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RESEARCH ARTICLE

CLINICO-MICROBIOLOGICAL SPECTRUM OF HEMODIALYSIS CATHETER-RELATED BLOOD STREAM INFECTIONS: A CONCISE REVIEW

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Abstract

The disease burden of chronic kidney disease is increasing worldwide, and with the growing population of patients requiring hemodialysis, more patients are placed on central venous catheters (CVCs). Vascular access infections significantly cause hospitalization and mortality among end-stage renal disease (ESRD) patients. As per the data from the United States, Gram-positive organisms account for almost 56% of the total cases of catheter-related bloodstream infection (CRBSI), in stark contrast to Indian studies showing a dominance of Gram-negative organisms. The prolonged use of non-tunnelled catheters, poor hygiene, lack of catheter care protocols, and the tropical climate pose unique challenges to control CRBSIs in resource-poor countries. The most effective strategy to prevent CRBSI is to minimize the duration of dialysis catheters. Other strategies include the introduction of strict catheter care protocols, using tunnelled cuffed catheters, anti-microbial lock solutions, and topical antimicrobials. Eradicating nasal carriage of Staphylococcus aureus also reduced the incidence of CRBSIs.Treatment of suspected CRBSI should be promptly initiated with empirical broad-spectrum antibiotics covering Gram-positive and Gram-negative organisms. Catheter removal is indicated only if the patient is clinically unstable, has metastatic infections, and those who do not respond to antibiotic therapy.

Introduction:-

CKD affects about 850 million people globally and is projected to be the sixth leading cause of death by 2040 [1]. As per United States Renal Data System (USRDS) 2020 data, about 7.8 lakh patients have end-stage renal disease (ESRD), and 5.5 lakhs among them are on maintenance dialysis in the United States [2]. Limited dedicated centres, a lack of access to renal replacement therapy (RRT), and the absence of a registry blur the accurate picture of ESRD in India. In India, over 170,000 patients were on maintenance dialysis in 2018, and their number is ever-increasing [3].

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Prevalence of each type of dialysis access

Both the European Renal Best Practice (ERBP) position statement and the Kidney Disease Outcomes Quality Initiative (KDOQI) have emphasized the significance of minimizing the utilization of central venous catheters (CVCs) among those undergoing dialysis.Despite this, studies have shown that at least 10–20% of patients in most dialysis clinics have CVCs as vascular access [4].

As an increasing number of patients require hemodialysis, many are starting the same on CVC. In the US, dialysis therapy is initiated with a CVC in more than 80% of cases [5]. The catheter usage rate has stayed the same for many years, with India being no different, with more than three-quarters of patients starting dialysis on uncuffed catheters [6].

Types of temporary catheters

A hemodialysis catheter used for RRT is essentially an indwelling artificial channel in the transcutaneous plane, accessing the intravascular space. A broad classification of dialysis central venous catheters (CVC) is non-tunnelled (short-term, non-cuffed) and tunnelled catheters (long-term, cuffed). The cuffed catheters have lower rates of infection compared to the uncuffed ones.

In developing countries, a significant proportion of incident dialysis patients, ranging from 81% to 100%, rely on a non-tunneled hemodialysis catheter (NTHC) as their primary vascular access [7-9]. This prevalence can be attributed to factors such as low socioeconomic status, limited access to education, and inadequate reimbursement options, which often lead to delayed referral and the need for emergency dialysis initiation [10]. The insertion of non-tunnelled hemodialysis catheters (NTHC) can be performed safely using ultrasonic guidance, eliminating the need for costly fluoroscopic equipment. As a result, this method has become the preferred vascular access option for emergency dialysis in settings with limited resources.

