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Infective Endocarditis in the Central Coast of New South Wales, Australia: A Snapshot

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Abstract

Background: The epidemiology and management of infectious endocarditis (IE) in the Central Coast has not, to the best of our knowledge, been previously described. We sought to characterize it and shed light on any peculiarities that may define IE in the Central Coast.

Methods: Retrospective review of details of patients who admitted in the hospital and undergone a diagnosis of IE over a three-year period was done. We paid particular attention to risk factors for IE and results of blood cultures, cardiac ultrasonography and other imaging. We looked at patient outcomes. A total of 78 admissions fulfilled the inclusion criteria for the study. Patients with more than one admission during the study period were counted as one, leaving a total of 63 patients. Of the 63 patients included, 9 were incorrectly diagnosed as having IE.

Results: Ten patients (18.5%) had a history of current or prior intravenous drug use (IVDU). IVDU was associated with smoking, a greater likelihood of more than one admission with IE-related issues, younger age and hepatitis B and/or C infection. *Staphylococcus aureus* infection accounted for the greatest number of cases of IE, present in 17 patients (31%). Most cases of *S. aureus* infection were methicillin sensitive (15 patients of 17 patients (88%)). *Streptococcus* was the second most prevalent pathogen. Gentamicin, used alone or in combination, was the most commonly used antimicrobial agent. All patients underwent transthoracic echocardiography (TTE) at least once and 50 patients (89%), transesophageal echocardiography (TEE). The aortic valve (AV) was the most commonly affected, being involved in 25 patients (44%), and followed by the mitral valve (MV). Twenty four patients, representing 48%, were transferred to a tertiary hospital with cardiothoracic surgery availability. During the study period, there were 4 deaths, representing 7% mortality.

Conclusions: Aortic valve involvement was the commonest valve lesion. Prosthetic valves conferred the greatest risk for IE. Most cases of IE were due to methicillin sensitive *S. aureus* (MSSA) infection and gentamicin was the most commonly used antimicrobial therapy. Cases of misdiagnosis were due to non-adherence to established diagnostic criteria.

Keywords: *Staphylococcus aureus;* Infectious endocarditis; Echocardiography

Introduction

IE is an inflammation of the endocardium due to infection. From the initial characterization in 1885, the definition of IE has evolved from inflammation of the endocardium (and associated structures) to inflammation involving intra-cardiac devices such as pacing/defibrillator leads and pacemakers [1]. In the modern era, IE presents most frequently as an acute rather than a chronic problem [2]. *Staphylococcus aureus* is the commonest cause of IE, in IVDU patients as well as the general population [3]. The remainder of cases is due to streptococci, enterococci, gram negative rods (GNR), *Candida* species, and other less common organisms. Unlike *S. aureus*, *Streptococcus* is a common cause of community acquired IE. Polymicrobial infection occurs in 2% to 5% of cases [4].

The incidence of IE has remained relatively stable from 1,950 through to 2,000 at about 3.6 to 7 per 100,000 patient years [5]. In the developed world, risk factors have shifted from rheumatic heart disease and congenital heart disease to modern day risk factors such as: IVDU, degenerative valvular heart disease in the elderly, healthcare-associated infection and hemodialysis [6]. At least twice as many men are affected by IE as are women [7].

Echocardiography remains the gold standard in the diagnosis of IE, allowing visualization of vegetation, documentation of local spread and complications as well as visualization of any resulting valvular heart disease [8]. Transesophageal echocardiography (TEE) allows better visualization of intra-cardiac structures and has a higher sensitivity than does transthoracic echocardiography (TTE) [9].

Methods

We reviewed the medical records of patients with a discharge diagnosis of 'infective endocarditis' - either as a primary or as a secondary/additional diagnosis. We used the search terms, 'infective endocarditis', 'bacterial endocarditis' and 'subacute bacterial endocarditis' on our hospital database. Medical records of patients who met these inclusion criteria over a 3-year period between April 01, 2012 and March 31, 2015 were assessed. We sought to characterize the nature of IE at our institution, its presentation, investigations undertaken, management, complications and patient outcomes.

Seventy eight patient admissions met the inclusion criteria. Of that 78 cases, 15 cases involved patients with more than one admission for IE. Further review revealed that 9 cases of the remaining 63 cases had been incorrectly diagnosed as IE. This was entirely due to non-adherence to the Modified Duke criteria for the diagnosis of IE [10]. Our center, a regional hospital, is one hour by road from the nearest tertiary center with surgical capability. We do not have cardiothoracic surgeons or a dedicated cardiothoracic intensive care unit. Consequently, we refer patients warranting a surgical opinion or intervention.

