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Septic Embolism: A Potentially Devastating Complication of Infective Endocarditis

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Additional information is available at the end of the chapter

Abstract

Infective endocarditis is associated with significant cardiac and noncardiac morbidity. Among many complications, septic embolism has the potential of causing devastating sequelae and even life-threatening clinical situations. This dreaded clinico-pathologic entity is characterized by its heterogeneous presentation and the ability to affect various body systems and organs. Septic emboli to the brain, kidneys, spleen, and the pulmonary system constitute the vast majority of metastatic infections. However, other organ systems can also be affected. This chapter provides an overview of septic embolism associated with infective endocarditis, focusing on key diagnostic and therapeutic considerations in the most commonly seen and clinically relevant scenarios.

Keywords: endocarditis, infective endocarditis, septic embolism, diagnosis, treatment

1. Introduction

The importance of septic embolism (SE) associated with infective endocarditis (IE) is both under-appreciated and under-stated [1, 2]. In one large series, systemic arterial embolization or septic pulmonary infarction occurred in approximately 33% and 11% of cases, respectively [1]. Although mortality attributable to IE can exceed 30% [1, 3], it is even higher among patients who experienced SE events [4]. Accurate and timely identification of IE and SE is of critical importance because the presence and type of SE is one of the most important factors taken into consideration when formulating a treatment strategy. Sound clinical judgment and a high

index of suspicion are required as the diagnosis of IE and SE is not based on a single test but rather on the combination of clinical findings and diagnostic studies. Microbiologic studies guide antimicrobial therapy. Advanced imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), is used to identify both the extent and location(s) of postembolic infarcts or abscesses. Surgical management, both cardiac and noncardiac, is beyond the scope of the current chapter and is discussed elsewhere in this comprehensive textbook.

2. Infective endocarditis and septic embolism: general clinical, diagnostic and treatment considerations

2.1. General clinical and microbiological considerations

The estimated crude annual incidence of IE is approximately 1 case per 33,000 population, with peak incidence among men between the ages of 70 and 80 years (approximately 1 in 6,900) [1]. Infective endocarditis is a predominantly male disease (50–65% patients) with mean age at the time of presentation between 52 and 63 years, depending on the causative microorganism [1, 3]. Major risk factors for IE include underlying heart disease, cardiac surgery and interventional procedures, prosthetic valve, intravenous drug use, immunosuppression, dental infections, and previous infective endocarditis [1, 3, 5]. Alimentary, genitourinary, respiratory tract, orthopedic, and skin infections, as well as pregnancy-related infection events have also been associated with IE, although far less commonly [3, 6]. Mortality ranges between 6% and 30%, again depending on patient factors and the microorganism(s) involved [1, 3]. Of note, mortality rate was noted to be higher (20%) among patients with IE who experienced embolic or "metastatic" events when compared to individuals without such occurrences (12%) [4].

Clinical presentation of IE involves the development of fever in >90% of cases, with approximately one out of three affected patients experiencing congestive heart failure [1]. Heart murmurs can be present, but may be more reflective of primary valvular disease rather than IE itself [7]. Elevated serum creatinine suggesting renal failure may be present in >25% of cases, and approximately 10% of patients develop septic shock [1]. Rarely, associated life-threatening events such as cardiac tamponade have been reported [8]. According to large clinical series on IE, the most commonly encountered bacteria include *Staphylococci* (19–29% cases), *Streptococci* (44–48%), *Enterococci* (8–19%), Gram-negative organisms, (5–7%), polymicrobial occurrences (0.7–3%), with 5–10% of cases having no microorganisms identified (also known as "culture negative" endocarditis) [1, 3]. Of importance, nosocomial/iatrogenic cases of IE are more likely to be associated with staphylococcal infection when compared to community-acquired IE (35% versus 21%, respectively) [1].

2.2. Pathophysiologic considerations

Septic embolism is most commonly associated with IE, septic thrombophlebitis, periodontal and various systemic infections, as well as central venous catheter and implanted device

infections [2]. The combination of aging population, implantable device miniaturization, and the emergence of multi-morbidity have all synergistically contributed to the increased risk of both IE and SE [2, 9]. Thrombogenic characteristics associated with intravascular infections, combined with the relative lack of antibiotic efficacy to clear bloodstream infections, result in elevated risk of SE [10]. According to Millaire et al. [4], embolic events may occur in >50% of IE cases. Fortunately, such events are not associated with significant attributable mortality when properly managed [4]. Further focusing on the cardiac etiology of SE, one of the largest series reported that embolization to the central nervous system was seen in approximately 20% cases of mitral valve IE, 15% cases of aortic valve IE, and 18% combined cases of aortic and mitral IE [1]. When examining right-sided endocarditis, 68% of cases were associated with pulmonary embolization [1]. Finally, it is important to recognize that IE is distinct from nonbacterial thrombotic endocarditis—a pathologic entity that can also result in distal embolization and is beyond the scope of the current chapter [11].

