Clinical & Experimental Cardiology

Gülmez, J Clin Exp Cardiology 2017, 8:4
DOI: 10.4172/2155-9880.1000511

Review Article OMICS International

Infective Endocarditis in Chronic Hemodialysis Patients: A Review Article for Assessment and Treatment

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Abstract

Infective Endocarditis (IE) is a life-threating condition especially in patients with end-stage renal disease (ESRD). It has been particularly associated with recurrent bacteremia because of vascular access via dual lumen catheters. Patients with ESRD receiving hemodialysis (HD) are prone to metastatic bloodstream infections and the calcified or degenerative mitral valve (up to 50% of cases) is more frequently affected than aortic valve. The most common pathogen is *S. aureus*. Methicillin-susceptible *S. aureus* (MSSA) accounts for 33% of the cases whereas methicillin-resistant *S. aureus* (MRSA) accounts for 25% of the cases. The diagnosis of IE in patients with ESRD using Duke Criteria is problematic since the clinical presentation usually resembles to an access infection. Mortality still remains high with reported rates ranging from 30% to 50%. Mitral valve involvements, septic embolism, IE related to drug resistant organisms are the mortality risk factors in this population. Transthoracic echocardiography as well as trans esophageal echocardiography should always planned in any ESRD patient with suspicion of IE. Appropriate antibiotic treatment and duration as well as surgery in selected cases should be considered according to the guidelines. Anti-staphylococcal penicillin or first generation cephalosporin should be selected for MSSA. Coversly, vancomycin should be selected for MRSA. Strict hygiene, cleaning the site and sterile techniques when accessing artriovenous fistulas or vascular catheters can minimize the potential for infection.

Keywords: Infective endocarditis; End-stage renal disease; Hemodialysis

Introduction

Cardiovascular Disease (CVD) represents the first cause of death (almost half of the total mortality) and morbidity in patients with end-stage renal disease (ESRD), whereas infection represents the second cause of death with an incidence ranging from 12% to 22% [1,2]. Infective endocarditis (IE) is a life-threating condition associated with high morbidity and mortality. Furthermore, it is significantly more common in patients with ESRD receiving chronic hemodialysis (HD). Therefore, health-care-associated and HD-associated IE is proposed to be added as a fifth category to the historical categorical classification of IE which are native valve IE, prosthetic valve IE, IE in e.v. drug users, nosocomial IE [3].

The current review summaries the epidemiology, pathogenesis and microbiological profile, clinical presentation and diagnosis, prognosis and management of IE in HD patients.

Epidemiology

The first case of IE in a HD patient was reported in 1966 [3]. Retrospective studies reported the incidence of IE in HD patients as 6% [4]. In US population, the incidence of IE in HD patients has been estimated to be approximately 308 cases/100,000 patient-years, an age-adjusted incidence ratio of 17.9 for HD patients compared with the general population (1.7-6.2 cases/100,000 patient-years) [5]. A 1 year IE French Survey found the incidence of IE in HD patients 50-60 times higher than the overall incidence of IE in France [6]. Moreover, in a study using Taiwan National Health Insurance Research Database, the incidence of IE was 201.4/100000 person-years [2]. Of note, the frequency of IE in patients receiving peritoneal dialysis (PD) is not higher when compared with the general population. However, HD is associated with a 42% higher risk of IE when compared with PD [2,5].

Pathogenesis and microbiological profile

Patients with ESRD have impaired immune system because of uremia, biochemical abnormalities, malnutrition, elderly, and comorbid conditions such as diabetes mellitus and underlying systemic disease which increase the bacteremia risk [2,3]. The other risk factor for bacteremia causing IE is the presence of vascular access. Patients with ESRD receiving HD are prone to metastatic bloodstream infections due to tunneled catheters with one of the most common form as IE. Although, native arteriovenous fistula has been recommended as the preferred vascular access by National Kidney Foundation clinical guidelines, 28% of patients continue to undergo HD via central venous catheter [7]. Recurrent bacteremia because of vascular access infection during HD occurs with a rate of one episode per 100 patient-months of which IE develop in 1-12% of them [3,8,9]. Moreover, the incidence of HD access-related bacteremia is reported to be from the highest to the lowest as: patients with temporary catheter, patients with permanent central venous catheter, patients with arteriovenous grafts, and patients with native arteriovenous fistula [10]. The sources of bacteremia can be endogenous (patient's own cutaneous flora) or exogenous (hands of personnel, contaminated equipment) [3]. The prominent role of recurrent bacteremia because of vascular-access in HD patients may explain the reason of unincreased frequency of IE among PD patients when compared with general population.