Epidemiology

There were 31 male patients and 23 female patients. The mean age was 64.8 years. The age range varied from 22 years to 94 years. Smoking status was available (documented) for 41 patients (75%), of the cohort. Twenty-eight patients (51%) were nonsmokers and 14 (29%) were smokers. Smokers tended to be younger, with a mean of age of 48 years. There were more male smokers (8, i.e., 57%) than female smokers (6, i.e.,42%)

We defined the following as risk factors:

- IVDU
- History of prior IE
- Prosthetic heart valves
- Rheumatic heart disease (RHD)
- Childhood rheumatic fever (RF)
- Hemodialysis
- Immunosuppression
- Cardiac implantable electronic devices (CIED)
- Congenital heart disease

There have been reports of an association between HIV infection and IE. We were not able to test this further as HIV status was not documented in any of the study subjects.

Ten patients (18.5%) had a history of current or prior IVDU. IVDU was associated with younger age (mean age 40.8 years) and hepatitis virus infection (Table 1).

Pathological Criteria
- Microorganisms on histology or culture of a vegetation or intracardiac abscess
- Evidence of lesions: vegetation or intracardiac abscess showing active endocarditis on histology
Major Clinical Criteria
Blood cultures positive for infective endocarditis
- Typical microorganisms consistent with IE from two separate blood cultures: *S. aureus*, *S. bovis*, viridans streptococci, HACEK* organisms or community-acquired enterococci in the absence of a primary focus (OR)
- Microorganisms consistent with infective endocarditis from persistently positive blood cultures: At least two positive blood cultures from blood samples drawn >12 h apart, or All of three, or most of ≥ 4 separate cultures of blood (with first and last sample >1 h apart) (OR)
- Single positive blood culture for *Coxiella burnetii*, or phase 1 IgG antibody titer > 1:800
Evidence of endocardial involvement
- Echocardiography positive for infective endocarditis defined by presence of a vegetation, abscess, or new partial dehiscence of prosthetic valve
- New valvular regurgitation
Minor Clinical Criteria
- Predisposition: predisposing heart condition, intravenous drug use
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhages, conjunctival hemorrhages, Janeway lesions
- Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
- Microbiological evidence: positive blood culture that does not meet a major criterion or serological evidence of active infection with organism consistent with infective endocarditis
- Fever: temperature >38°C
Diagnosis of infective endocarditis is definite in the presence of one pathological criterion, or two major criteria, or one major and three minor criteria, or five minor criteria
Diagnosis of infective endocarditis is possible in the presence of one major and one minor criteria, or three minor criteria
Haemophilus aphrophilus (subsequently called *Aggregatibacter aphrophilus* and *Aggregatibacter paraphrophilus*), *Actinobacillus actinomycetemcomitans* (subsequently called *Aggregatibacter actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*

Table 1: Modified duke criteria.

Five patients (9%) had hepatitis C virus (HCV) infection and 2 patients (4%) hepatitis B (HBV) infection. There was 1 case of HCV/HBV coinfection.

Prosthetic valves conferred the highest risk for developing IE, with most cases being late prosthetic valve endocarditis (PVE) 12 patients had prosthetic valves, i.e., 22%. Patients with PVE were 2 times more likely to be transferred to a tertiary center for further care than patients with native valve endocarditis (NVE). Allowing for the incomplete data of referred patients, PVE patients were more likely to undergo surgical intervention than were NVE patients.

Physical examination

Fever was the commonest symptom on admission with 30 patients (55%), having a presenting complaint of 'fever'. Forty-seven patients (87%) had at least one temperature recording on admission. Of the patients with a documented temperature, the mean admission temperature was 38.3°C. Other symptoms recorded on initial assessment include malaise, 'aches and pains', anorexia and back pain. The physical examination in most cases was not directed at eliciting the signs of IE. Terms unique to IE, such as 'splinter hemorrhages' and 'palmar erythema' as well as less specific terms like 'stigmata of IE' or 'signs of IE' were documented in 10 patients' medical records (18.6% patients).

The clinical manifestations of infective endocarditis are highly variable; IE may present as an acute, rapidly progressive infection or as a subacute or chronic disease with low-grade fever and nonspecific symptoms [11]. The non-specific nature of the clinical presentation makes arriving at a clinical diagnosis challenging.

Twenty-four patients (45%) had blood drawn for culturing within 1 h of arrival to the emergency department (ED). Blood culturing in the rest of the study patients generally occurred in the first 4 h of hospital presentation. Study subjects had a mean of 2.4 blood cultures drawn.