2.3. Septic embolization by anatomic location

When examining the anatomic distribution of nonpulmonary SE in the setting of IE, the most commonly affected organs and organ systems included the central nervous system (48–65%), extremities (30%), spleen (19–32%), and kidney (6–14%) [1, 4, 12]. Less commonly affected structures/organs included the lung (14%), coronary vessels (6%), the liver (3–11%), bone and joint structures (11%), iliac arterial system (6%), and mesenteric arteries (3%) [1, 2, 4]. From anatomic standpoint, a special and more "diffuse" category of embolic events includes musculoskeletal manifestations, which are thought to occur in as many as 44% of cases of SE [13]. Due to their self-limiting nature and nonspecific manifestations (e.g., arthralgias, myalgias, back pain, arthritis), this category of events is often under-reported and tends to be
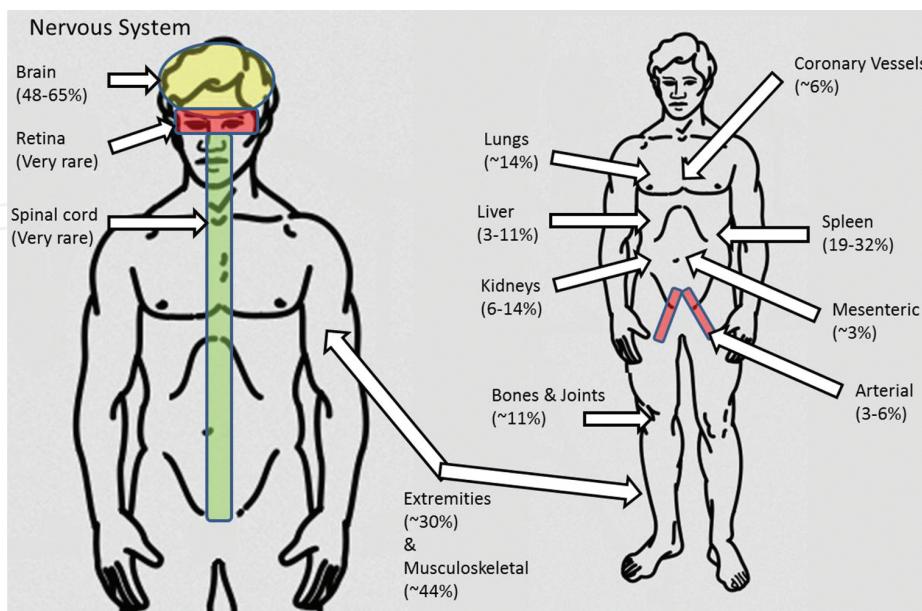

Figure 1. Diagram showing the anatomic distribution of septic emboli in the setting of infectious endocarditis. Compiled from multiple literature sources [1, 2, 4, 12–14].

neglected [14]. **Figure 1** summarizes the anatomic distribution of septic emboli in the setting of IE [1, 2, 4, 12–14]. Of note, anatomic distribution of septic emboli associated with infective endocarditis (48–65% cerebral, 35–52% noncerebral [1, 2, 4]) approximates that of valvular atrial fibrillation (56–63% cerebral, 38–44% noncerebral [15, 16]) suggesting that structural anatomic factors play a role in the pathophysiology of emboli originating from cardiac valves [16–18].

2.4. Diagnostic considerations

Diagnosis of SE requires high index of clinical suspicion, combined with accurate identification and recognition of IE as a source. In the setting of native heart valves, trans-thoracic echocardiography (TTE) should be performed as an initial screening test [19]. If results of the TTE are negative, IE can usually be ruled out if Duke criteria suggest low probability [20, 21]. However, if Duke criteria suggest high suspicion of IE, or if TTE is positive or suspicious for IE, or the patient has a prosthetic valve, the next diagnostic step should be the performance of trans-esophageal echocardiography (TEE) [7, 19–21]. If the TEE is positive, the diagnosis is confirmed. However, if negative, the test can be repeated in 1–2 weeks if clinical suspicion continues to be high [19]. If the above diagnostic steps continue to produce negative results, alternative diagnosis should be entertained.

Multiple, repeated blood culture determinations are often required to identify the causative organism. Although microbiological studies provide critical information regarding targeted antibiotic therapy in IE, results are not always immediately available or universally accurate [22, 23]. Among more recent developments, real-time polymerase chain reaction (PCR) is more sensitive and specific in addition to providing clinically relevant results quickly [24]. Initial antimicrobial coverage should be broad, and once the involved microorganism is identified and antibiotic susceptibilities are known, the therapy can be appropriately narrowed to optimize long-term management. When SE is suspected, advanced imaging (CT and/or MRI) constitutes the cornerstone of confirmatory testing [2, 14, 25, 26].

2.5. Therapeutic considerations

Infective endocarditis complicated by SE requires a multidisciplinary, multimodality therapeutic approach. As outlined in previous sections, broad-spectrum antibiotic management is the most important initial step in management of both IE and SE. Once the offending microorganism is confirmed by microbiological testing, antibiotic coverage should be narrowed according to established sensitivity data. The decision to proceed with cardiac surgical therapy of IE is a complex one, most indications are not absolute, and pertinent decision-making is discussed elsewhere in this text. When cardiac surgery is indicated, early intervention has been associated with decreased all-cause mortality (including deaths following SE) due largely to the lower risk of subsequent systemic embolization [27]. When SE is present, the type and location of emboli guides the treatment strategy. Other surgical and interventional procedures may be utilized to treat complications resulting from SE, including vascular or endovascular interventions for arterial aneurysms [2, 28, 29], percutaneous drainage of abscesses [2], or organ

resections (i.e., splenectomy or bowel resection) for infarctions and/or refractory infections [30, 31].

