers. The antibiotic therapy provided was collected from the ordinate page, the CRP levels were collected from the blood biochemistry and finally leucocytosis and neutrophilia were collected from CBC.

Concerning the diagnosis of the bacteria and the antibacterial sensitivity all blood samples and CVC received by the PSKUS laboratory were cultured strictly by following special PSKUS protocol. Specific genus and species of the bacteria causing the infection was always revealed when blood samples were cultured, where as only the genus of bacteria was revealed while culturing the CVC. All CVC samples are cultured only qualitatively, revealing only if there was bacteria or not, without specifying the amount. Antibacterial sensitivity was mainly checked using the disk diffusion test. Also used to determine the sensitivity was an automated MIC test operated by 'BIOMERIEUX VITEK 2' machine. The choices of antibacterial products evaluated for sensitivity was based on the CLSI approved standards 2012 (M100-S22).

If an organism is found to be susceptible to tetracycline, it is also considered susceptible to doxycycline and minocycline. However, if resistance to tetracycline is found, the organisms may still be susceptible to doxycycline, minocycline or both.

For Staphylococcal species, penicillin-susceptible staphylococci are also sensitive to other penicillins, β-lactam/β-lactamase inhibitor combinations, antistaphylococcal cephems and carbapenems. Penicillin resistant but oxacillin sensitive strains are resistant to penicillinase-labile penicillins but susceptible to other penicillinase-stable penicillins, β-

lactam/β-lactamase inhibitor combinations, antistaphylococcal cephems and carbapenems. Oxacillin-resistant Staphylococci are resistant to all currently available β-lactam antimicrobial agents, with the exception of the newer cephalosporins with anti-MRSA activity. Thus, wide sensitivity or resistance can be deduced by testing only penicillin and either cefoxitin or oxacillin. Sensitivity to cefoxitin was checked for to determine if it was methicillin sensitive or resistant. For Staphylococcus aureus and Staphylococcus lugdunensis either cefoxitin disk diffusion or MIC tests can be used to predict the presence of mecA-mediated oxacillin resistance where as for coagulase-negative Staphylococci (except Staphylococcus lugdunensis), the cefoxitin disk diffusion test is the preferred method.

For Enterococcus species cephalosporins, aminoglycosides, clindamycin and TMP-SMZ may appear active in vitro, but are not effective clinically and therefore should not be reported as sensitive. Enterococci that are sensitive to penicillin, are predictable sensitive to ampicillin, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam for non-β-lactamase-producing Enterococci. On the other hand, Enterococci which are sensitive to ampicillin, cannot be assumed to be sensitive to penicillin. Combination of ampicillin, penicillin or vancomycin (for sensitive strains) plus an aminoglycoside is indicated for serious Enterococcal infections as they have a synergistic effect in killing Enterococcal bacteria.

For Enterobacter species, cephalothin interpretive criteria should be used only to predict results to oral agents, cefadroxil, cefpodoxime, cephalexin and loracarbef.

**Table 1A. Suggested Groupings of Antimicrobial Agents With FDA Clinical Indications That Should Be Considered for Routine Testing and Reporting on Nonfastidious Organisms by Clinical Microbiology Laboratories in the United States**

| | *Enterobacteriaceae*[e] | *Pseudomonas aeruginosa* | *Staphylococcus* spp. | *Enterococcus* spp.[k] |
|---|---|---|---|---|
| GROUP A PRIMARY TEST AND REPORT | Ampicillin[e] | Ceftazidime | Azithromycin[c] or clarithromycin[c] or erythromycin[c] | Ampicillin<br>Penicillin[l] |
| | | | Clindamycin[c] | |
| | | | Oxacillin (cefoxitin)[h,j] | |
| | Cefazolin[f] | Gentamicin<br>Tobramycin | Penicillin[h] | |
| | Gentamicin<br>Tobramycin | Piperacillin | Trimethoprim-sulfamethoxazole | |
| GROUP B[e] PRIMARY TEST REPORT SELECTIVELY | Amikacin | Amikacin | *Daptomycin | *Daptomycin |
| | | Aztreonam | Linezolid | Linezolid |
| | Amoxicillin-clavulanic acid<br>Ampicillin-sulbactam<br>Piperacillin-tazobactam<br>Ticarcillin-clavulanic acid | Cefepime | Telithromycin[c] | |
| | Cefuroxime | | Doxycycline<br>Minocycline<br>Tetracycline[a] | Vancomycin |
| | | Ciprofloxacin<br>Levofloxacin | Vancomycin | |
| | Cefepime | Doripenem<br>Imipenem<br>Meropenem | Rifampin[b] | |
| | Cefotetan<br>Cefoxitin | Piperacillin-tazobactam<br>Ticarcillin | | |
| | Cefotaxime[e,f] or ceftriaxone[e,f] | | | |
| | Ciprofloxacin[e]<br>Levofloxacin[e] | | | |
| | Doripenem<br>Ertapenem<br>Imipenem<br>Meropenem | | | |
| | Piperacillin | | | |
| | Trimethoprim-sulfamethoxazole[e] | | | |
| GROUP C[f] SUPPLEMENTAL REPORT SELECTIVELY | Aztreonam<br>Ceftazidime | | Chloramphenicol[c] | Gentamicin (high-level resistance screen only) |
| | | | Ciprofloxacin or levofloxacin or ofloxacin<br>Moxifloxacin | Streptomycin (high-level resistance screen only) |
| | Chloramphenicol[c,e] | | Gentamicin | |
| | Tetracycline[a] | | Quinupristin-dalfopristin[l] | |
| GROUP U SUPPLEMENTAL FOR URINE ONLY | Cephalothin[d] | Lomefloxacin or ofloxacin<br>Norfloxacin | Lomefloxacin<br>Norfloxacin | Ciprofloxacin<br>Levofloxacin<br>Norfloxacin |
| | Lomefloxacin or ofloxacin<br>Norfloxacin | | | |
| | Nitrofurantoin | | Nitrofurantoin | Nitrofurantoin |
| | Sulfisoxazole | | Sulfisoxazole | |
| | Trimethoprim | | Trimethoprim | |
| | | | | Tetracycline[a] |

* MIC testing only; disk diffusion test unreliable.

## 7. RESULTS

In the study, 39 patients that were diagnosed with CVC infection caused by HD catheters were collected. Among them, six patients were excluded from the analysis as no CVC or blood cultures were performed for these patients. So presence of an infection is questionable.

Among the remaining 33 patients, gender distribution was such that 48.5% (16) were male and 51.5% (17) were female [Figure 4]. The mean and median age of the patients both were 59 [Figure 5] and ranged from 34-86 years of age.

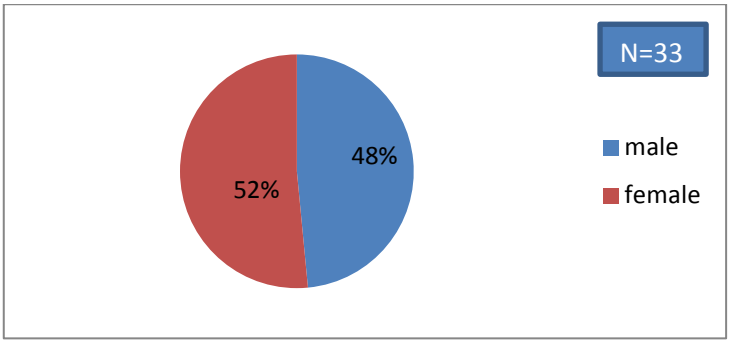


Figure 4: Gender distribution among CVC infection patients.

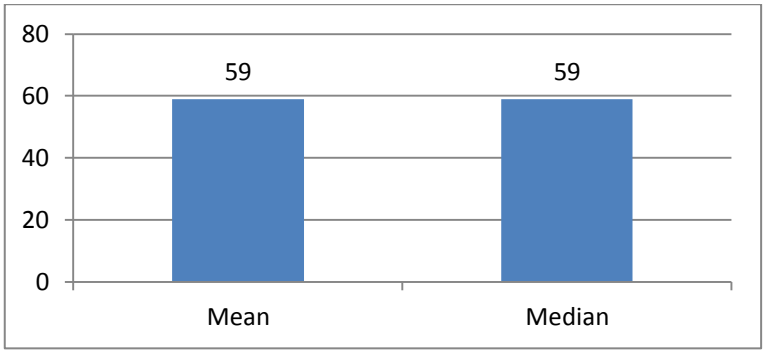


Figure 5: Mean and median age in patients with CVC infection

In the 33 patients included in the study, in 70% (23) of cases the bacteria was found only in CVC and in 30% (10) cases bacteria was grown both in CVC and in blood [Figure 6]. Therefore, according to the CDC criteria, in this study, among the catheter related bacteremia,

there are 30% (10) cases with definite bloodstream infection and the rest 70% (23) are categorized as probable bloodstream infections.

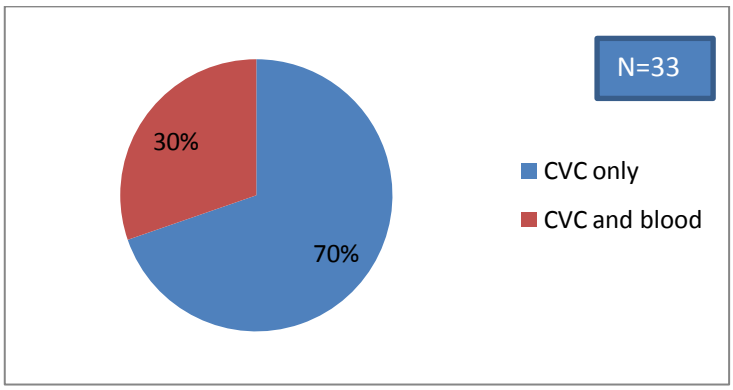


Figure 6: Distribution of material where bacteria was grown in culture

### 7.1. Catheters

Among the 33 patients that were included in the study, 72.7% (24) were tunneled long term catheters and 27.3% (9) were non-tunneled temporary catheters. 39.4% (13) patients did not have the information of the date of insertion of the catheter. 33.3% (11) of them were tunneled catheters and 6.1% (2) were non tunneled catheters.