S. aureus accounted for the majority of cases, being present in 17 patients, representing 31% of cases. There were 5 cases of penicillin-sensitive *S. aureus* infection. Seven patients (13%) had polymicrobial IE. There was no uniformity in the frequency with which blood cultures were taken after the first day of hospitalization. The frequency varied with clinician preference. Despite the lack of consistency and difficulty in drawing reliable conclusions from our study, *S. aureus* IE was associated with a greater duration of bacteremia and more complications in severity and frequency. There were no cases of IE caused by the HACEK group of organisms.

Empiric antibiotics were administered to 38 patients (71%) within the first 24 h of hospitalization. Gentamicin was the most commonly prescribed antibiotic, alone or in combination with benzylpenicillin, ceftriaxone, flucloxacillin or vancomycin. This is consistent with our local guidelines for "sepsis of unknown source". In all cases of culture-confirmed IE, anti-microbial therapy was tailored to culture sensitivities. Consistent with guidelines, penicillin therapy was used in all cases of penicillin-sensitive *S. aureus* infection [8].

There were 3 cases of blood culture negative IE (BCNIE), representing 6% of the cohort, and 1 case of presumed fungal IE ("typical" IE with vegetations and stigmata of IE in a patient with allergic bronchopulmonary aspergillosis, ABPA, and negative blood cultures). Blood samples were sent to an external laboratory for analysis. Results of this analysis were not available for review. Seven patients (13%) had polymicrobial IE.

Imaging

All study patients had at least one chest radiograph (CXR). Chest radiography was abnormal in 7 patients (12%) and consolidation was the most common abnormality. Antimicrobial therapy directed against respiratory pathogens was initiated for a community-acquired pneumonia in this subgroup of patients with a penicillin/cephalosporin and macrolide/tetracycline combination, consistent with local guidelines.

Computed tomography (CT): CT imaging of the chest was undertaken in 11 patients (20%). CT abdomen in 7 patients (13%) and CT brain in 9 patients (17%). Magnetic resonance imaging (MRI) of the brain was undertaken in 5 patients all of whom had undergone prior CT brain imaging. The most common indication for doing CT/MR imaging was to rule out or confirm complications, namely metastatic seeding of infection. Ultrasonography of the abdomen and/or the renal tract was undertaken in 4 patients (7%) to investigate for complications of IE and/or as work up for acute kidney injury (AKI). One patient underwent MRI of the left ankle on suspicion of concomitant septic arthritis (Figure 1).

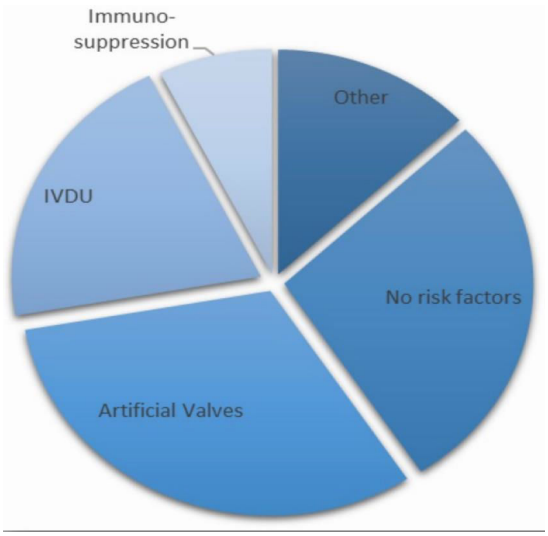

Figure 1: Risk factors for IE.

Echocardiography: The aortic valve (AV) was involved in 25 patients (44%), most commonly manifesting as mild-to-moderate aortic insufficiency. Thirteen patients (23%) had tricuspid valve (TV) vegetations, with severe tricuspid regurgitation (TR) occurring in 5 patients. There were 13 cases of right-sided TV IE and 10 were in IVDU patients (77%). There were 13 cases of mitral valve (MV) endocarditis. There were no cases of pulmonary valve (PV) endocarditis. Endocarditis affecting more than one valve was seen in 2 cases. Eustachian valve endocarditis is rare [12]. There were no such cases during the study period.

All patients underwent TTE at least once, with a mean of 1.3 TTEs per patient. TEE was undertaken in 50 patients (89%) with a mean of 1.1 TEEs per patient. TEE was more sensitive in demonstrating vegetations than TTE with 5 more AV, 4 more TV and 5 more MV vegetations identified. Of patients not undergoing TEE, 2 were deemed too unwell for the procedure and the other 2 were frail and older (age ≥ 85 years old) with clearly visible vegetations on TTE. There was a mean

of 2.4 days between the first echocardiographic study (which was invariably transthoracic) and the second, which was TEE in most cases (Figure 2).