3. Septic emboli to central nervous system

Neurologic complications are a hallmark of left-sided IE and contribute to its unfavorable prognosis [32, 33]. The reported incidence of SE is likely underestimated [4, 34]. In the absence of abnormal intracardiac communication, neurological symptoms develop secondary to emboli originating from left-sided valvular vegetations (**Figure 2**) [1]. Less commonly, neurologic complications can also occur in cases of right-sided endocarditis with patent foramen ovale or other atrial septal defects [35]. A major risk factor for SE to the central nervous system is the delay or lack of appropriate antibiotic therapy [36]. In one study, the incidence of stroke decreased from 4.82 per 1000 patient-days to 1.71 per 1000 patient-days between the first and second weeks of appropriate antimicrobial therapy, respectively [37]. Other risk factors for septic cerebral embolism include vegetation size >10 mm, mobile and multiple vegetations, mitral and/or aortic valve endocarditis, preoperative empiric antibiotic therapy, annular abscess, anticoagulant therapy at the time of IE diagnosis, and the causative organism being *Staphylococcus aureus* [37–43]. Of note, SE to the spleen and kidneys commonly co-occur in patients with cerebral emboli [39].
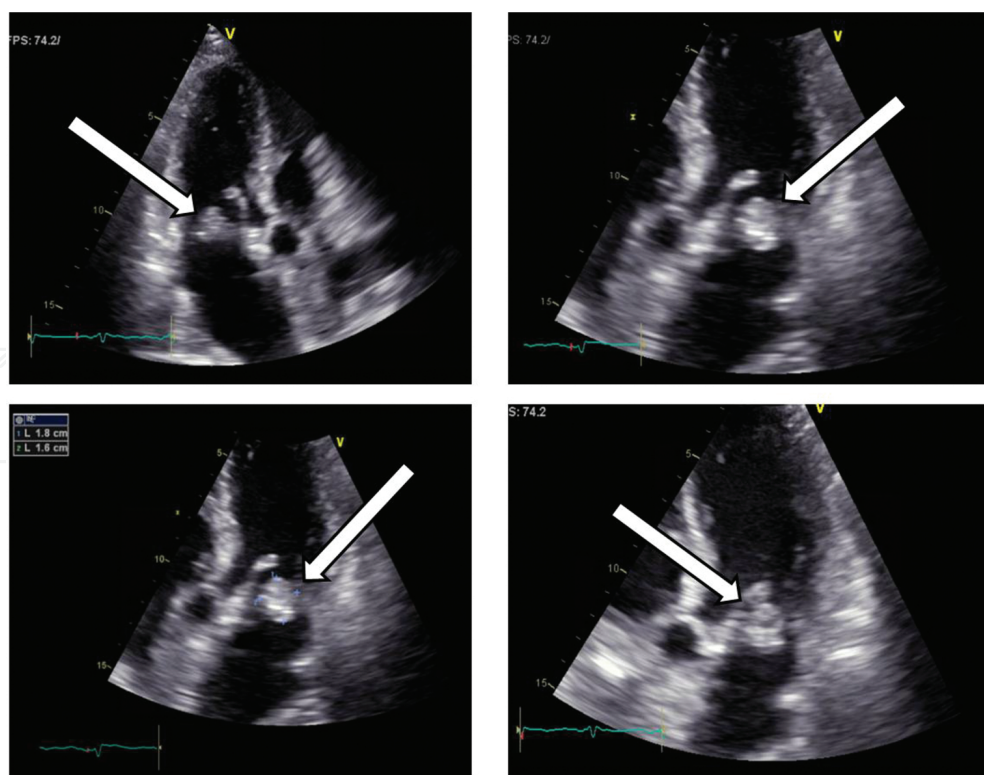

Figure 2. Echocardiography showing large (1.8 × 1.6 cm) mitral valve vegetation (arrows).

Clinical manifestations may include ischemic stroke (**Figure 3**), transient ischemic attack (TIA), cerebral hemorrhage, meningitis, brain abscess, encephalopathy, and mycotic aneurysms [38, 39, 42, 44, 45]. Taken together, these complications often occur early (within the first 7 days of IE) and negatively impact patient outcomes [46]. Among all neurologic manifestations of IE, ischemic stroke and TIA are the most common (16–50% of all occurrences) [38, 39, 44, 45, 47–49]. In approximately 70% of patients with SE of the central nervous system, the middle cerebral artery distribution is involved [38, 44]. Focal neurological symptoms (hemiparesis, facial droop, diplopia, aphasia, vertigo) are present in approximately 40% of affected patients, and nonfocal presentations (headaches, seizures, altered mental status) occur in approximately one-third of cases, with roughly one in five patients remaining asymptomatic [40]. Evaluation should include MRI with and without gadolinium, or CT with and without contrast if MRI is not possible. Vascular imaging should be performed routinely, and CTA or MRA is probably sufficient for screening, with catheter angiography reserved for cases where a mycotic aneurysm was noted and in those patients with an acute brain hemorrhage [50].
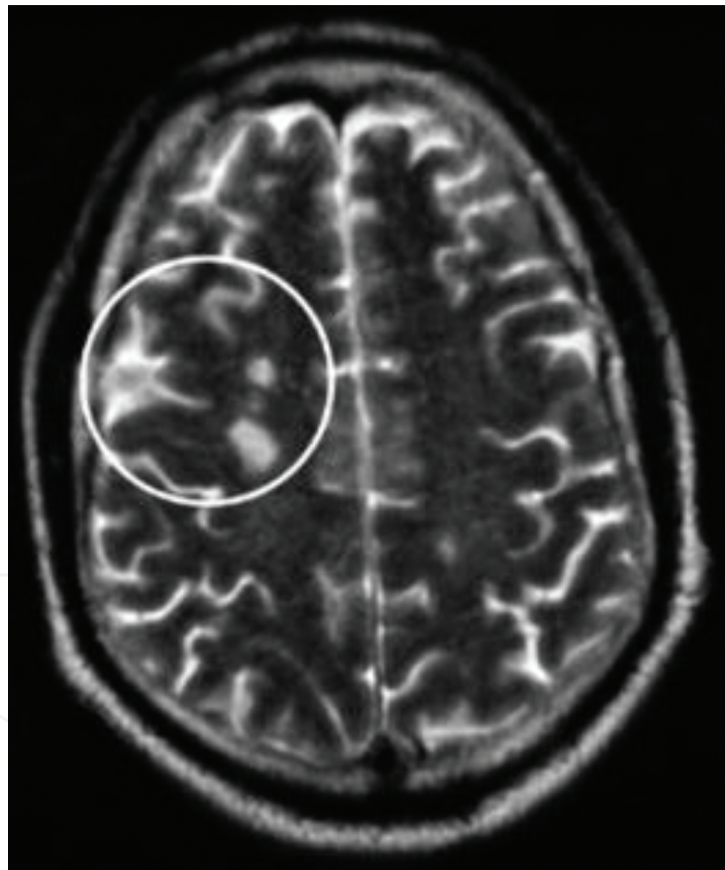