Amongst the nine patients that had non-tunneled CVC inserted, 67% (6) were inserted in V. jugularis interna dx, 22% (2) were inserted in V. jugularis interna sin and 11% (1) was inserted in V. femoralis dx [Figure 7].

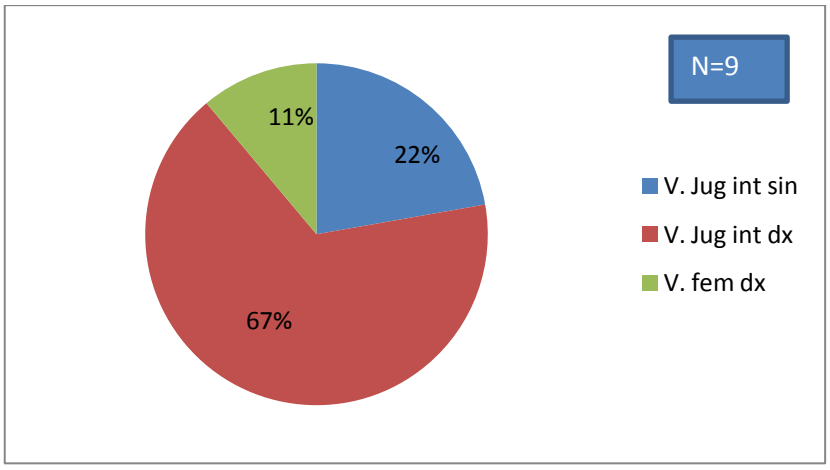


Figure 7: Location of non-tunneled CVC used for HD

Among the 24 patients that had tunneled CVC inserted, 71% (17) were inserted in V. jugularis interna dx, 25% (6) were inserted in V. jugularis interna sin and 4% (1) was inserted in V. subclavia dx [Figure 8].

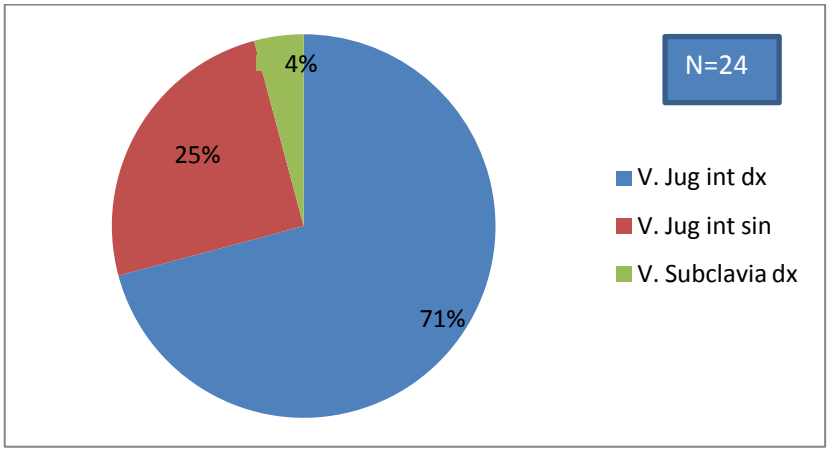


Figure 8: Location of tunneled CVC used for HD

### 7.2. Duration of catheter use

Again, in the group of patients that had tunneled catheters, the mean number of days the catheter was used was 21 and the range was from 14-49 days. The mean number of days the catheter was inserted until infection occurred was 16.7 and the range was 2-49 days. The mean number of days the catheter was left in the patient after the infection was found was 2.9 and the range was 0-17 days.

In the group of patients that has non-tunneled catheters, the mean number of days the catheter was used was 20.4 days and range was 5-79 days. The mean number of days the catheter was inserted until infection occurred was 17.1 day and the range was from 4-75 days. The mean number of days the catheter was left in the patient after the infection was found was 2.6 days and the range was 0-7 days.

### 7.3. Laboratory markers

Among the 33 patients, all but two patients did not have any laboratory examinations as they decided to leave the hospital against medical advice.

The mean and median CRP before therapy was 102.8 and 52.1 respectively, after empirical therapy was 67.2 and 41.9 respectively and after targeted therapy was 25.6 and 20.1 respectively. [Figure 9].

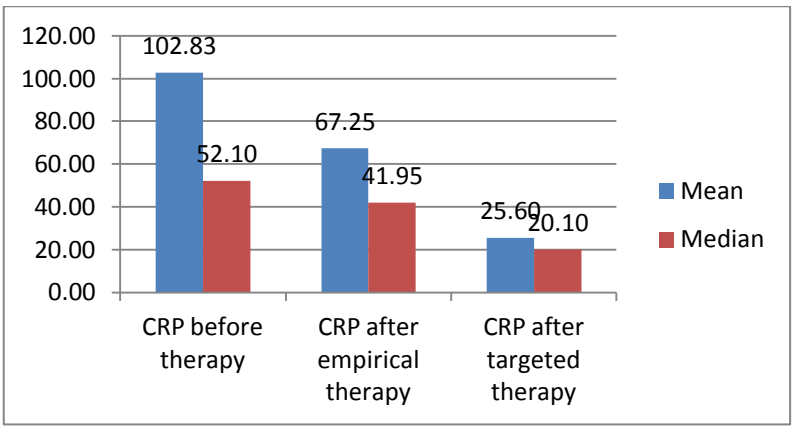


Figure 9: Mean and median CRP (mg/L) in patients with CVC infection

The mean and median leucocytosis before therapy was 10.42 and 8.65 respectively, after empirical therapy was 9.26 and 7.60 respectively and after targeted therapy was 7.16 and 6.90 respectively. Leucocytosis was not checked for in 5 additional patients after targeted therapy [Figure 10].

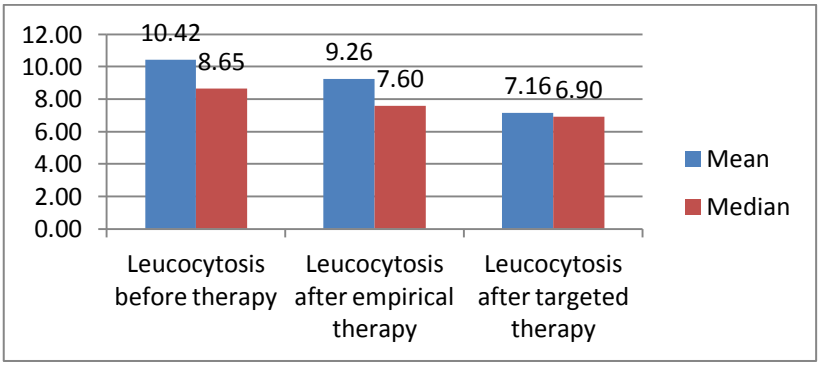


Figure 10: Mean and median leucocytosis ($x10^9$) in patients with CVC infection

The mean and median neutrophilia before therapy was measured in 12 patients and the value was 6.64 and 6.1 respectively, neutrophilia after empirical therapy was measured in 15 cases and value was 7.25 and 4.7 respectively and after targeted therapy was measured in six cases and value was 4.15 and 4.2 respectively [Figure 11].

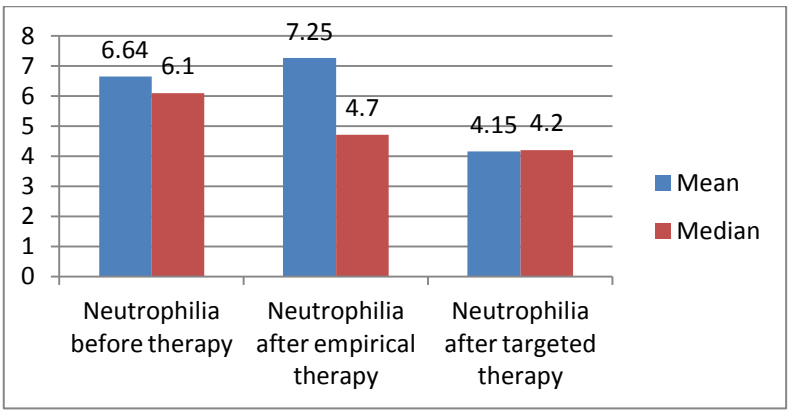


Figure 11: Mean and median neutrophilia ($x10^9$) in patients with CVC infection

### 7.4. Bacterial spectrum

In the 33 patients, 15.2% (5) had two causative agents together causing the infection, and the other 84.8% (28) had single pathogens causing the infection. Therefore, there were a total of 38 bacterial strains that were found by culture and their antibiotic sensitivity was checked. 94.7% (36) of the bacteria were gram-positive and 5.3% (2) were found to be gram-negative [Figure 12].

Among the gram positive bacteria, 57.9% (22) were Staphylococcus coagulase-negative, 31.6% (12) were Staphylococcus aureus and 5.3% (2) were Enterococcus spp. All the Staphylococcus aureus were methicillin sensitive, whereas 44.7% (17) of the Staphylococcus coagulase-negative were methicillin resistant and 13.2% (5) were methicillin sensitive. Further, among the MR coagulase-negative bacteria, 10.5% (4) were found to be S. epidermidis, 2.6% (1) S. haemolyticus, 2.6% (1) S. saprophyticus and in 28.9% (11) cases the species was not specified whereas among the MS coagulase-negative bacteria, 2.6% (1) was S. capitis, 2.6% (1) S. saprophyticus and in 7.9% (3) of the cases the species was not specified. Among the gram negative bacteria 50% (1) was Enterobacter cloacae and 50% (1) was Pseudomonas aeruginosa [Figures 13, 14, 15].

