Chapter 1

Complications of Endocarditis

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1. Introduction

Infective endocarditis (IE) is an endovascular infection and inflammation with vegetation formation, usually caused by infectious agents. Bacterial infection is most common for IE, but other pathogens such as fungi, richettsia, chlamydia and virus, can also cause IE [1]. The vegetations vary in size and shape and are composed of platelet and fibrin blocks with plenty of microbial and small amounts of inflammatory cells inside [2]. IE occurs mostly in the patients with cardiac abnormalities or lesions including rheumatic heart disease, ventricular septal defect, patent ductus arteriosus, valvular stenosis or incompetence [3]. Nevertheless, IE can also be seen in other conditions, such as valve replacement, pacemaker implantation, intravenous drug users and a few people without cardiac lesions. Most patients are young and clinically exhibit low to mild fever, progressive anemia, asthenia, night sweat, hepatosplenomegaly and clubbed finger (toe) [1-3].

The incidence of IE is 30 per million persons per year [4]. Despite major improvements in diagnosis and treatment, the mortality of IE still remains high at 14% of in-hospital and even higher at 20% to 30% complicated with age and heart failure, especially in developing countries [5,6]. Based on different criteria, IE can be divided by several classifications. By duration, IE can be classified to subacute bacterial endocarditis (SBE) and acute bacterial endocarditis (ABE); By culture result, IE can be divided by *staphylococcal* endocarditis, *streptococcal* endocarditis, *enterococcal* endocarditis, *fungal* endocarditis; By individual valve type, IE can be classified by native valve endocarditis, prosthetic valve endocarditis and endocarditis in intravenous drug abusers [2-4]. As reported in a study with an IE population of 223 episodes, complications occurred in 74% patients, including cardiac, neurological, septic, renal, embolism and infarction/ abscess [7]. It also suggests that neurologic and septic complications are the leading causes of death in IE patients [7]. With the improvement of diagnosis and therapy, the frequencies of IE complications have changed. For example, septic and embolic symptoms are relatively rare because of early and adequate dosage of antibiotic therapy [4]. On the contrary, there are increasing

complications in prosthetic valve IE and intravenous drug abuse patients which may bring new challenge for clinical diagnosis and therapy. Since there are different diagnostic criteria for IE, it is difficult to conclude the true incidence of IE [8]. Overall, diagnosis is missed until autopsy in 38.2% of cases, especially when the patients are absence of fever, cardiac murmurs and other typical symptoms of IE [9]. In this chapter, several most common complications and related pathophysiologic process in IE patients will be summarized.

2. Intracardiac infection and local spread

Cardiac complications are the most common complications seen in IE patients, occurring in one-third to one-half of patients in most recent case series [10, 11].

2.1. Congestive Heart Failure (CHF)

CHF is a leading cause of death in IE patients [12]. The size of nodular or polypoid-like vegetation varies from 1 micrometer to several centimeters which can block the valve entrance [13]. The vegetation can cause valvular perforation and lead to prolapse. When the infection is controlled, valve lesions may still go on with fibrosis and contracture in some cases. All of these pathologic changes induce valvular insufficiency, mainly involved in aortic valve (50%), mitral valve (40%) and tricuspid valve (6%) [14]. A study on 511 IE patients show that moderate or severe congestive heart failure accounts for 44% in total complications [15]. According the report enrolling 4166 IE patients from multi centers in 28 countries, 33.4% patients have heart failure and 66.7% of the heart failure patients are classified as New York Heart Association class III or IV symptom status [16]. The total in-hospital mortality is 29.7% for the CHF cohort. They conclude that the severities of CHF in IE patients are associated with surgical status and mortality [16]. Based on the seriousness of CHF in the course of IE patients, the timing for early prophylaxis and treatment will influence its prognostic significance.