Figure 3. Magnetic resonance imaging (MRI) showing septic embolus to the brain. Source: Stawicki et al. [2]. Used under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

A relatively less common manifestation of SE associated with IE is bacterial meningitis, usually presenting with fever, neck stiffness, and altered mental status [51]. The most common

causative bacterial species are *Streptococcus pneumoniae* (54%) and *Staphylococcus aureus* (33%) [51]. The diagnosis is confirmed via cerebrospinal fluid analysis, and management requires long-term antibiotic administration and control of the septic source [44, 51].

In addition to being associated with worse clinical outcomes, neurologic complications of SE often force the alteration in therapeutic plans for IE, including the timing/type of operative intervention and the duration of antibiotic treatment [42, 46–49]. Neurological complications negatively impact clinical outcomes, with mortality as high as 45% (compared to 24% in patients who did not experience neurologic sequelae) [43]. Cerebral hemorrhage and moderate-to-severe ischemic events are the main determinants of mortality [43]. Early and appropriate antibiotic therapy remains the cornerstone of IE management and a major preventive strategy to reduce SE to the brain [52]. Although thrombolysis has been traditionally contraindicated for ischemic stroke in the setting of IE due to the risk of massive cerebral hemorrhage [53], some authors have reported good outcomes with thrombolytic therapy in selected cases [44, 54]. Having said that, rates of intracerebral hemorrhage following thrombolysis in such circumstances may be as high as 20% [55].

The use anticoagulation may increase the risk of cerebral hemorrhage without appreciable reduction in the incidence of embolic events, and, as of now, there is no evidence to support this practice [43]. Likewise, antiplatelet agents (including aspirin) were not found to be beneficial in preventing the occurrence of embolic events in a double-blinded, placebo controlled trial [56]. It is recommended to discontinue anticoagulation for at least 2 weeks in patients with IE who develop central nervous system embolic complications regardless of the other indications for anticoagulation, including the presence of mechanical heart valves. The final decision regarding anticoagulation and antiplatelet therapy should be made by a multidisciplinary team including cardiologist, cardiac surgeon, and neurologist [57, 58].

Although uncommon, intracranial mycotic aneurysms are among the most dreaded complications of IE with mortality as high of 16–30% in unruptured cases and 49–80% in ruptured ones [58, 59]. The presentation is variable, with some patients remaining asymptomatic while others developing focal neurologic signs, meningitis, subarachnoid, or intraventricular hemorrhage [58]. Approximately one in five patients may have multiple aneurysmal lesions [60]. Unruptured mycotic aneurysms should be serially monitored and treated conservatively with antibiotic therapy [61]. The treatment of a ruptured cerebral mycotic aneurysm depends on its location, as well as the presence or absence of any associated mass effect [61, 62].

Indications for valvular surgical intervention include, but are not limited to: new severe valvular regurgitation, congestive heart failure, large vegetation (>10 mm), abscess formation, persistently positive blood cultures or emboli despite appropriate antibiotic therapy, prosthetic valve dehiscence, or the presence of highly resistant organisms [63, 64]. Although most patients continue to have an indication for valve surgery after a cerebral SE [47], the timing of cardiac surgery is controversial because the hemorrhagic conversion of an ischemic brain lesion in the setting of intraoperative anticoagulation can be devastating [65–67]. The traditional recommendation is to postpone cardiac surgery for at least 4 weeks [65–67]. The relatively uncommon nature of hemorrhagic conversion of preoperative brain lesions has led some to consider earlier operative therapy in acute IE, hoping to prevent deaths that otherwise would have occurred

during the 1 month delay, as well as reducing further embolic events that can cause permanent disability [39]. As a result, evidence is emerging that early operative treatment for patients with nonhemorrhagic cerebral embolic events does not lead to worse outcomes. In a recent report, 198 patients undergoing valve replacement following cerebral infarction were analyzed with 58 undergoing early surgery (1–7 days) and 140 undergoing late surgery (>7 days). There was no survival benefit in delaying otherwise indicated surgery for IE among patients with cerebral SE [68]. Another retrospective study reviewed operative results of 308 patients with IE, finding no difference in key outcomes (postoperative stroke, 30-day mortality, long-term survival) when comparing patients with cerebral SE undergoing early surgery (<14 days) to patients undergoing surgery for IE without cerebral complications [40]. However, some authors report that early cardiac surgery is associated with neurological complications [43]. Both the American Heart Association and The Society of Thoracic Surgeons workforce on evidence-based surgery report that it is probably safe to proceed with an early operation in patients with small ischemic infarction, while delaying a surgery for 2–4 weeks might be preferred for those with a large ischemic infarction or a hemorrhagic event, respectively. In those with worsening cardiac function, recurrent stroke, uncontrolled infection or recurrent emboli, a delay of less than 4 weeks may be reasonable [50, 58].