Left-sided endocarditis is predominant and occurs twice as often as right-sided endocarditis in HD patients. Mitral valve is more frequently affected than the aortic valve (up to 40% of cases), reaching a frequency

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Received March 20, 2017; **Accepted** April 13, 2017; **Published** April 20, 2017

Citation: Gülmez Ö (2017) Infective Endocarditis in Chronic Hemodialysis Patients: A Review Article for Assessment and Treatment. J Clin Exp Cardiolog 8: 511. doi:10.4172/2155-9880.1000511

up to 50% of cases [3,8]. Multiple valve infections occurs in 20% of cases [3,9]. There are several potential explanations for these findings. Mitral annular classification, aortic and mitral valve thickening and calcification due to abnormalities of calcium-phosphorus homeostasis increases the susceptibility to IE related to alterations in laminar flow [3]. Moreover, premature degeneration of heart valves begins 10-20 years earlier in this population than the general population [3]. In contrast, in the developing world, most of the cases are due to underlying rheumatic heart disease [2].

S. aureus is the most common cause of IE with a frequency ranging from 40% to 80% in this population. The possible explanation for this finding may be the high rates of nasal carriage of *S. aureus* among HD patients [9]. Methicillin-susceptible *S.aureus* (MSSA) accounts for 33% of the cases whereas methicillin-resistant *S. aureus* (MRSA) accounts for 25% of the cases [8]. However, the frequency of MRSA is increasing among both in general population and ESRD patients [11,12]. In 2002, the number of MRSA isolated in HD patients is reported to be 50% of all *S. aureus* strains [13]. The other common causative organisms of IE in HD patients are coagulase-negative *staphylococci, enterococci, viridans* group streptococci, and less commonly *Pseudomonas aeruginosa* and *candida* [9].

Clinical presentation and diagnosis

The modified Duke criteria have been validated for the diagnosis of IE (Table 1) [14]. However, diagnosis of IE in HD patients remains a clinical dilemma as the clinical presentation usually resembles to an access infection and the modified Duke criteria requires typical microorganism from two separate blood cultures drawn 12 h apart, in the absence of a primary focus for the blood culture to be a major criteria. Moreover, less frequently presentation with fever (45-70%) which is one of the minor Duke criteria makes the diagnosis of IE in patients with ESRD problematic (Table 2) [3].

Symptoms of heart failure, embolic complications in descending order of frequency as brain, joints, extremities, spleen, kidney, liver and lung may be the symptoms of IE [9,15]. Valvular complications such as new valvular regurgitation, perivalvular abscess, and conduction abnormalities such as heart block due to local extension of aortic valve endocarditis to membranous interventricular septum may be the first findings of IE in HD patients [9,15,16].

Any ESRD patient with suspicion of IE should be screened by transthoracic echocardiography (TTE). Moreover, trans esophageal echocardiography (TEE) should always plan after TTE in patients with poor image quality, suspicion of valvular and paravalvular complications and high clinical suspicion features for IE such as:

1. New-onset heart failure,
2. Other stigmata of endocarditis,

Definite IE **1. Pathological criteria** a. Microorganism demonstrated by culture or on histological examination of vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or b. Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis **2. Clinical criteria** a. 2 major criteria; or b. 1 major criterion and 3 minor criteria; or c. 5 minor criteria
Possible IE 1. 1 major criterion and 1 minor criterion; or 2. 3 minor criteria
Rejected IE 1. Firm alternate diagnosis; or 2. Resolution of symptoms suggesting IE with antibiotic therapy for ≤ 4 days; or 3. No pathological evidence of IE at surgery or autopsy; with antibiotic therapy for <4 days; or 4. Does not meet criteria for possible IE, as above
IE: Infective Endocarditis

Table 1: Modified Duke criteria for the diagnosis of infective endocarditis [14].