Outcomes

Twenty-four patients (45%) were transferred to other hospitals, in most cases to centers with a cardiac surgical service. Records on the outcomes of such patients were incomplete, being available for 18 patients (75%). Twelve of the 18 transferred underwent surgery-AV, MV and/or TV surgery.

Three patients were transferred to subacute facilities, such as community hospitals, for in-patient completion of anti-microbial therapy or rehabilitation posthospitalization. In the remainder of patients, the mean duration of antimicrobial therapy was 46.2 days.

Four patients (7%) died in hospital. Twenty-six patients (48.2%) were discharged home for out-patient completion of antimicrobial therapy or after successful in-patient completion of therapy.

Thirty three patients (61.7%) did not have any complications. Of the 21 patients that developed complications, embolic seeding with septic emboli was the commonest complication, occurring in 8 patients (14%). Most embolic spread was to the brain and lungs (5 cases of spread to the brain and 3 of spread to the lungs).

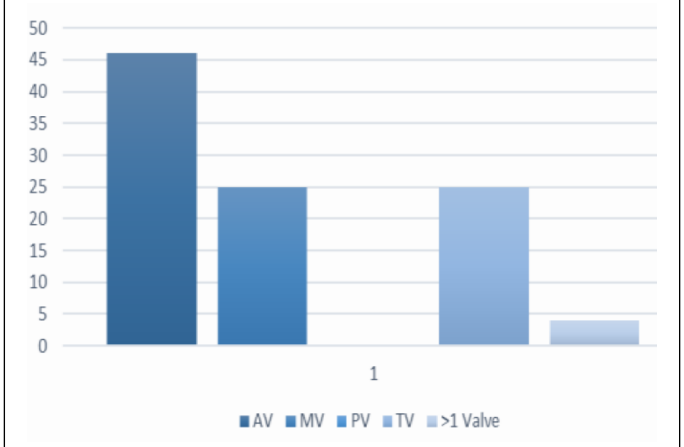

Figure 2: Valve involvement.

Five patients developed severe aortic regurgitation; another 4 developed a peri-aortic abscess. Two patients developed perforations of the tricuspid valve. These patients were transferred to tertiary centers (Figure 3).

While individual electrocardiograms (ECG's) for each patient were not reviewed by the investigators, there were no documented cases of heart block or arrhythmias, recognized complications of IE, particularly with aortic valve involvement.

Thirty-three patients (61%) underwent insertion of a peripherally inserted central venous catheter (PICC line). Of those 33, 21 (63%) were enrolled in the hospital-in-the-home (HITH) program. Patients enrolled in the HITH program had the least complications and were followed up in all cases by the HITH team, which includes infectious diseases personnel. Additionally, patients were followed up in cardiologists' offices or out-patient cardiology resident (trainee) clinics.

Records on subsequent follow-up post-discharge/completion of anti-microbial therapy were not available for review (Figure 4).

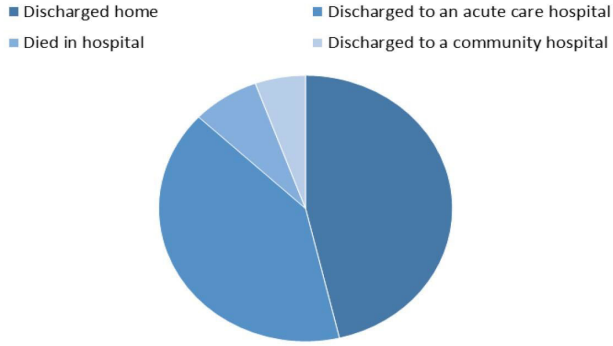

Figure 3: Patient outcomes.

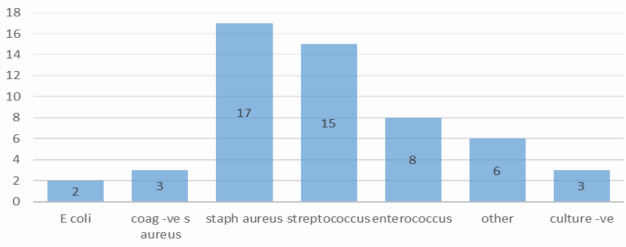

Figure 4: Microbiology (% of total).

Discussion

We sought to describe the epidemiology and diagnostic and management practices of IE at our hospital. We aimed to identifying determinants of patient outcomes as well as at-risk groups which are overrepresented in the IE cohort. We also hoped to identify interventions that may reduce this overrepresentation. Additionally, we were curious to determine whether data collected and analyzed from our study would address as yet unanswered issues pertaining to IE, and possibly be hypothesis generating.