4. Septic embolism to the kidneys

Despite numerous case reports, available clinical data on SE to the kidneys continue to be limited [2, 69–71]. Embolic events associated with IE involve kidneys in 6–14% cases (**Figure 1**) and exhibit highly variable pattern of presentation [2, 69]. Most patients complain of an acute onset of abdominal, flank, or back pain. The pain is typically constant. Approximately half of reported cases present with fever and vomiting. Acute secondary hypertension from renin release due to decreased arterial perfusion may be seen. Laboratory findings may include leukocytosis, proteinuria, hematuria, elevated levels of lactate dehydrogenase, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, and alkaline phosphatase [70]. Potential complications of septic emboli include hematuria, glomerulonephritis, or infarction leading to loss of renal function. Three types of severe renal manifestations may be seen: renal infarcts, focal "embolic" glomerulonephritis, and acute diffuse glomerulonephritis [72]. Renal loss due to embolic occlusion of the renal artery has been reported [71]. Of interest, localized renal infarcts were found in over 30% of necropsy samples, with more than half attributable to SE in patients infected with *Staphylococcus aureus* [69]. Renal SE and infarction may be associated with concurrent embolic events to other organs (**Figure 4**) [73]. In one reported case, renal infarction was found in conjunction with SE to the coronary arteries and the spleen [74]. In another case, multiple acute SE infarcts due to Gram-positive aortic valve IE were found in the brain, spleen, kidneys, and the intestine [75]. Treatment is usually supportive, consisting of systemic antibiotics, renal replacement therapy (if indicated) [69], and only rarely involves percutaneous or open procedural interventions [14, 76]. Preservation of renal function is the primary goal.
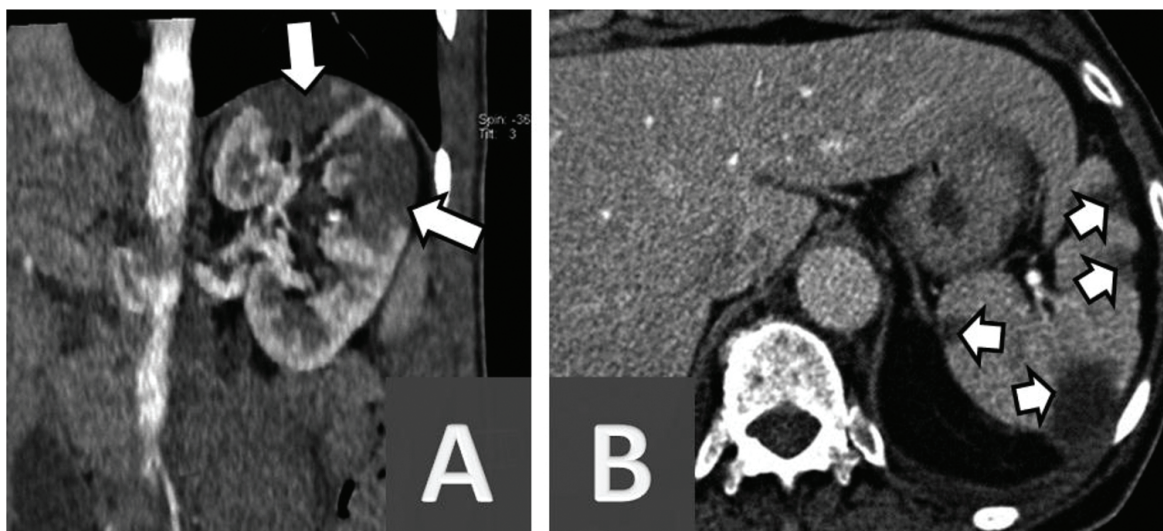
Figure 4. The presence of simultaneous renal (A) and splenic (B) infarctions secondary to septic embolism. Source: Modified from Grob et al. [73]. Used under the terms of the Creative Commons Attribution License (http://creative-commons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

5. Septic embolization to spleen

Splenic involvement is often seen in the setting of left-sided valvular vegetations from IE [12]. The two primary manifestations are splenic infarction (most common) and splenic abscess. Although often asymptomatic, splenic infarct may be associated with acute abdominal (usually left upper quadrant) pain and can be complicated by abscess formation (the primary source of subsequent morbidity and mortality) [12, 77]. Splenic abscess formation is due to hematogeneous spread from a distant source of infection, with IE being associated with up to two-thirds of such instances, either via bacteremic seeding or direct embolization of infected valvular debris [78, 79].

In one study, splenic infarcts were found in 19% of cases of IE, including asymptomatic cases identified on CT examination [12]. Streptococci and staphylococci are among the most common offending microorganisms, accounting for >80% of cases [4, 12]. While *Streptococcus viridans* and *Staphylococcus aureus* are frequently encountered, other bacterial species including *K. pneumoniae, S. epidermidis,* and *P. mirabilis* have been described in this setting [79].