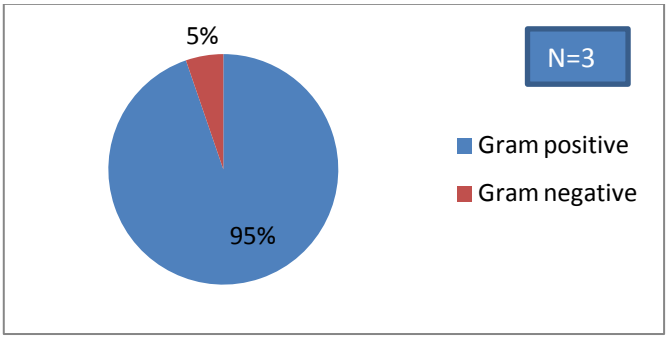


Figure 12: Distribution of gram-positive and gram-negative bacteria

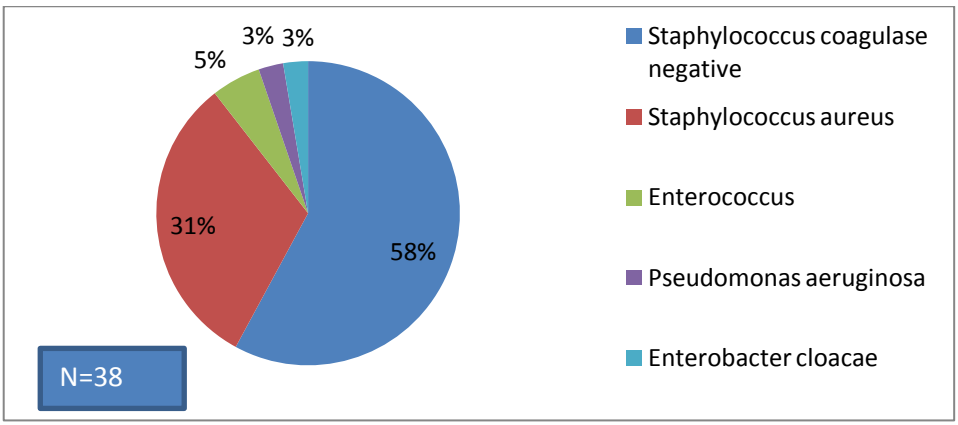


Figure 13: Etiological agents causing the CVC infection

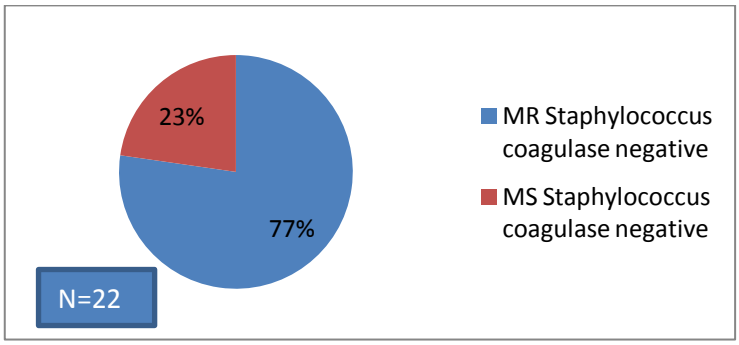


Figure 14: Distribution of methicillin resistant and sensitive Staphylococcus coagulase-negative

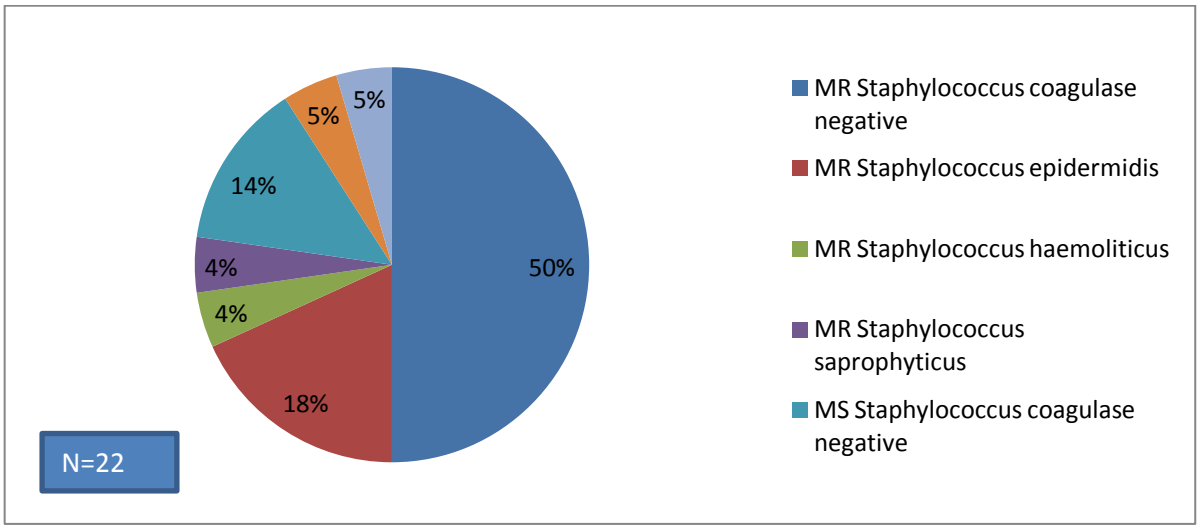


Figure 15: Distribution of Methicillin sensitive and resistant Staphylococcus coagulase-negative

The five cases which had two causative agents were with Enterococcus and MR Staphylococcus coagulase negative, Enterococcus and MS Staphylococcus aureus, MR Staphylococcus haemolyticus and MR Staphylocuccus epidermidis, MR Staphylococcus

coagulase negative and MS Staphylococcus auereus and finally MR Staphylococcus coagulase negative and Pseudomonas aeruginosa [Table 2].

### 7.5. Empirical therapy

From the study, there were 37 patients that received empiric therapy among the 39 patients initially collected, and two have been excluded as they left the hospital against medical advice before the initiation of antibiotic therapy.

The most common empirical therapies used were ceftriaxone in 21.6% (8) cases followed by a combination of ceftriaxone and vancomycin in 20% (7) cases. Also often used were amoxiclav 13.5% (5) vancomycin 10.8% (4), vancomycin and amoxiclav 8.1% (3) and ciprofloxacin 8.1% (3). Other empirical treatments were used only once- oxacillin, ciprofloxacin+ceftriaxone, cefazolin+ceftriaxone, ceftriaxone+oxacillin, ceftazadine, vancomycin+ ciprofloxacin [Figure 16].

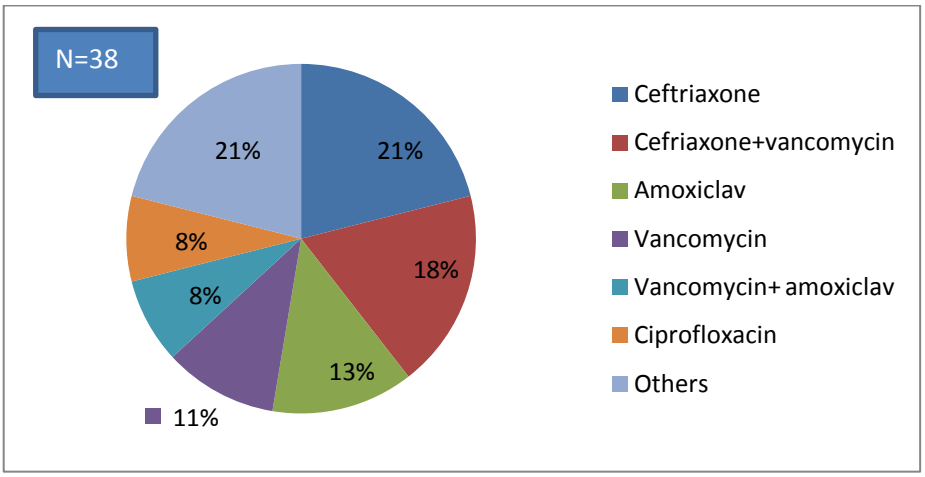


Figure 16: Empirical therapy chosen to treat the CVC infections

### 7.6. Targeted therapy

The targeted therapy has been found and divided according to MR Staphyloccous coagulase negative, MS Staphylococcus aureus, MS Staphylococcus coagulase negative and therapy for cases with more than one causative agent.

For MR Staphylococcus coagulase-negatives, following antibiotics were used: vancomycin28% (3), amoxiclav and vancomycin 9% (1), amoxiclav 28% (3), ciprofloxacin

9% (1), amoxiclav and ciprofloxacin 9% (1) and clindamycin and vancomycin 9% (1) [Figure 17].

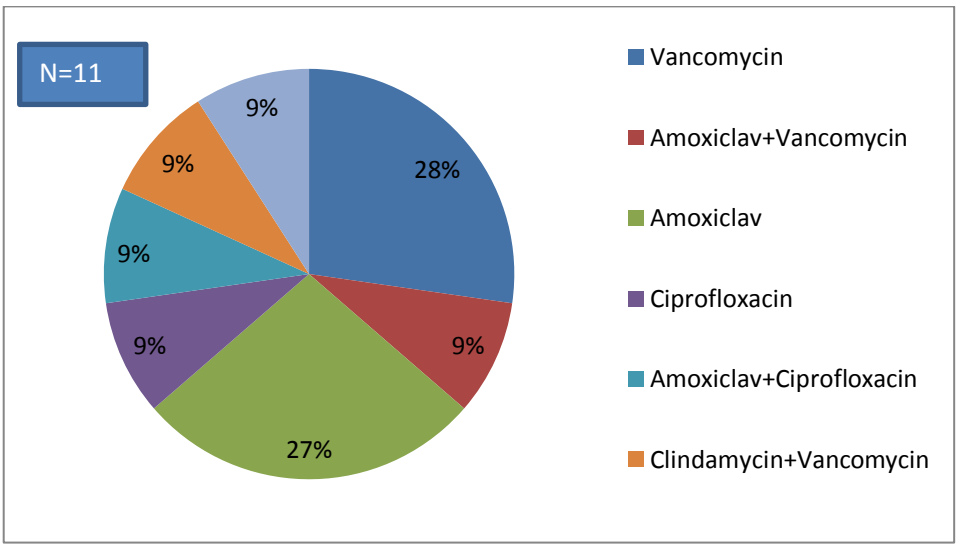


Figure 17: Post culture therapy for MR Staphylococcus coagulase-negatives

For Staphylococcus aureus, following were the antibiotics used: oxacillin 30% (3), ceftriaxone 10% (1), ciprofloxacin 10% (1), oxacillin and vancomycin 20% (2), oxacillin and TMP-SMZ 10% (1), ceftriaxone and vancomycin 10% (1) and oxacillin and ciprofloxacin 10% (1). [Figure 18].