Major Criteria **1. Blood cultures positive for IE** a. Typical microorganisms consistent with IE from 2 seperate blood cultures: i) viridans streptococci, *streptococcus gallolyticus* (*Streptococcus bovis*), HACEK group, *Staphylococcus aureus*; or ii) community-acquired enterococci, in the absence of a primary focus b. Microorganisms consistent with IE from persistently positive blood cultures: i) at least ≥ 2 positive blood cultures drawn >12 h apart; or ii) all of 3 or a majority of ≥ 4 separate cultures of blood with first and last samples drawn 1 h apart; or c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800 **2. Imaging positive for IE** a. Echocardiogram positive for IE: i) vegetations; abcess, pseudoaneurysm, intracardiac fistula; or ii) valvular perforations or aneurism; new partial dehishence of prosthetic valve. b. Abnormal activity around the site of the prosthetic valve detected by ^{18}F-FDG PET/CT implanted >3 months ago or radiolabelled leukocytes SPECT/CT c. Definite paravalvular lesions by cardiac CT
Minor Criteria: 1. Predisposition such as predisposing heart condition, or injection drug use 2. Fever defined as temperature >38^{0}C 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurism, intracranial hemorrhage, conjuctival hemorrhages, and Janeway's lesions 4. Immunological phenomena. Glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor 5. Microbiological evidence: positive culture does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
IE: Infective Endocarditis; FDG: Fluorodeoxyglucose; PET: Position Emission Tomography; CT: Computed Tomography; SPECT: Single Photon Emission Computerized Tomography

Table 2: Definitions of major and minor criteria [14].

3. Development of HD related hypotension especially in a previously hypertensive patient,
4. History of IE, repeated past episodes of IE,
5. Prior valvular surgery or an intracardiac device is present,
6. Bacteremia with typical organism for IE,
7. Relapsing bacteremia after antibiotic discontinuation, regardless of the causative pathogen,
8. Patients with HD catheters [3]

It is also recommended to repeat TTE and/or TEE within 5-7 days in case of initially negative examination when clinical suspicion of IE remains high.

Prognosis

Although the prognosis of IE in PD patients is significantly better than those of HD patients, mortality still remains high with reported rates ranging from 30% to 50% and have changed only a little during the past decade despite the improvement in medical and surgical therapy in this population [2,4,8,9]. Impaired immune system, metabolic abnormalities, comorbid conditions such as diabetes mellitus are the conditions that alter the immune defence of HD patients and possible explanations of higher mortality.

Heart failure, age, renal failure, stroke at the time of presentation and *S. aureus* bacteremia are classical risk factors of mortality in patients with IE [16]. Recently, the presence of persistent positive blood cultures after 48-72 h of appropriate antibiotic treatment is reported to be an independent risk factor for in-hospital mortality in general population [17]. Moreover, elevated troponin levels are associated with high risk for poor outcome such as higher mortality and surgery rates, central nervous system events, more extensive infection, and local invasion of the myocardium, coronary embolism and cardiac abscess in patients with IE [18]. Presence of persistent positive blood cultures and elevated baseline troponin levels may identify high-risk patients that need more aggressive treatment. The 2015 European Society of Cardiology (ESC) guideline of IE defines the predictors of poor outcome in patients with IE as:

1. **Patient characteristics**: Elderly, prosthetic valve IE, diabetes mellitus, comorbidity (renal or pulmonary disease, immunosuppression)
2. **Clinical complications**: Heart failure, renal failure, >moderate area of ischemic stroke, brain hemorrhage, septic shock
3. **Microorganism:** *Staphylococcus aureus*, Fungi, non- HACEK Gram negative bacilli
4. **Echocardiographic findings:** Periannular complications, severe left-sided endocarditis, low left ventricular ejection fraction, pulmonary hypertension, large vegetation, severe prosthetic valve dysfunction, premature mitral valve closure and other signs of elevated diastolic pressures [19].