Because mortality associated with splenic abscess is high, prompt and appropriate therapy is critical. Management includes antibiotics based on microbial sensitivity, image-guided aspiration or drainage, and surgical intervention by splenectomy (open or laparoscopic) in selected cases [80–83]. Early detection may help reduce the need for surgical intervention. Although the identification of SE to the spleen does not constitute a surgical indication, the presence of an abscess refractory to nonoperative approaches (e.g., antibiotics with or without percutaneous drainage), uncontained abscess rupture, or the presence of vascular complica-

tions (e.g., pseudoaneurysm or a large infarction) should prompt the consideration of splenectomy [84–87]. Likewise, refractory pain may also constitute a surgical indication (or be a clinical warning sign of one of the above complications) [80, 87, 88]. The decision to operate in the setting of therapeutic uncertainty should be considered in the context of the simultaneous presence of any other relative indications, risks, and benefits. The diagnosis of splenic infarct is not a contraindication for a cardiac operation when such intervention is indicated. The situation is not as clear in the presence of a splenic abscess. In most cases, it is preferable to perform splenectomy prior to valve surgery in order to prevent re-infection of the valve prosthesis or annuloplasty ring [58, 89]. Combined cardiac procedure and splenectomy has been reported with good outcomes [90].

6. Septic emboli to mesenteric vasculature

Septic embolization to the mesenteric vessels is a serious, potentially life-threatening complication of IE [4]. Small valvular vegetations can break off, enter the circulation, and become lodged in the mesentric arteries, endangering blood supply to the small intestine and colon [91, 92]. Compared to other organ systems affected by metastatic or embolic events of IE, mesenteric embolization is relatively rare, constituting approximately 3% of SE [2]. However, general surgeons must consider this entity on their differential list of causes leading to acute bowel ischemia. In terms of vascular distribution, the inferior mesenteric artery (IMA) involvement is much less common than SE to the superior mesenteric artery (SMA, approximately 3% versus <1%, respectively) [93]. Clinical indications for operative abdominal intervention following mesenteric SE are similar to those for other acute abdominal emergencies and have been discussed elsewhere [94, 95].

Septic embolism involving the mesenteric vessels can also be associated with mycotic aneurysms [96]. Pathophysiology involves embolization of small valvular vegetation fragments to the arterial vasa vasorum or the intraluminal space with subsequent extension of the infection through the intima and outward through the media of the vessel wall [58, 97]. This process gradually weakens the arterial wall, resulting in pathologic dilation and pseudoaneurysm formation [58]. Depending on the anatomic characteristics of the pseudoaneurysm, and the presence versus absence of associated distal embolization/thrombosis, management may include resection or vascular bypass of the lesion [98]. Inherent to the nature of pseudoaneurysms secondary to SE, high complication rate and/or mortality may be encountered [98].

In one unusual case, *Streptococcus bovis* endocarditis was reported to be associated with SE to the superior mesenteric artery (SMA) resulting in a mycotic aneurysm. Computed tomography (CT) imaging demonstrated a saccular aneurysm of the SMA and follow-up angiography showed evidence of SE to the left femoral artery [99]. A duplex ultrasound further characterized the femoral artery lesion as an intravascular mass at the left femoral artery bifurcation. Echocardiography confirmed mitral valvular vegetations. The patient underwent surgical resection of the mesenteric aneurysm, embolectomy of the femoral artery, as well as mitral valve replacement procedure [99].

In another report, *Coxiella burnetii* endocarditis led to concurrent SMA embolism and renal infarction. The patient presented with acute abdominal and flank pain, with subsequent CT of the abdomen demonstrating acute infarct of the right kidney and suspected SMA emboli [100]. The patient underwent laparotomy and successful SMA balloon thromboembolectomy. Subsequent TEE demonstrated a heterogeneous, mobile aortic valve mass. The patient was started on triple antibiotic regimen of vancomycin, gentamicin, and ceftriaxone. Subsequent aortic valve replacement was performed using a pericardial valve, with good long-term clinical outcome [100].

7. Right-sided endocarditis and septic pulmonary embolism

Right-sided IE (**Figure 5**) usually manifests as persistent fevers, bacteremia, and multiple septic pulmonary emboli (SPE, **Figure 6**). Isolated pulmonary valve endocarditis accounts for only about 2% of IE cases [101]. Due to its rarity, SPE is often difficult to diagnose due to its nonspecific presentation. In addition to the signs and symptoms of IE, SPE may cause pleuritic chest pain, cough, and/or hemoptysis [102] and may be complicated by pulmonary infarction, abscess, pneumothorax, pulmonary infiltrates, and purulent pulmonary effusion [103–105]. Although rare, right-sided heart failure due to increased pulmonary arterial pressure or severe right-sided valvular regurgitation/obstruction may occur. Historically, SPE was associated with intravenous drug use [106]. However, today the most common clinical risk factors include indwelling intravascular catheters, intravascular devices, and noncardiac sources of sepsis, especially in hospitalized patients [107–110].
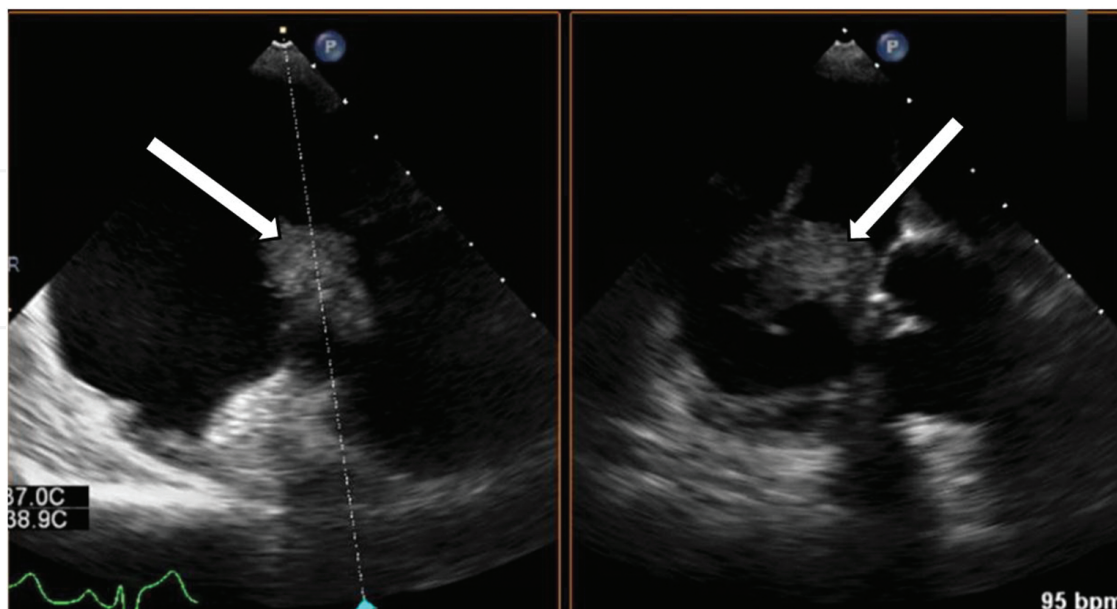