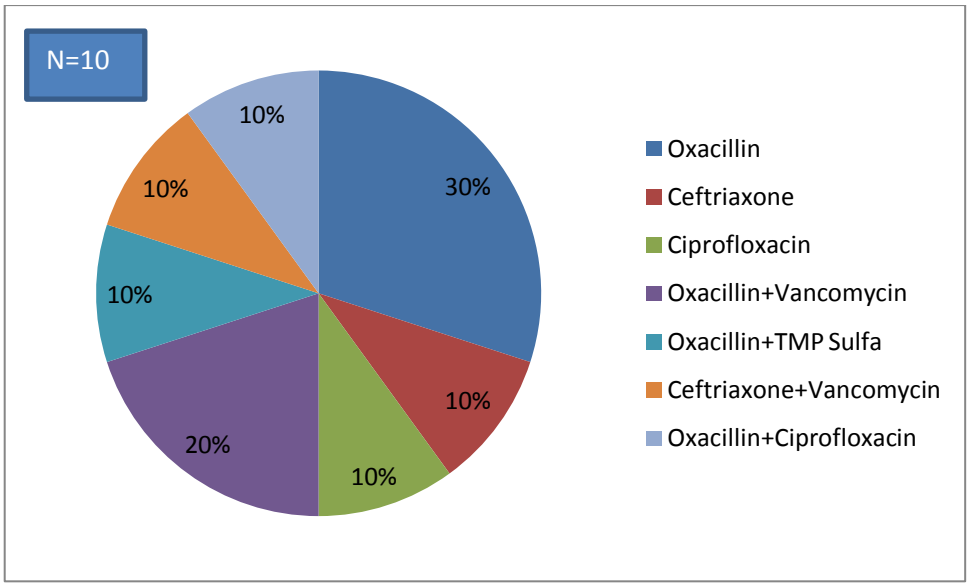


Figure 18: Post culture therapy for MS Staphylococcus aureus

For MS Staphylococcus coagulase-negative, following were the antibiotics therapy used: Ciprofloxacin 34% (1), amoxiclav 33% (1) and amoxiclav and ceftriaxone 33% (1) [Figure 19]

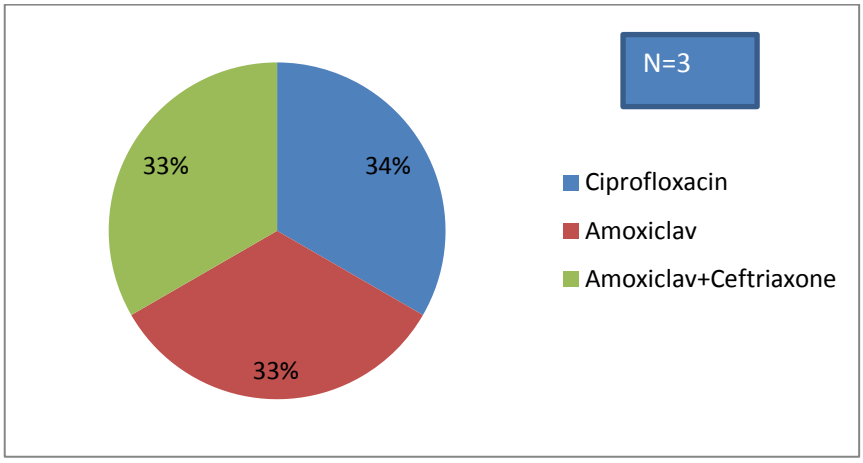


Figure 19: Post culture therapy for MS Staphylococcus coagulase-negatives

The Table 2 shows the antibiotic therapy used in cases where more than one causative agent was found.

Table 2: Post culture therapy for the five specific cases with combined infection

| **Bacteria** | **Antibiotic Therapy** |
|---|---|
| MR Staph coag neg+MSSA | Oxacillin+Ciprofloxacin |
| MR Staph coag neg+Pseudomonas aeruginosa | Vancomycin+Ceftriaxone |
| MR Staph haemolyticus+MR Staph epidermidis | Amoxiclav |
| MSSA+Enterococcus | Vancomycin |
| MR Staph coag neg+Enterococcus | Vancomycin |

### 7.7. Antibacterial sensitivity

Antibacterial sensitivity was checked for the 38 strains of pathogens that were found via culture. Complete charts for the antibacterial sensitivity are found in appendix 2.

**Gram-negative bacilli**

The only strain of Enterobacter cloacae was resistant to ampicillin, cephalothin and cefazolin whereas it was sensitive to amoxiclav, piparec/tazobactam, imipenam, ceftazidime, cefotaxime, amikacin, gentamicin, ciprofloxacin, chloramphenicol and TMP-SMZ.

Pseudomonas aeruginosa was found to be sensitive to amoxiclav, aztreonam, ceftazidime, amikacin, gentamicin, ciprofloxacin, cefepime and ampicillin/sufbactam.

**Gram-positive bacilli**

**MR staphylococcus coagulase-negative**

**MR Staphylococcus coagulase-negative** (unspecified) was found the be resistant to penicillin 100% (11), gentamicin 63.3% (7), erythromycin 63.3% (7), ciprofloxacin 54.5% (6), chloramphenicol 18.1% (2), clindamycin 63.3% (7), rifampin 18.1% (2), tetracycline 18.1% (2) and TMP-SMZ 63.3% (7) where as it was sensitive to gentamicin 27.2% (3), erythromycin 36.6% (4), ciprofloxacin 36.6% (4), chloramphenicol 81.8% (9), clindamycin 36.6% (4), rifampin 81.8% (9), tetracyclin 81.8% (9) and TMP-SMZ 36.6% (4) and finally minimal sensitivity in gentamicin 9% (1) and ciprofloxacin 9% (1)

In the patient that was infected with **MR staphylococcus haemolyticus**, resistance of the agent was found against, penicillin, erythromycin, ciprofloxacin and TMP-SMZ whereas it was sensitive to gentamicin, chloramphenicol, clindamycin, rifampin and tetracycline.

**MR staphylococcus saprophyticus**, was resistant against penicillin, gentamicin, ciprofloxacin, ciprofloxacin and TMP-SMZ, intermediately sensitive against erythromycin and sensitive against clindamycin, rifampin, linezolid and fucidin acid.

**MR staphylococcus epidermidis**, 100% (4) were resistant to penicillin and ciprofloxacin, 75% (3)were resistant to TMP-SMZ, 50% (2)were resistant to gentamicin, erythromycin, clindamycin and tetracycline, while 25% resistance against chloramphenicol. So, sensitivity was found in 25% (1) against gentamicin and TMP-SMZ, 50% (2) against erythromycin, clindamycin and tetracycline, 75% against chloramphenicol and 100% against rifampin. Intermediate sensitivity was found in 25% (1) patient against gentamicin.

**MS Staphylococcus aureus**

**MS Staphylococcus aureus** was found to be resistant to penicillin in 75% (9) of the patients and sensitive to it in 25% (3) patients. They were sensitive all the other antibiotics checked for – gentamicin, erythromycin, ciprofloxacin, clindamycin, rifampin, tetracycline, TMP-SMZ, linezolid and fucidin acid.

**MS Staphylococcus coagulase-negative**

Among the 3 patients with MS **Staphylococcus coagulase-negative** (unspecified) bacterial infection, 66% (2) agents were resistant to penicillin and 33% (1) were sensitive to it. In 33% (1) patients ciprofloxacin was resistant and in 66% (2) was sensitive. Also against chloramphenicol, 33% (1) was resistant and 66% (2) were sensitive. Finally these bacteria were all found to be sensitive to gentamicin, erythromycin, clindamycin, rifampin, tetramycin and TMP-SMZ.

In one patient infected with **MS Staphylococcus saprophyticus**, the agent was found to be sensitive to penicillin, gentamicin, erythromycin, ciprofloxacin, chloramphenicol, clindamycin, rifampin, tetracycline, TMP-SMZ and linezolid where as it was resistant to fucidin acid.

In one patient infected with **MS Staphylococcus capitis**, the strain was found to be sensitive to oxacillin, gentamicin, erythromycin, clindamycin, rifampin, tetracycline, TMP-SMZ and linezolid where as it had intermediate sensitivity to ciprofloxacin.

**Enterococcus spp.**

In the patients infected with **Enterococcus spp**, both isolated strains were found to be ampicillin sensitive. 50 % (1) sensitivity and 50% (1) resistance was registered to gentamicin, erythromycin, ciprofloxacin and tetracycline. These two cases were also both sensitive to chloramphenicol, linezolid and streptomycin. In one patient, nitrofurantoin sensitivity was also checked and it was found to be sensitive.

# 8. DISCUSSION

## 8.1. Catheter choices and insertion locations

In this study, it was found that 72.7% of CVC infections in HD patients occurred when using tunneled catheters, while 27.3% of the infections occurred when non-tunneled catheters were inserted in the HD patients. As HD patients require vascular access 2-3 times per week for a long period of time, long-term catheters are used most often, as according to previous studies, temporary or non-tunneled catheters infection rate increases if they are used longer than one week [IDSA], regardless of the location. This leads to the increased number of infected long-term catheters. Also, as a negative to this study, the total number of catheters inserted is not known as the patients came to PSKUS for treatment for infection episode, but they receive HD in PSKUS and other HD centers in Latvia. Therefore, monitoring of all the catheters that were inserted in HD patients was not possible. In other studies, the results found were that bacteremia occurred in 29% of the 129 tunneled catheters that were inserted in the HD patients [Jean et al, 2002], and it was found that 10.1% of tunneled catheters were found to cause bacteremia [Lemaire et al, 2009] and CVC infections in HD patients occurred in 81% (47 of 58) of the bacteremia patients that had long-term catheters inserted. [Bruno et al, 1997].