Incidence of infection with temporary catheters

Of all infections in ESRD patients resulting in hospitalization, 28% can be assigned to vascular access infections. Infection is a prominent contributor to the death rate observed in individuals with end-stage renal disease (ESRD), ranking second only to cardiovascular events. CRBSIs are the significant contributors to infection-related morbidity and mortality among these patients, compelling it to be reported for surveillance in hospitals and dialysis units, earmarking it as a benchmark and performance indicator [11]. According to the National Healthcare Safety Network Dialysis Event Surveillance report for 2014, in catheter-dependent patients, 2.16 per 100 patient months was the mean rate of all bloodstream infections in the US, and 1.83 per 100 patient-months for access-related bloodstream infections (both permanent and temporary catheters) [12].

The duration of the catheter and left-sided internal jugular vein catheters are some of the catheter-related risk factors that increase the chance of bloodstream infections (BSI) in a tunnelled cuffed catheter (TCC). In contrast, a history of catheter-related bacteremia, hypoalbuminemia, and immunosuppression are patient-related factors [13-15].

Research undertaken in developing nations has documented a greater prevalence of catheter-related bloodstream infections (CRBSI). In one study by Parameswaran et al., the CRBSI rate was 8.75 cases per 1,000 catheter days [10]. A recent study conducted in India by Agrawal et al. examined non-tunneled dialysis catheters and documented an incidence rate of 7.34 incidents per 1,000 patient days at risk[16]. When comparing different types of catheters, it is generally observed that uncuffed catheters tend to have a higher infection rate (3.8 to 6.6 episodes per 1,000 days) than cuffed catheters (1.6 to 5.5 episodes per 1,000 days). Among uncuffed short-term catheters, femoral catheters stand out with the highest infection rate, averaging 7.6 episodes per 1,000 days of catheter use, more than 10% of which become infected within just one week of placement [17-19].

Defining CRBSI

According to the guidelines established by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI 2019), catheter-related bloodstream infection (CRBSI) is characterized by clinical symptoms and the presence of at least one positive blood culture obtained from a peripheral source, such as the dialysis circuit or vein, without any other identifiable cause. Additionally, a positive culture from the catheter is required, where the same organism is isolated from both the catheter segment (e.g., hub or tip) and a blood sample obtained from a peripheral source (dialysis circuit or vein) [20]. While adhering to internationally accepted standardized criteria for defining CRBSI is advisable, it is worth noting that in stable hemodialysis patients,

identifying the source of bloodstream infection is often clinically evident. This is in contrast to patients in intensive care units, where the source of bloodstream infections is often unclear.

Hence, isolating the same organism from the catheter segment and peripheral blood may not be obligatory for stable hemodialysis patients to classify it as CRBSI and provide appropriate treatment. In this regard, the North American Vascular Access Consortium defines CRBSI as definite, probable, or possible as follows [21];

1. "Definite": refers to an organism that has been cultivated from both a percutaneous blood culture and the catheter hub.
2. "Probable": refers to cases where positive blood cultures are acquired from both a catheter and a peripheral vein in a symptomatic patient, after ruling out other potential sources of infection.
3. "Possible": refers to situations where patients did not have a culture test or were administered empirical antibiotics prior to obtaining a negative blood culture. However, in these cases, there was no other plausible explanation for a protracted febrile illness that was temporally associated with the use of TCC.

Pathogenesis of CRBSI

An in-depth knowledge of the development of CRBSI, starting from catheter insertion to microbial colonization, biofilm formation, and then blood-stream infection, is essential to formulate effective preventive strategies for CRBSI.

A structural community of bacteria producing a matrix that encloses it and firmly attaches to the catheter surface comprises a biofilm with or without host constituents. Formed within the lumen or the outer wall of catheters, this structure produces a physical barrier against hostile host cells and antimicrobial agents. The bacteria can thus survive in an unfavourable environment, multiplying very slowly. Biofilm formation on the outside of the CVC and migration of bacteria along the surface into the bloodstream, leading to CRBSI, is generally seen within the first two weeks after catheter insertion. Beyond two weeks, contamination of the catheter hub and migration of bacteria to the inner surface of the catheter and then to the bloodstream is the predominant route of infection. After a few weeks, almost all the CVCs have an intraluminal biofilm, but not all lead to CRBSI [22]. Though the factors leading to the seeding of bacteria into the bloodstream from the biofilm are not well understood, the microbe species and strain characteristics play an essential role.