Figure 5. Echocardiographic images of tricuspid valve endocarditis characterized by the presence of a large vegetation (arrows).
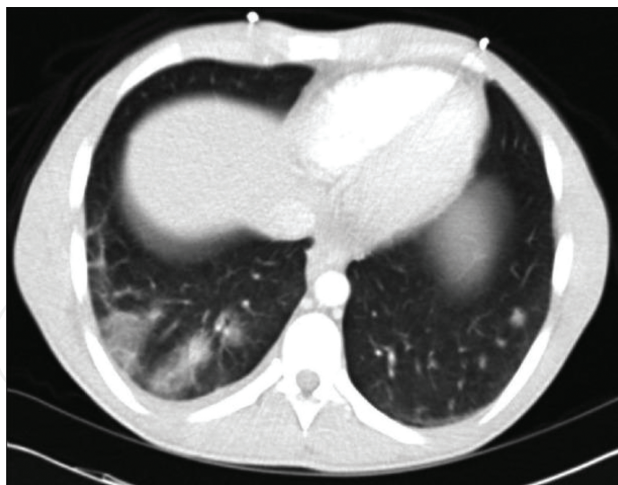
Figure 6. Septic pulmonary emboli associated with tricuspid valve endocarditis due to methicillin-resistant Staphylococcus aureus. Source: Stawicki et al. [2]. Used under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Regarding diagnostic modalities used in the setting of suspected SPE, chest radiography is nonspecific and usually shows poorly marginated peripheral lung nodules, possibly with cavitary features [25]. Computed tomography provides much better image granularity and usually demonstrates bilateral nodules or multifocal infiltrates, often involving peripheral lung zones and associated cavitary lesions [102]. These features, in conjunction with extrapulmonary infection, should raise suspicion of SPE as the underlying cause. The "feeding vessel" sign, or the finding of a vessel which projects into a peripheral lung lesion, is fairly specific for SPE [111, 112]. Patients with SPE and suspected IE should undergo echocardiography to rule out valvular infection and to assess for any associated cardiac complications [113, 114]. TEE is preferred over TTE due to better image resolution and improved diagnostic accuracy for detecting small vegetations, abscesses, and leaflet perforations up to 5 mm in size [113, 114].

A conservative approach is recommended in most patients with right-sided IE because significant majority of the cases will resolve with antimicrobial therapy alone [115, 116]. The role of surgery remains unclear because the presence of SPE and/or recurrent SPE is not an absolute indication for operative intervention. Surgery is usually indicated in cases of persistent sepsis, lack of response to appropriate antimicrobial therapy, right heart failure secondary to severe tricuspid regurgitation, and persistent large vegetation [50, 58, 117, 118]. Thoracoscopy or thoracotomy may be required in complicated cases of SPE (e.g., empyema, pulmonary abscess) [102, 106].

8. Additional considerations and special topics

Majority of the literature on IE and SE is devoted to the most common and clinically relevant presentations, leading to a degree of "neglect" toward the unusual yet still potentially

significant complications. In this section, the authors will discuss other, less common mani-festations of SE. More specifically, we will focus on septic emboli to various anatomic locations, in decreasing order of incidence.

8.1. Septic emboli to solid abdominal organs

A significant proportion of SE involves abdominal and retroperitoneal solid organs (e.g., liver, spleen, pancreas, kidneys). Emboli to the more commonly affected locations (e.g., spleen and kidney) have been discussed earlier in this manuscript. It is important to remember that septic embolic phenomena tend to simultaneously involve more than one anatomic location, with significant proportion of events being asymptomatic [75, 119]. At times, smaller septic embolic lesions may coalesce to form well-defined abscesses [120]. The next two sections will discuss hepatic and pancreatic SE occurrences.

8.2. Septic embolism to the liver

Liver abscesses due to SE associated with IE are well documented in the medical literature [121]. As outlined above, larger hepatic abscesses may evolve over time from smaller, adjacent microabscesses [120]. Infectious endocarditis should be entertained in the setting of any hepatic abscess of uncertain etiology, with echocardiography undertaken in order to rule out cardiac valvular source [122]. Clinical approach is usually multi-modal, including broad-spectrum antibiotics, endoscopy, percutaneous drainage, and/or surgery [2].