In this study, most number of infections was found in CVCs that were placed in V. jugularis interna. V. subclavia and V. femoralis were found to be the location sites in equal number of times. Although again, the total number of catheters placed was unknown, which leads to false or rather incomparable results. In PSKUS, as also found in IDSA recommendations, V. jugularis interna dexter is the first choice location for insertion of CVC catheters, followed by V. jugularis interna sinister. V. subclavia and V. femoralis respectively are the following choices. In PSKUS, V. femoralis is the last option of CVC insertion due to studies and clinical experience of high risk of infections, whereas, IDSA states that V. subclavia should be the last choice due to high risk of stenosis and this is especially important for HD patients are that extremity then would no longer be viable to be used for vascular access. According to other studies, non-tunneled catheters that were inserted in V. jugularis interna, the rate of infection increases after one week of use and femoral catheters should not be used for more than five days and only in bed-bound patients [Gulati et al, 2003 and Butterly et al, 2000 and the KDOQI]. The site of insertion of CVC catheters to minimize CVC infections should be first V. subclavia, followed by V. jugularis interna and finally V.

femoralis with 2.3% in V. subclavia, 6.4% with V. jugularis interna and 20% in V. femoralis [Leonardo et al, 2005]. It is mentioned that among non-tunneled catheters, femoral catheters have the highest infection rate averaging 7.6 episodes per 1000 days with more than 10% being infected by one week [KDOQI].

### 8.2. Bacterial spectrum, therapy and antibacterial sensitivity

The spectrum of bacterial agents that cause catheter-related bacteremia in HD patients have shown remarkably varying results in various studies. [Marr et al, 1997] found that 65% were gram-positive, with 44% being S. aureus, 14% S. epidermidis and 5% being Enterococcus where as 24% of the bacteria were found to be gram-negative. Another study's results showed that 67% were gram-positive with 22% being S. aureus, 40% being S. epidermidis and 20% Enterococcus, with 45% being gram-negative [Saad et al in 1999]. [Beathard et al, 1999] found that 86% were gram-positive with 30% S. aureus, 37% with S. epidermidis and 17% Enterococcus, while 335 were gram-negative. [Mokrzycki et al 2000] found that 95% were gram-positive with 74% being S. aureus, only 7% S. epidermidis, 2% Enterococcus and 5% were gram-negative. [Krishnasami et al, 2002] found that 61% were gram-positive, with only 3% being S. aureus and 32% S. epidermidis and 15% Enterococcus while 39% were gram-negative. Also, [Lok et al, 2003] found that 77% were gram-positive with 23% being S. aureus, 42% being S. epidermidis and 8% being Enterococcus while 19% were gram-negative. [Poole et al, 2004] found that 72% were gram-positive with 21% S. aureus, 41% S. epidermidis, 10% enterococcus while 28% were gram-negative. According to this study, 95% of the infections were caused by gram-positive bacteria with 58% being caused by S. coagulase-negatives, 31% caused by S. aureus and 5% caused by Enterococcus while only 5% were caused by gram-negative bacteria.

In this study, all the Staphylococcus aureus found were methicillin sensitive. There were no MRSA infections. In the US, the prevalence of MRSA in intensive care units is 60% [National Nosocomial Infections Surveillance, 2004] and overall, more than 90,000 invasive infections occurred due to MRSA in the united states in 2005 [Klevens et al, 2007]. In a review of 5287 cases of invasive MRSA infection, 15% occurred in dialysis patients. In fact, the incidence of MRSA infection was 100 times higher among dialysis patients than in the general population (45 versus 0.4 per 1000 patients) [CDC, 2005]. Although there is high risk of MRSA in patients undergoing dialysis, in the PSKUS nephrology department, there were no MRSA infections among patients undergoing HD via CVC in 2012.

In 2008, CDC's National Healthcare Safety Network published a summary data stating that vancomycin resistance had increased to 335 among Enterococci that caused healthcare-associated infections in 2006 and 2007 [Hidron et al, 2008]. In fact the rate of hospitalization with VRE essentially doubled during 2003-2004 from 4.60 to 9.48 hospitalizations per 100,000 population [Ramsey et al, 2009]. Although there is presence of VRE worldwide, according to this study, there was no VRE in the PSKUS nephrology department among patients that were undergoing HD in 2012.

Resistance to methicillin has been observed in more than 80% of coagulase-negative staphylococcal isolates [Diekema et al, 2001]. In this study also similar resistance was seen with 77% of the coagulase-negative Staphylococcus methicillin resistant and overall, 44.7% of all bacteria were methicillin resistant.

### 8.3. Empirical therapy

According to the guidelines of IDSA, the recommended empirical therapy is to provide antibacterial coverage for both gram-positive and gram-negative bacteria by using vancomycin plus gentamicin (aminoglycoside) or ceftazidime (third generation cephalosporin). Also it has been said that cefazolin (first generation cephalosporin) can be used instead to vancomycin is regions where methicillin resistant staphylococci have low prevalence. In this study, it is found that the most common empirical therapies in order of prevalence are ceftriaxone, ceftriaxone plus vancomycin, amoxicillin-clavulanate, vancomycin and others.

As the spectrum of bacteria causing the CVC infections in HD patients in the nephrology department of PSKUS is predominantly gram-positive, it is essential to have antibiotic agents that have coverage for this. Furthermore, as 77% of the Staphylococcus coagulase-negative were found to be methicillin resistant, using vancomycin for empirical therapy seems to be a good idea and once culture and sensitivity tests are obtained, vancomycin, if possible should be changed to another antibiotic. The resistance to β-lactam antibacterial therapy was 84.8%, so they should not be used as empirical therapy. Also, high resistance was found with gentamicin (28.9%), erythromycin (30.5%), ciprofloxacin (37.8%) and clindamycin (26.4%). In this study, there were no patients which had MRSA as causative agents.

Although only 5% of pathogens were found to be gram-negative, it should still be covered in patients with neutropenia, severely ill patients with sepsis, or patients known to be colonized with such pathogens until culture results are obtained. Whether these were the conditions in this study is unclear as neutrophilia was not checked for in most cases and in those that it was checked for were normal and the clinical status of the patient unfortunately was also not known either. In this study, the choice of antibacterial drugs chosen against gram-negative infections was mainly ceftriaxone. Although, as ceftriaxone is a third generation cephalosporin with good effect against gram-negative pathogens, it has minimal effect against Pseudomonas aeruginosa and in this study, it was shown that there was this pathogen causing CVC infection, therefore, ceftazidime should be the choice of antibacterial drugs chosen as empirical therapy to cover the gram-negative spectrum.

### 8.4. Targeted therapy

The recommended antibacterial treatment for MR Staphylococcus coagulase-negative according to the guidelines of IDSA is vancomycin as first choice with daptomycin or linezolid as alternatives. In this study, in order of predominance, the antibacterial therapy chosen were vancomycin, amoxiclav, clindamycin plus vancomycin, ciprofloxacin and amoxiclav plus ciprofloxacin.

The recommendation for treatment by IDSA for MS Staphylococcus coagulase-negative is penicillinase-resistant penicillins such as nafcillin or oxacillin or as alternatives first generation cephalosporins, vancomycin or TMP-SMZ. In this study, MS Staphylococcus coagulase-negative bacteria were treated by the following antibacterial agents in order of predominance: amoxiclav, amoxiclav plus ceftriaxone and ciprofloxacin.

The recommendation of for treating MS Staphylococcus aureus according to IDSA is again penicillinase-resistant penicillins such as nafcillin or oxacillin or as alternatives first generation cephalosporins or vancomycin. According to this study, in order of prevalence, the antibacterial therapy chosen was oxacillin, ceftriaxone, oxacillin plus vancomycin and ciprofloxacin, oxacillin plus TMP-SMZ, ceftriaxone plus vancomycin and oxacillin plus ciprofloxacin.

The recommendation by the IDSA for treating Enterococcus if it is ampicillin susceptible is ampicillin with or without aminoglycoside or alternatively vancomycin and if the enterococcus is resistant to ampicillin recommendation is to use vancomycin or finally if

resistance to vancomycin, then linezolid should be used. In this study, both the cases of Enterococcus occurred in combination with MSSA once and MR staphylococcus coagulase-negative. In both the cases Enterococcus was ampicillin sensitive, but considering the combination of pathogens, vancomycin was chosen for therapy.

The treatment of choice as recommended by the IDSA for Enterobacter species is carbapenems or alternatively cefepine or ciprofloxacin and Pseudomonas aeruginosa should be treated with fourth generation cephalosporins or carbapenems. In this study, Enterobacter were treated by amoxiclav and Pseudomonas aeruginosa was treated by vancomycin plus ceftriaxone as it occurred together with MR Staphylococcus coagulase-negative.

Choice of antibacterial therapy chosen after culture results as well as antibiotic sensitivity is based not only on the results themselves but also the clinical condition of the patient. As Staphylococcus coagulase-negative are the leading cause of the infections and that they are found on the skin as normal flora also leads to the question of contamination. When they are found in the results, according to the guidelines, repeat cultures from CVC and peripheral blood culture must be taken. These repeat cultures are not performed in PSKUS by clinicians in the nephrology department. Finally, it is the clinician who chooses the antibacterial medication and they take into consideration, the patient's symptoms and condition as well, especially in cases when Staphylococcus coagulase-negatives are found. Although, in this study, the patients symptoms were not taken into consideration, CRP, leucocytosis and neutrophilia were recorded and in all the cases, the CRP was found to be increased, where as leucocytosis was increased in 50% of cases which was not related in other studies. In some cases, based on the results of the culture, antibacterial sensitivity and the choice of antibiotics used post culture, it is clear that the Staphylococcus coagulase-negatives were accepted as contaminations.