Microbiological spectrum

Various studies done in the US showed the predominance of Gram-positive organisms being isolated from cases of CRBSI in hemodialysis patients, with coagulase-negative staphylococci (CoNS) leading the chart (32-45%), followed by *Staphylococcus aureus*(22-29%) and Enterococci (9-13%), whereas Gram-negative bacteria were isolated in only 21-30% of cases [23, 24, 25]. Many studies have shown 4-21% of CRBSI to be polymicrobial [26, 27], and a recent retrospective study showed the percentage of polymicrobial CRBSI to be 14% [28].

According to the 2014 National Healthcare Safety Network report, access-related bloodstream infections (BSIs) within in-centre hemodialysis patients were primarily caused by Staphylococcus aureus (S. aureus) and Coagulase negative Staphylococci (CoNS). These two pathogens accounted for over 50% of all reported cases. Gram-negative organisms constituted a mere 12% of the infections. *S. aureus* is known for its propensityto cause secondary metastatic infections of the heart (endocarditis), bones (osteomyelitis), brain (epidural abscess), and other cardiac and vascular devices, often resulting in high morbidity and mortality. Methicillin resistance was detected in 40% of the S. aureus isolates [12].

There is a high risk of acquiring multi-drug resistant organisms (MDROs) as well as cross-contamination in dialysis units, as evidenced in a prospective cohort study of 67 patients from an outpatient HD unit, where more than a quarter of the patients were colonized with one or more antibiotic-resistant bugs like MDR gram-negative bacteria, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA) [29].

Indian studies have shown a dominance of Gram-negative organisms in CRBSI, in stark contrast to most studies worldwide where Gram-positive organisms are in pre-ponderance [16, 30, 31]. There has also been an increased incidence of CRBSI caused by drug-resistant organisms constituting up to 40% of CRBSI in the Indian dialysis population [16]. This increased prevalence of Gram-negative organisms can be attributed to patients and healthcare workers' lack of adherence to catheter care protocols and hygienic standards [24, 32].

Prevention
There is a need for an increased number of meticulously planned and executed randomized controlled trials (RCTs) to comprehensively evaluate the efficacy of infection prevention strategies in hemodialysis patients primarily utilizing central venous catheters (CVCs).

Several studies suggest that stringent catheter care practices reduce CRBSI.Though most of these studies were conducted in intensive care units (ICUs), one study done in stable hemodialysis patients demonstrated a decrease in the episodes of CRBSI to 1.6 from 6.7 per 1,000 catheter days after a catheter care protocol was introduced [33]. Strict catheter care should be practised during catheter placement, handling, or manipulation of the catheter and even during its replacement over a guidewire in case of any malfunction.

Catheter design
Studies comparing tunnelled, cuffed CVCs to non-tunnelled CVCs found no significant difference in CRBSI rates when the subclavian vein was used as the implantation site [34]. An RCT by Timsit et al., done in ICU patients with CVCs placed in the jugular vein, showed a significantly lower infection rate when tunnelled catheters were used than non-tunnelled ones (p=0.02) [35].A prospective cohort study by Menduet al. reported no observable difference in blood culture positivity between tunnelled and non-tunnelled CVCs [36].

The available data is insufficient to conclude that cuffed and tunnelled CVCs are necessary to prevent infection in hemodialysis patients instead of uncuffed CVCs. Strict implementation of catheter care protocol and appropriate selection of venous access are more important in preventing CRBSI. Novel designs of non-tunnelled catheters, like pre-curved CVC in a lower jugular location, can provide a similar benefit to tunnelled cuffed catheters.