The mortality risk factors for IE in HD patients are less clear. Mitral valve involvement is strongly associated with in-hospital mortality which may be due to clinically significant septic emboli caused by larger sizes of mitral valve vegetation's. Lower gradient across the mitral valve might have allowed the lesions to attain a larger size [15]. The other factors that are associated with higher in-hospital mortality are septic embolism specifically embolus to the brain resulting stroke, IE related to drug resistant organisms such as MRSA and vancomycin-resistant *Enterococcus* sp [15]. The poor prognostic factors are defined as right sided endocarditis, large vegetation size, and diabetes mellitus [4].

Management

Therapy of IE in HD patients, indications and timing of the surgery, or duration of the antimicrobial therapy, remains a clinical dilemma. Pathogen specific antibiotic treatment and duration as well as surgery in selected cases should be considered according to the guidelines on IE that can apply to both patients with and without ESRD [19]. A minimum of two sets of blood cultures should be obtained from separate peripheral venipuncture sites in order to reduce the possibility of catheter infection before empiric antibiotic therapy started [9].

Anti-staphylococcal penicillin or first generation cephalosporin should be selected for MSSA IE. Vancomycin should not be used for the treatment of MSSA IE as it has lower bactericidal activity when compared with oxacillin or cefazolin. Conversely, treatment of MRSA starts with vancomycin possibly in combination with rifampicilin. However, treatment of MRSA IE is a growing problem, both for to maintain a though plasma level of vancomycin about 15-20 mg/L without toxicity and for the rising incidence of *S. aureus* strains with increase vancomycin minimal inhibitory concentration. In such conditions alternative drugs such as linezolid and daptomycin can be preferred [3]. A minimum of 4-6 weeks of parenteral therapy is required to cure IE [19].

The 2015 ESC guideline of IE defines candidates for surgery as:

1. Patients with heart failure refractory to medical therapy,
2. Uncontrolled infection (caused by fungi or multiresistant organisms),
3. Recurrent embolic events,
4. Enlarging vegetation or >10 mm vegetation,
5. Mechanical complications such as new heart block,
6. Valvular complications such as perivalvular or aortic abscess, fistula, and valvular perforation [19].

However, there is no study which examined the issue of whether the standard indications for surgery in general population can be applied to patients with ESRD receiving HD. The decision should be made after the benefits versus risks of operation complicated with the operative mortality and morbidity for this population as HD was shown to be an independent predictor of operative and long-term mortality [19]. Although high perioperative mortality and morbidity related to a more advanced stage of the disease, 25-30 % of patients require surgery during the acute phase of infection which is consistent with reports from the general population [8]. Moreover, appropriately timed valve surgery was showed to be independently associated with reduced mortality in left-sided endocarditis [8]. The choice of type of prostheses used for valve replacement in HD patients with IE should be individualized. Risk factors for both bleeding and thrombotic complications, life expectancy (accelerated degeneration and calcification of bioprosthetic valves), suitability for long-term anticoagulant therapy and risk of prosthetic valve reinfection have great importance while decision making the type of prostheses [8,9]. Because of the limited life expectancy and tendency for bleeding complications of HD patients, bioprosthetic valves should be considered in this population.

One important consideration relates to the decision making about

the removal of HD catheters in patients with IE since the effectiveness is not clearly defined and data from controlled trials are scarce. While limited number of series suggest to remove and transfer the patient on PD, the others suggest to exchange the infected catheter with a new catheter [3,20,21].

Conclusion

IE is a potential lethal disorder of HD patients that requires rapid differential diagnosis and accurate treatment defined as timely initiation and duration of appropriate antimicrobial therapy as well as surgery in selected cases. Diagnosis of IE should be considered in all HD patients presenting with bacteremia, particularly in those with vascular access and when the pathogen is *S. aureus*, coagulase-negative staphylococci, or enterococci. What is more important than that is strict hygiene, cleaning the site, and sterile techniques when accessing arteriovenous fistulas or vascular catheters can minimize the potential for infection.

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