### 8.5. Antibacterial lock therapy

According to several literature, the success rate of treatment of CVC infection with systemic antibacterial therapy plus antibiotic lock solution was highest 87-100% in patients with gram-negative infections, 75-84% in patients with Staphylococcus epidermidis infections, 61% for Enterococcus infections but only 40-55% in patients with Staphylococcus aureus infections [Maya et al, 2007; Poole et al, 2004; Vardhan et al, 2002; Fernandez-Hidalgo et al, 2006; Peterson et al, 2009]. Also according to the IDSA guidelines, the use of

antibiotic lock solutions has been indicated for patients with CRBSI involving long-term catheters with no signs of exit site or tunnel infection for which catheter salvage is the goal unless the infection is due to S. aureus and Candida species. In the PSKUS, according to clinicians that were consulted, antibiotic lock solutions are not used for HD patients with CRBSI.

### 8.6. Drawbacks

There are unfortunately several drawbacks to this study. The largest drawback being that only the pool of infected patients was collected. Hence, as there is no control group, specific comparisons were impossible to make and along with that comparisons with the situation worldwide were also impossible.

Also the total number of patients was relatively low. In the future, several years and/or multiple centres should be analysed. As always, performing a prospective study, rather than retrospective, it would be possible to collect a lot more relevant data.

The complete clinical picture of the patient was not collected as it was impossible to read most of the anamnesis data. This again emphasises on the fact that prospective data collection would have been more effective.

Concomitant diseases of the patients were also not recorded. Due to this there could be varying values in laboratory markers as well as antibiotics chosen for treatment, both empirically and post culture.

# 9. CONCLUSIONS

- The three most common ethiological agents that cause central venous catheter related infection in hemodialysis patients in order of prevalence are gram-positive agents- Staphylococcus coagulase-negative, Staphylococcus aureus and Enterococcus.

- The predominantly used empirical antibacterial therapy in the nephrology department of Pauls Stradins Clinical University Hospital for hemodialysis patients with suspected catheter-related infections are ceftriaxone or ceftriaxone plus vancomycin.

- Resistance to β-lactam antibiotics was observed in 84.8% of patients and methicillin resistance in 44.7% of patients

- Recommended empirical antibiotic therapy is vancomycin plus ceftazidime.

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# 11.APPENDICES

## 11.1. Appendix 1

Initials:
Gender:
Date of Birth:
Age:
Occupation:
Date of CKD diagnosis:
Date of hemodialysis:

Date of Infection:

| Access Type | Date Placed | Date removed | Site |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

| | Date of Medication | Antibiotic/s | Dosage | Times per day | Method | Duration (days) |
|---|---|---|---|---|---|---|
| Empirical Th | | | | | | |
| Post culture Th | | | | | | |

| | CRP | Leucocytosis | Neutrophilia |
|---|---|---|---|
| Before Th | | | |
| End of empirical Th | | | |
| End of bacteria-specific Th | | | |

Patient Initials- **Patient No.**

| Material tested | | | |
|---|---|---|---|
| Date of material collection | | | |
| Date of result | | | |
| Antibiotic\Microorganism | | | |
| Penicillin | | | |
| Oxacillin | | | |
| Ampicillin | | | |
| Amoxicillin/Clavulanate | | | |
| Piparec/Tazobactam | | | |
| Aztreonam | | | |
| Imipenam | | | |
| Cephalothin | | | |
| Cefazolin | | | |
| Cefoxitin | | | |
| Cefuroxime | | | |
| Cefoperazone | | | |
| Ceftriaxone | | | |
| Ceftazidime | | | |
| Cefotaxime | | | |
| Amikacin | | | |
| Gentamicin | | | |
| Tobramycin | | | |
| Erythromycin | | | |
| Ciprofloxacin | | | |
| Ofloxacin | | | |
| Norfloxacin | | | |
| Chlorampfenicol | | | |
| Clindamycin | | | |
| Rifampin | | | |
| Doxycyclin | | | |
| Tetracyclin | | | |
| Trimethoprim/Sulfamethoxazole | | | |
| Vancomycin | | | |
| Nitrofurantoin | | | |
| Linezolid | | | |
| Meropenem | | | |
| Cefepime | | | |
| Ampicillin/ Sufbactam | | | |
| Streptomycin | | | |
| Fucidin Acid | | | |

S=sensitive
R=Resistant
I=Slightly
Sensitive

## Appendix 2

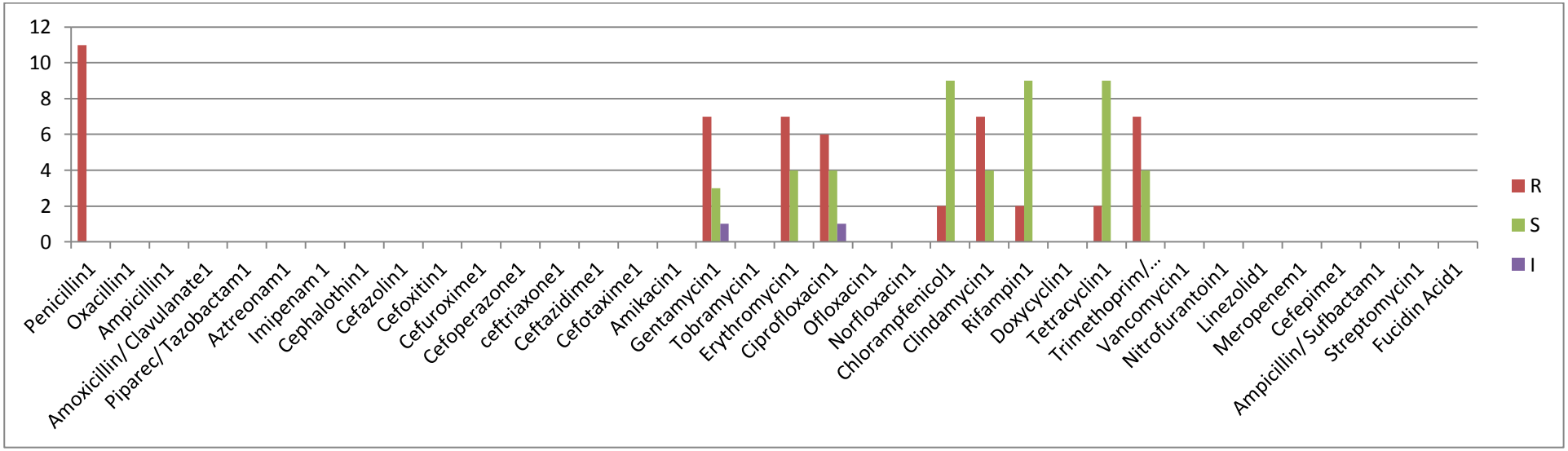


Figure: Antibacterial sensitivity for MR Staphylococcus coagulase negative (x=antibiotics, y=number of bacteria)

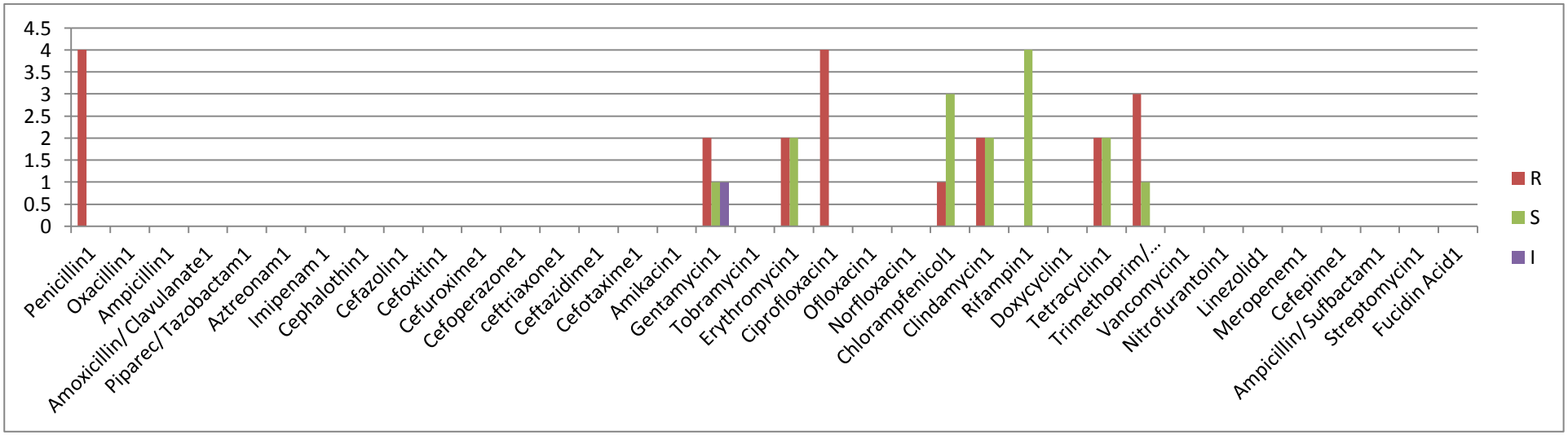


Figure: Antibacterial sensitivity for MR Staphylococcus epidermidis (x=antibiotics, y=number of bacteria)