Antimicrobial lock solutions
Numerous randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of antimicrobial lock solutions in preventing CRBSIs. The most studied antimicrobial lock solutions contain antibiotics or chemicals such as trisodium citrate or taurolidine. A meta-analysis pointed out that antimicrobial lock solutions appreciably reduced CRBSI risk [37, 38]. Fortunately, taurolidine and citrate-containing solutions have not shown any development of resistance by the bacteria, which is always a matter of grave concern. Ethanol or calcium-binding ethylene-diamine-tetra-acetic acid (EDTA) based antimicrobial lock solutions are also being used at different centres. However, sufficient clinical data from large RCTs have yet to be available to comment on their efficacy.

Topical antimicrobial agents
Evidence from a meta-analysis on topical antimicrobial agents for preventing CRBSI has shown chlorhexidine's superiority in cleaning the exit site to povidone-iodine [39]. However, most of the studies included hospitalized patients on CVCs, thus needing better representation of stable hemodialysis patients on CVC. Various agents like medicinal honey, mupirocin, 10% povidone-iodine, and bacitracin–polymyxin have been used in various studies. A meta-analysis of topical antimicrobials concluded that topical mupirocin alone at the exit site can prevent CRBSI.

Eradication of Staphylococcus aureus
Staphylococcus aureus, a common isolate from patients with CRBSI, is also associated with high mortality. The nasal carriage of Staphylococcus aureus is high among dialysis patients. It is shown to be associated with CRBSI. Mupirocin applied daily to the anterior nares for five days can eliminate *S. aureus* nasal carriage, and once-weekly application or repeating the short course can reduce recolonization. This approach can lead to the development of S. aureus resistance to mupirocin and increased incidence of other bacterial infections [40].

Treatment
In a suspected case of CRBSI, broad-spectrum antibiotic coverage should be initiated empirically after obtaining blood cultures. Due to the high prevalence of MRSA in these patients, Vancomycin or Teicoplanin should be included. Local antibiogram should guide the selection of empirical Gram-negative coverage. Whenever options are available, preference should be given to the antibiotic, which can be administered at the end of dialysis. This improves treatment efficacy and patient compliance. The Infectious Diseases Society of America (IDSA) has outlined guidelines for the duration of antimicrobial therapy for long-term catheter-related infections. The recommendation for uncomplicated CRBSI by *S. aureus* is 4–6 weeks, whereas the same for Gram-negative bacilli or Enterococcus species is only 7–14 days. For CRBSI with *Candida* species, a minimum of 14 days is suggested. Complicated CRBSI, as distinguished by evidence of septic thrombophlebitis and/or endocarditis, should receive 4–

6 weeks of treatment, whereas if osteomyelitis is present, treatment should be prolonged to a minimum of 6–8 weeks [41, 42].

Catheter removal is indicated if the patient is clinically unstable, has metastatic infections, and those who do not respond to antibiotic therapy.

Conclusion:-

As the prevalence of chronic kidney disease is rising, the number of patients on CVC for hemodialysis is also increasing. With 80% of incident dialysis patients in developed nations starting dialysis on CVC, the figures are between 80 and 100% in developing countries. The high prevalence of non-tunnelled catheters, poor hygiene and catheter care protocols, high rates of antibiotic resistance, socioeconomic factors leading to prolonged usage of CVCs, higher rates of gram-negative organisms and MDR organisms along with the tropical climate increase the rates of CRBSI in resource-poor countries. Implementing strict catheter care protocols is an effective strategy to reduce the rate of CRBSI. In addition, topical antimicrobial agents, antimicrobial lock solutions, and eradication of nasal staphylococcal carriage may reduce the rate of CRBSI. When indicated, the prompt institution of broad-spectrum antibiotics with both Gram-positive and negative coverage in all suspected cases of CRBSI and catheter removal is essential to prevent severe complications of metastatic infections and sepsis.

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