2.2. Cardiac abscess

Abscess is most common in acute patients and may happen anywhere in the heart [17]. The most frequent cardiac abscess occurs in aortic root of 56.5% of (26/46) IE patients, and the infecting organism is staphylococcus (52.3%) in patients with abscesses more often than in those without abscesses (16.2%) [17]. Occasionally, cardiac abscess can cause papillary muscle rupture, ventricular septal perforation, and even purulent pericarditis when the infection infiltrates the myocardial wall [13]. Moreover, the infection beyond the valve annulus can spread to adjacent structures and cause an emergency and higher mortality which can be observed in 88% of cases [18]. Another study on a large number of cases with valvular ring abscesses suggests that early identification of abscesses is particularly important to improve the outcome after timely surgery [19]. They also conclude that the overall operative mortality is not correlated with patient's age, *staphylococcal* infection or abscess fistulization [19]. However, the diagnosis is difficult, especially for small abscesses located on the anterior aortic wall and mitral abscesses.

3. Embolic

Embolization is frequently observed in IE patients and can even occur in patients undergoing therapies. IE patients have high prevalence of embolic complications for 13-49% [20]. In a study of 65 IE patients, a total of 37 (56.9%) patients are diagnosed with a cerebral embolism (overt 13, clinically silent 24) by blood test, cultures, echocardiography, and MRI/CT imaging [21]. Their results suggest that both overt and clinical silent central nervous system embolism are common complications of IE patients and silent embolism needs further imaging tools for examination [21]. Recently, their group uses some new biological markers, such as S-100B, to predict embolism in central nervous system during the course of IE [22]. Since most of the S-100B protein are synthesized by astrocytes and released from damaged neural tissues, the biomarker provides another specific method for screening CNS stroke in IE patients. An early study shows that the microorganism, but not vegetations on echocardiography, is associated with a significantly higher risk for embolus in patients with left-sided IE [23]. With transthoracic echocardiography in predicting embolic events, another group found that the vegetations bigger than 10 mm were associated with a 50% incidence of embolic events, while vegetations less than 10 mm had a 42% incidence of emboli in IE patients [24]. Similarly, in the patients who are diagnosed with acute IE and have no confirmed or suspected embolism before, 44% (25 in 57) have embolic events by using both transthoracic and transesophageal echocardiograms [25]. They also suggest the characteristics of vegetations identified by echocardiograms are not helpful in predicting embolic risk in IE patients [25]. In combination with clinical antibiotic therapy, embolism occurred in 34.1% (131 in 384) patients before/after IE diagnosis and in 7.3% (28 in 384) patients after initiation of therapy [26].

Besides neurological embolism, other organs such as spleen, kidney, lung and limbs, are also involved in rare cases [27, 28]. According to a report by Luaces-Méndez *et al*, there are 10% hepatosplenic and renal embolisms infarctions in left-sided IE patients with characteristic clinical features [29]. But in fungi caused IE, emboli occurs in 25%(41 in 162) patients and symptomatic embolization appears to be more common of 17% (7 in 41) in peripheral limb, 7% (3 in 41) in pulmonary, 5% (2 in 41) in mesenteric [30].

The characteristics of bacterial embolus are multiple, fragile and movable, so in many cases IE patients present with stroke, meningitis, brain abscess and bacterial aneurysm.

3.1. Stroke

Ischemic and hemorrhagic strokes are important neurological complications and are frequent in IE patients during uncontrolled infection. There are about 21% complicated by stroke in 212 IE patients in a study between 1978 and 1986 [31]. In a population of 214 IE patients undergoing cardiac surgery, the prognosis for patients with uncomplicated ischemic stroke are better than patients with complicated stroke (meningitis, hemorrhage, or brain abscess) after 20 years following up [32]. In order to prevent cardioembolic stroke, additional diagnostic tools such as echocardiography and cardiac magnetic resonance imaging, can be applied to identify the sources of cardiac embolism. Another investigation in 707 patients who are diagnosed with

possible IE, strokes occur in 9.6% of total cases, which is lower than previous reports (21 to 39%) [33]. In order to study the relationship between vegetation 2-dimensional size and stroke in those IE patients, researchers use Duke Endocarditis Database to examine 145 IE patients and find 23.4% (34 in 145) complicated by stroke, suggesting vegetation 2-dimensional size and characteristics as predictors for stroke and mortality [34].