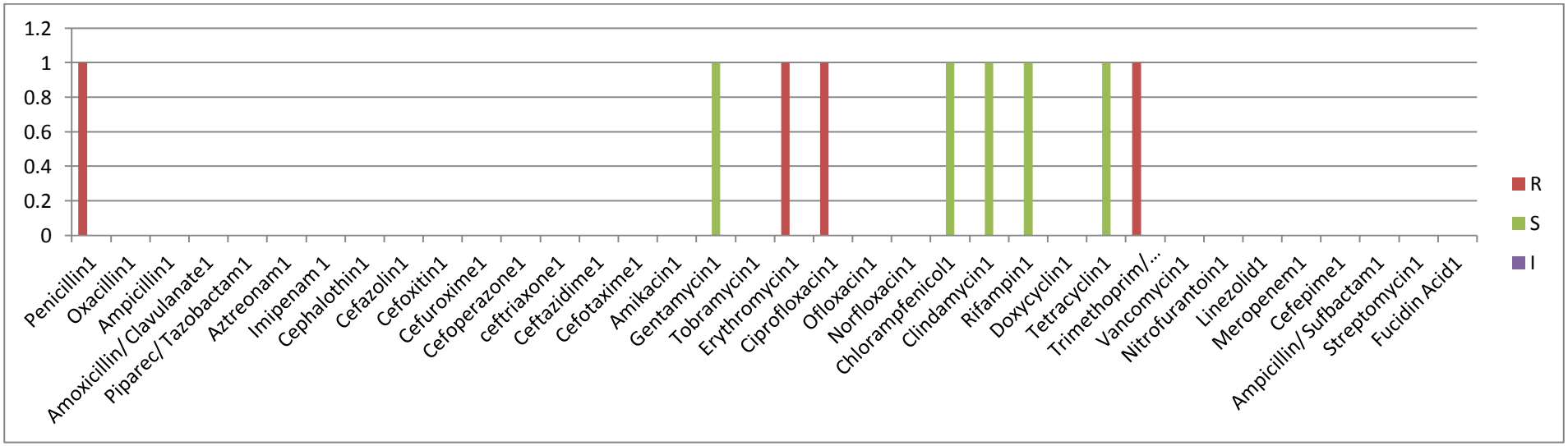


Figure: Antibacterial sensitivity for MR Staphylococcus haemoliticus (x=antibiotics, y=number of bacteria)

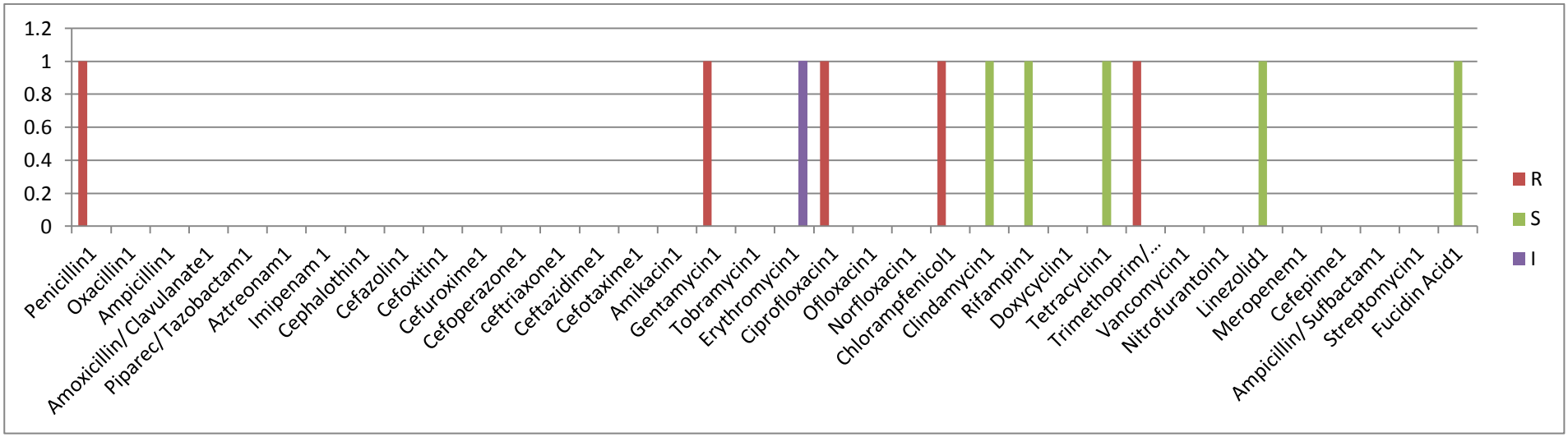


Figure: Antibacterial sensitivity for MR Staphylococcus saprophyticus (x=antibiotics, y=number of bacteria)

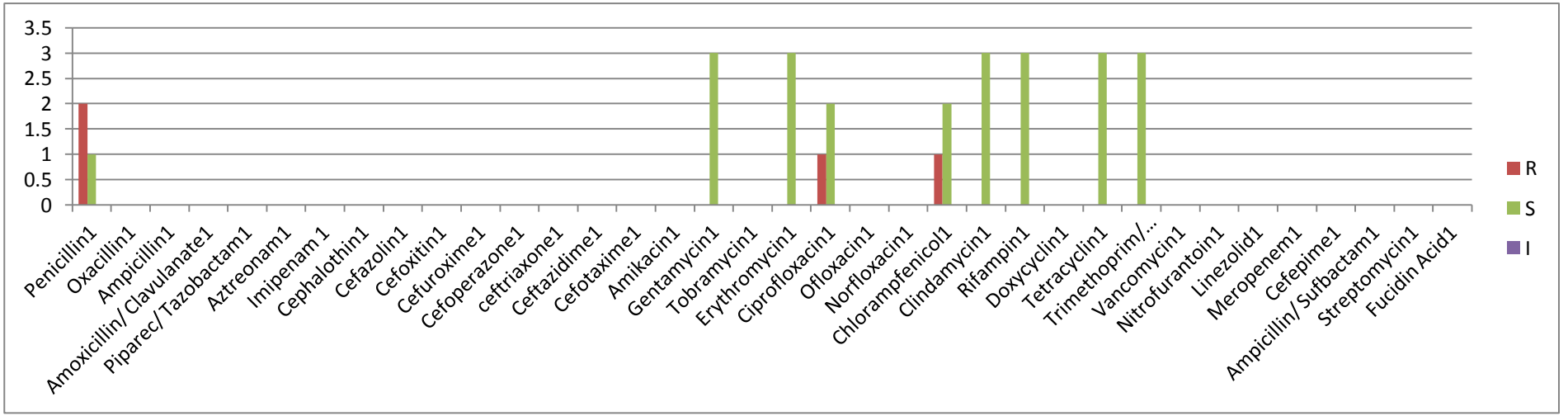


Figure: Antibacterial sensitivity for MS Staphylococcus coagulase negative (x=antibiotics, y=number of bacteria)

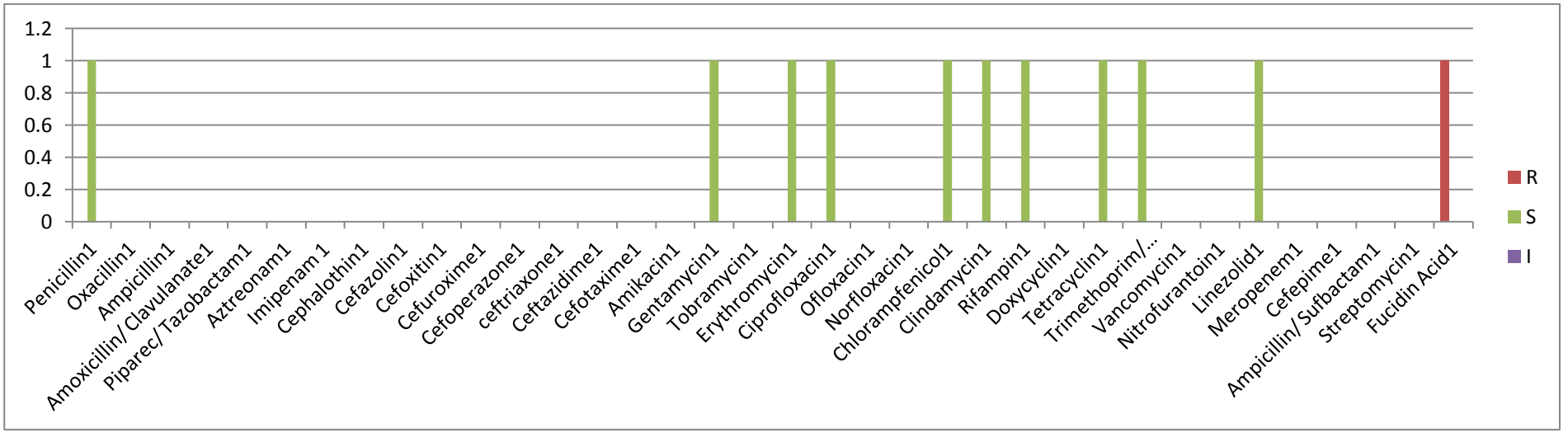


Figure: Antibacterial sensitivity for MS Staphylococcus saprophyticus (x=antibiotics, y=number of bacteria)

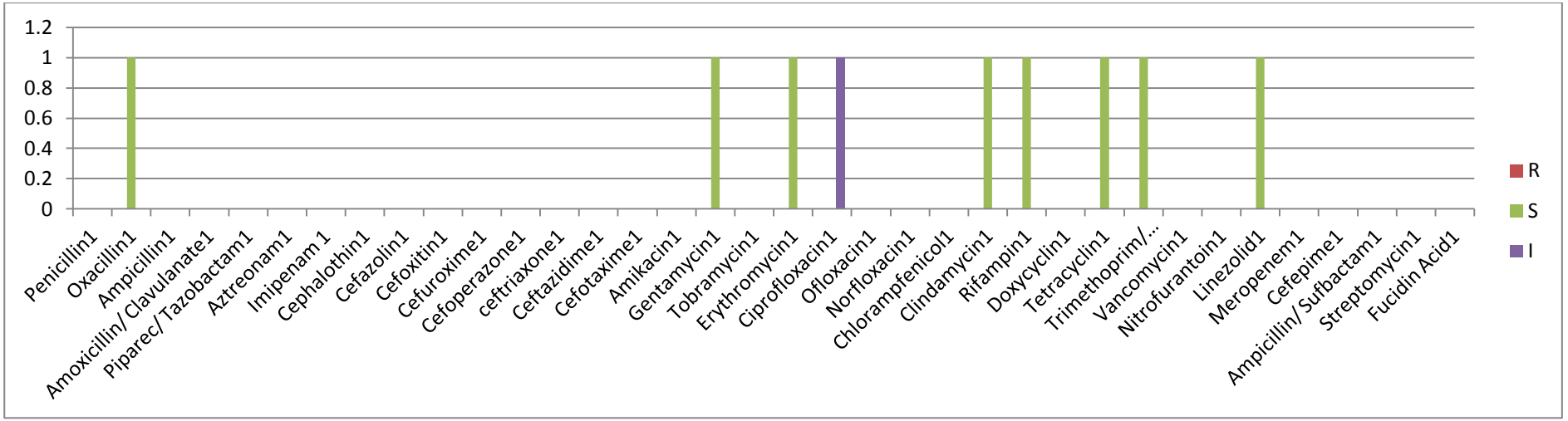


Figure: Antibacterial sensitivity for MS Staphylococcus capitis (x=antibiotics, y=number of bacteria)