8.3. Septic emboli to the pancreas

Pancreatic septic emboli have been described in the setting of multi-visceral SE [75]. Due to the disproportionate severity of concurrent embolic events, pancreatic SE is likely under-reported and under-appreciated. Clinical presentation of pancreatic SE may resemble that of pancrea-titis (e.g., abdominal pain, elevated serum amylase/lipase, leukocytosis, and peri-pancreatic inflammatory changes on advanced imaging) [2]. The range of possible clinical presentations spans from that of self-limited pancreatitis to an overwhelming necrotizing infection. Associ-ated findings may also include vascular abnormalities (e.g., pseudoaneurysms) involving nearby vasculature (i.e., pancreaticoduodenal artery) on advanced imaging [123].

8.4. Coronary septic emboli

Coronary embolization from a septic focus has been relatively well reported in the literature [74, 124] and usually originates from valvular vegetations in the setting of IE [125]. Septic coronary embolism has also been reported to occur intraoperatively during mitral valve surgery performed in the setting of IE [126]. Coronary arterial SE should be entertained in cases of known or suspected left-sided IE and evidence of concurrent acute myocardial ischemia (e.g., abnormal ECG or elevated cardiac enzymes). Echocardiography (preferably TEE) can reliably demonstrate the presence of valvular vegetations, in addition to documenting other changes characteristics of myocardial ischemia [127]. Coronary occlusion secondary to SE can also be confirmed via coronary angiography, with the potential for percutaneous coronary

intervention at the same time [128]. Acutely occluded major coronary arteries or branches may require surgical revascularization at the time of valve surgery. Patients with aortic valve endocarditis, in whom preoperative coronary angiography may be contraindicated due to concerns of dislodging debris, may require empiric grafting [2]. An example of a mycotic coronary artery aneurysm associated with IE is shown in **Figure 7**.
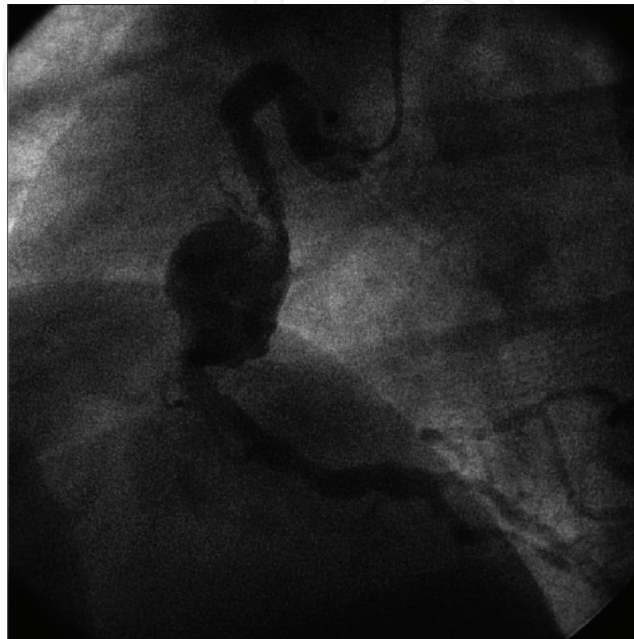

Figure 7. Mycotic aneurysm of the right coronary artery. The patient underwent venous bypass grafting. Source: Sta-wicki et al. [2]. Used under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

8.5. Septic emboli to extremities

Distal septic emboli are well described in the setting of IE [30, 129]. A nontrivial proportion of SE associated with IE requiring valvular replacement affects the extremities, with some patients experiencing multiple embolic events [30, 129]. Clinical manifestations can vary from extremity pain to limb-threatening ischemia [30]. In less severe cases, ischemic symptoms may resolve with anticoagulation and antimicrobial therapy, while in more acute presentations surgical embolectomy or even amputation may be required [30].

8.6. Arterial lesions associated with septic embolism

Secondary arterial changes and associated lesions have been reported in the setting of infec-tious embolization [75, 130]. Inflammatory changes were noted in the walls of arteries adjacent to an intracranial hematoma following septic embolization [75]. In one instance, brachial artery pseudoaneurysm (**Figure 8**) has been described in the setting of severe prosthetic aortic valve endocarditis [2]. In another case, a ruptured mycotic aortic abdominal aneurysm occurred in

a child with SE following the resection of an infected cardiac myxoma [131]. Due to rarity of such arterial lesions and the associated nonspecific clinical presentation(s), it is extremely important to maintain a high index of suspicion when potential infections of arterial structures are identified.

Figure 8. Large (2.5 cm) brachial artery pseudoaneurysm secondary to septic embolization from prosthetic aortic valve endocarditis. Source: Stawicki et al. [2]. Used under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

8.7. Uncommon presentations involving the central nervous system

Exceedingly rare, septic embolism may involve the spinal cord and lead to associated spinal cord infarction [132, 133]. In such cases, other organs are likely to become involved as well, including the kidneys and pulmonary circulation [132]. Finally, septic embolism to the retina has been reported in the setting of staphylococcal tricuspid endocarditis in intravenous drug abusers [119].

9. Conclusions

Despite significant evolution of both diagnostic and therapeutic approaches, septic emboli continue to present a formidable challenge to the practicing clinician. In addition to high index of suspicion and early clinical recognition, prompt identification of the offending cardiac source and the institution of immediate goal-directed antibiotic therapy are all critical to successful outcomes. More widespread awareness of risk factors, clinical presentations, and

management of SE is needed, with added focus on preventing embolic events and the management of associated complications.

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