3.2. Mycotic aneurysm

If the artery is blocked by the septic embolus, the wall may be necrosised and destroyed, and then develop bacterial aneurysm. Mycotic aneurysm is rare, about 4% (23 in 513), in IE patients [15]. Aorta, brain, viscera and limbs can become involved in turn [35]. Patients can show throbbing lump during the late stage. The disease is easily diagnosed while occuring at peripheral vessels. However, when the lesion happens in deep arteries such as brain and mesentery, aneurysm is always ignored until it is broken and bleeding [36]. Mycotic aneurysm has a high mortality rate for its potential catastrophic rupture but can be prevented by early diagnostic imaging techniques [37]. Cerebral mycotic aneurysms tend to occur in the more distal portions of the middle cerebral artery, especially in the region of the sylvian fissure, which clinically is different from berry aneurysms occurring near the Willis circle [38].

3.3. Cerebral hemorrhage

Cerebral hemorrhage will occur when the vessel is broken in bacterial aneurysm or embolism. It is easy to develop spotted or patched hemorrhage when there is big area of infarction in the brain. There are three different mechanisms for cerebral haemorrhage in IE patients: rupture of a mycotic aneurysm, septic arteritis without aneurysm, spontaneous haemorrhagic transformation of a blank brain infarction [39].

Subarachnoid hemorrhage is a rare but dramatic neurologic complication in IE patients and is always associated with aneurysm rupture in the early phase [40]. Previous reports show that high mortality is related to intracerebral haemorrhage [41, 42]. The species of microorganism seem to have relationship with brain haemorrhage. Data presented in an investigation shows that brain haemorrhages in 40.7% (35 in 86) IE patients are caused by *Staphylococcus aures* [43].

4. Hematogenous dissemination

4.1. Metastatic abscess

When the vegetation with infecting bacteria drops off, it will migrate with blood and cause embolism in the artery. During a report on 118 IE patients, 44 (37.3 %) patients have 46 definite regions of abscess in total and abscesses present more frequently in endocarditis from aortic-valve than other valves [17]. If the infection is not controlled well, abscesses can develop in the spleen, kidney, brain or soft tissues in IE patients. With the improvement of antibiotic treatment, metastatic abscess is relatively rare but still reported in recent years [44-46].

Splenic abscesses are found in up to 5% IE patients and usually exhibit abdominal pain, pleuritic or shoulder pain as of diaphragmatic irritation, or persistent fever [47]. According to the conclusion from 27 patients with splenic abscess, the cases could not survive without a timely splenectomy surgery [48]. If possible, the patient with IE should be treated first for splenic abscesses and then splenectomy should be performed for the requirements.[49].

Cerebral abscess is rare in IE patients including suppurative encephalitis, chronic granuloma and abscess envelope [50]. The time for envelope formation depends on the types of bacteria and the toxicity, body's resistance and reaction for antibiotic therapy [51]. According to the report on a series of cases, miliary microscopic abscesses are more common than macroscopic cerebral abscess in bacterial endocarditis patients, particularly in patients with acute miliary infection [41]. Cerebral abscesses in some IE patients are suggested to be related with *S. aureus* infection and purulent meningitis [41].