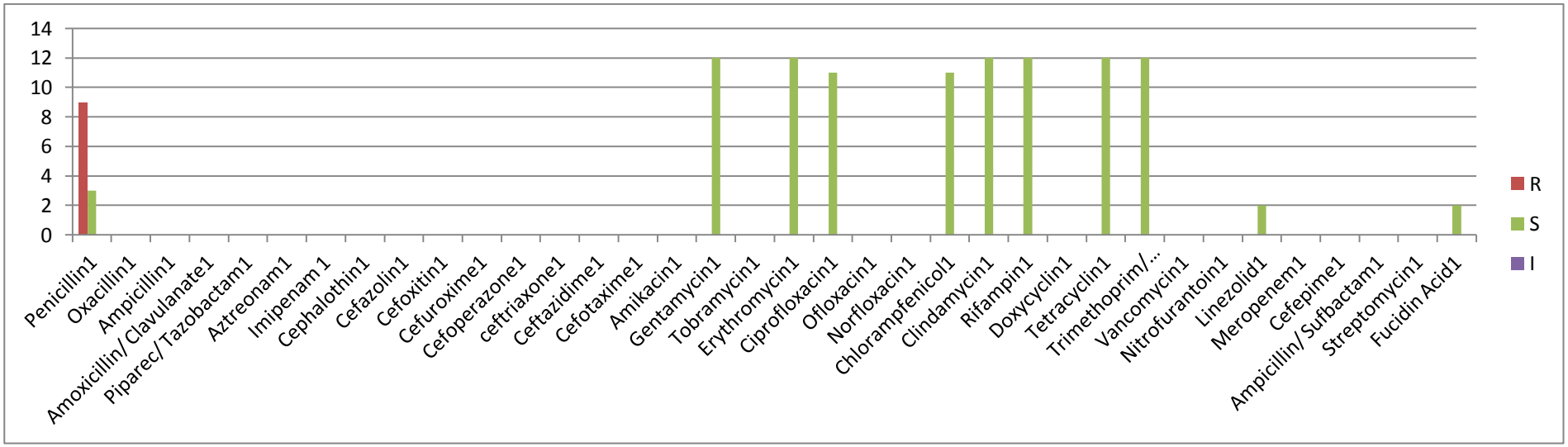


Figure: Antibacterial sensitivity for MS Staphylococcus aureus (x=antibiotics, y=number of bacteria)

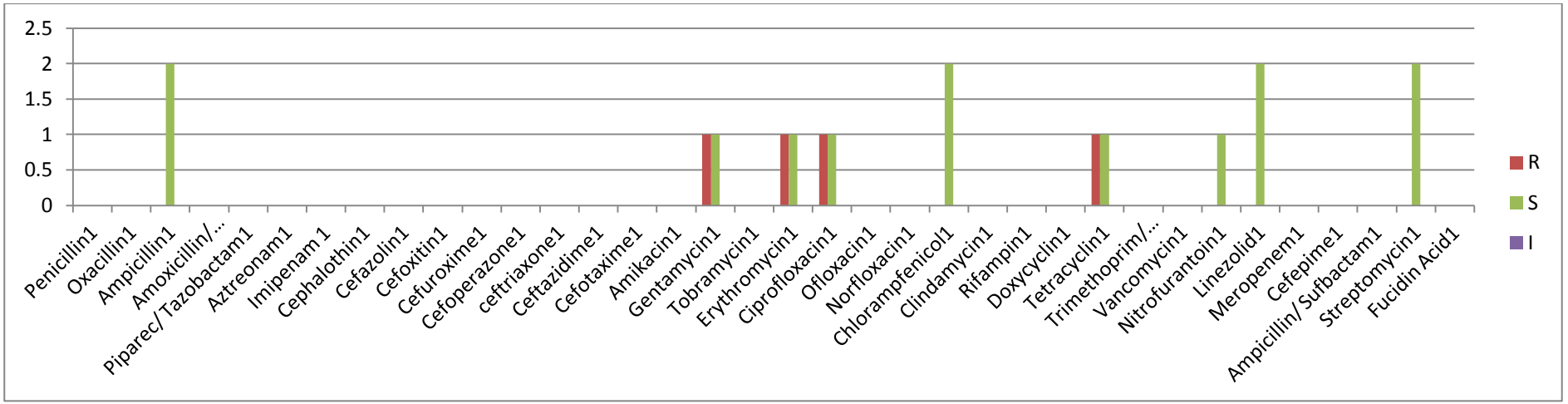


Figure: Antibacterial sensitivity for Enterococcus (x=antibiotics, y=number of bacteria)

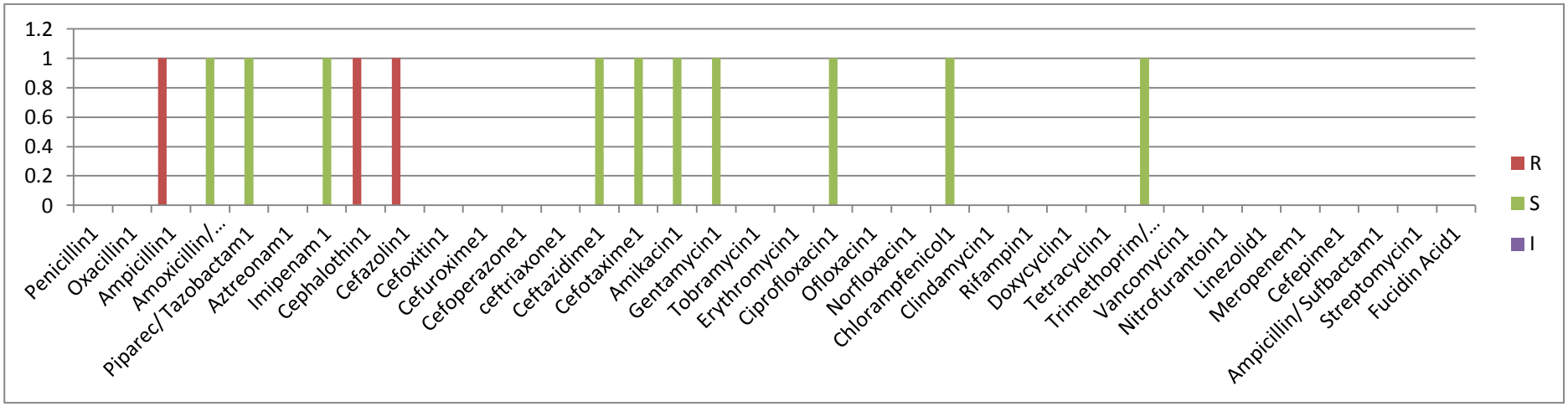


Figure: Antibacterial sensitivity for Enterobacter cloacae (x=antibiotics, y=number of bacteria)

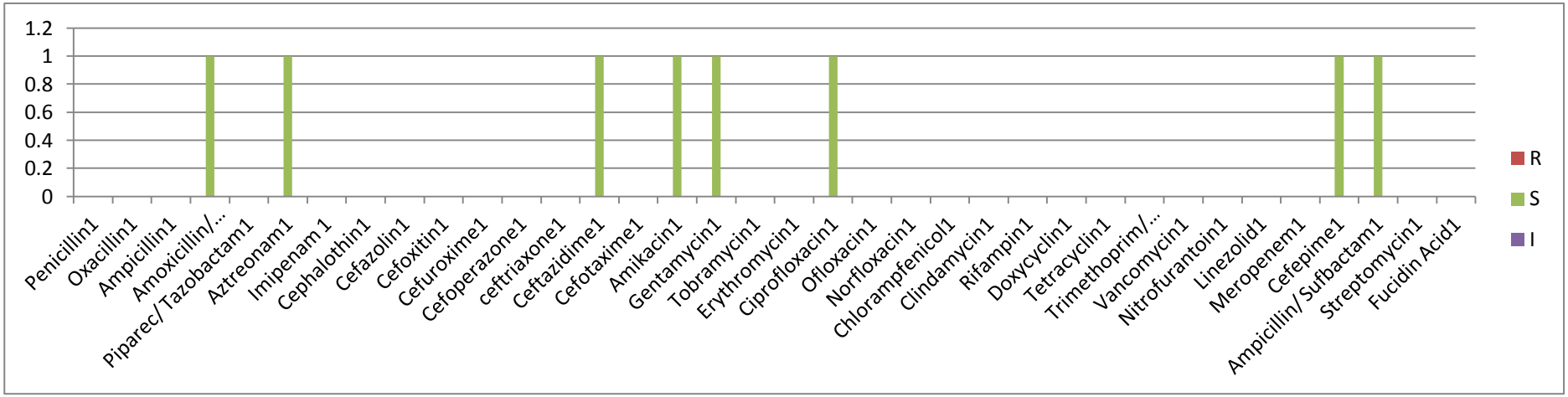


Figure: Antibacterial sensitivity for Pseudomonas aeruginosa (x=antibiotics, y=number of bacteria)