4.2. Toxic encephalopathy

Toxic encephalopathy occurs when plenty of bacteria enter the circulation and cause septicemia. In an investigation of 110 patients, 19.1% (21 in 110) show toxic encephalopathy, which is ranked the second common neurological manifestation of IE patients [52]. Frequently, the patients display a variety of symptoms, such as early stage of headache, dizziness, hypersomnia, nausea, vomit and late stage of hallucination, memory loss, small personality changes, seizures, disturbance of consciousness. The multiple cerebral emboli and multifocal microinfarcts cause formation of microabscesses, which may explain the pathophysiological mechanism for acute encephalopathy [53].

4.3. Purulent meningitis

This complication is uncommon and concomitant with cerebral abscess. Sometimes the intracerebral abscess may enter subarachnoid cavity and cerebral ventricle to invade meninges, which will cause purulent meningitis [54]. If *Streptococcus anaerobius*, *bacteroid*, *Staphylococcus* and mixed bacteria are separated in cerebrospinal fluid, it suggests that there are relationships between meningitis and broken intracerebral abscess.

5. Musculoskeletal complications

The musculoskeletal manifestations include spondylodiscitis, osteomyelitis, septic arthritis and peripheral soft tissue abscess, which occur frequently in up to 44% cases [55]. Because the existing of osteoarticular complications, the patients are at a higher risk of having major embolic events from the central nerve system to lungs [56]. Vertebral osteomyelitis is relatively rare complication in IE patients. Overall, 4.6% (28 in 606) cases in IE patients have pyegenic vertebral osteomyelitis [57]. The patients are needed to exclude IE if they have spondylodiscitis and pre-existing heart disease or microbiologic infection [58]. With MRI as a highly sensitive and specific tool for diagnosing, patients with spondylodiscitis usually can be found early before infection has spread to two vertebral body levels.

In IE patients, the percentages of osteomyelitis and septic arthritis are up to 4.3%, and they occur more frequently in patients with tricuspid valve involvement [56]. *S. aureus* are reported to have higher frequencies than other microorganisms for causing osteomyelitis complication in IE patients [59]. The infections usually occur at large joints and involve one or more joints, including the knee, shoulder, elbow, hip and sacroiliac joints [56]. If the patients are infected with multiple joints but don't have joint infection or trauma, they are suspicious for septic arthritis with IE.

6. Immune-mediated damage

With persistent bacteremia existing in IE patients, clinical manifestations, such as splenomegaly, glomerulonephritis and arthritis, may present because of cellular and humoral-mediated immune response [60]. Patients with splenomegaly occur in 20% of cases and are more likely in patients who have been ill for months rather than for days or weeks. Glomerulonephritis are most common in *S. aureus* caused ABE and *S. viridans* caused SBE with histologic immune deposits in the glomerular capillary wall [61]. With antibiotic prophylaxis and therapy in IE patients, the incidence of glomerulonephritis decreases to about 4.5% (9 in 198) in an investigation [62]. Under rare conditions, patients with glomerulonephritis will develop diffuse proliferative glomerulonephritis and extensive crescent formation with renal failure [63].

Other clinical manifestations, such as arthritis, pericarditis and micro-vessel vasculitis are also found in IE patients. Vasculitis may cause unspecific signs on skin and mucosa, including subconjunctival and soft palate petechiae, hemorrhages within the nail beds (splinter hemorrhages), oval retinal bleeding spots with white center (Roth spots), painful subcutaneous nodules on the palms or soles (Osler's nodes), painless bleeding spots on the palms and soles with diameter of 1 to 4 mm (Janeway lesions) [1]. The pathogenesis for above lesions may be caused by microemboli and microabscesses in the small vessels of dermis.

In summary, multidisciplinary approaches including clinician microbiologists, radiology, cardiology and surgery are necessary for treatment of IE with complications. In order to get better understanding, the complications are classified into several categories although some features are overlapping or broad. For example, the IE patients with embolic complication can have metastatic abscess, mycotic aneurysm or cerebral hemorrhage; patients with hematogenous dissemination can simultaneously have embolic and musculoskeletal symptoms. This content tries to describe the frequency of IE complications and may help for better prophylaxis and therapy.

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