The precise incidence of IE has been difficult to ascertain accurately as case definitions have varied over time and between different authors and between different centers [13]. Additionally, most studies pertaining to IE have been undertaken in tertiary centers, with the inherent problem of selection bias. Population-based observational studies in IE would be feasible but difficult to undertake as IE remains relatively rare. The advent of the Duke criteria, which were later updated to 'modified' Duke criteria, has aided in providing accuracy and consistency in the diagnosis. Established in 1994 and revised in 2000, the Duke criteria are a collection of major and minor criteria used to establish a diagnosis of IE utilizing: clinical manifestations, blood investigations, echocardiography and pathological examination of valve specimens [14]. The criteria are listed in (Table 1).

The 2015 European Society of Cardiology (ESC) guidelines for the management of IE published in the European Heart Journal of the same year place a greater emphasis on imaging in the diagnosis of IE [15]. Notably, the focus on echocardiography in the previous ESC

guidelines has been expanded to include other non-invasive imaging techniques, such as multi-slice CT, MRI and nuclear imaging, IE positron emission tomography-computed tomography (PET-CT) scan. The recommended use of these modalities is outlined in a novel diagnostic algorithm (Figure 5) [15].

Misdiagnosis in 14% of the study population was due to non-adherence to recommended diagnostic criteria. Non-adherence to diagnostic criteria raises questions about the possibility of genuine cases of IE being misdiagnosed leading to adverse patient outcomes.

While useful in helping establish a diagnosis of IE, the sensitivity of Duke criteria is limited in patients with suspected PVE, right-sided IE and cardiac device related IE [16]. As imaging continues to evolve and improve, and as suggested by the recent ESC guideline updates, imaging modalities beyond echocardiography will play an increasingly important role in diagnosis and management in the future.

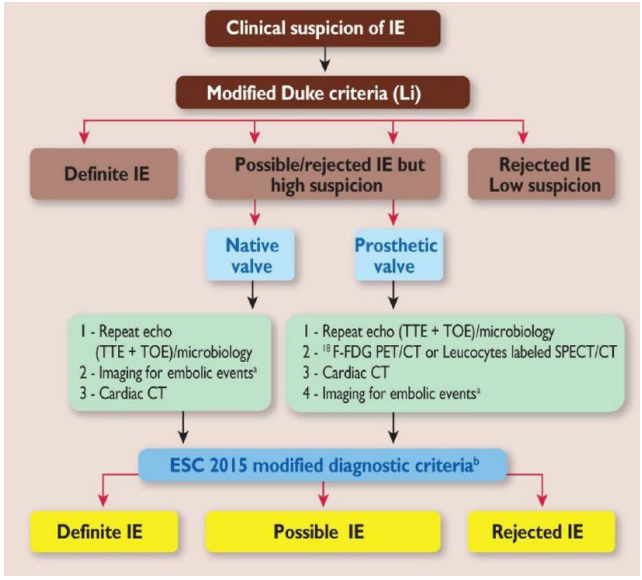

Figure 5: ESC algorithm for diagnosis of IE.

Males are more likely to develop IE than females [2]. The male-to-female ration in our review was 1.5:1. The reason for this remains undefined and needs further investigation. Fever was the commonest presenting symptom [2], consistent with other studies. Other non-specific symptoms were present and include malaise and IE in-hospital mortality has been reported at 18% to 23% [15]. There was a 7% in-hospital mortality in our audit. This disparity is likely explained by the incomplete records of patients transferred to other hospitals. The mortality figure will likely have been higher had there been follow-up of these high risk patients.

Fever was the commonest presenting symptom, consistent with other studies [14]. Other nonspecific symptoms were present and included headache, malaise and myalgias [13]. Physical examination in most cases was not directed to eliciting the signs of IE. Terms like "no stigmata of IE" were noted in some patient records but by and large, there was no specific mention of the 'stigmata', e.g., Janeway lesions and palmar erythema. Other rare but specific findings of IE such as Roth's spots were not mentioned in any of the patient records. Terms like "new murmur" and "changing murmur" were noted in 2 patient records. Whether this less-than-expected level of documentation of physical findings represents a true shift in clinical practice with less emphasis on physical examination or it represents suboptimal documentation was not addressed in our study. Alternatively, as has been previously described, the 'classic textbook signs' are rarely found in developed countries today [17].

In the present day, virtually all isolates of *S. aureus* are penicillin resistant and as such, penicillin therapy for *S. aureus* infections is not recommended. In the rare cases of *S. aureus* penicillin sensitivity, penicillin is recommended as initial therapy with or without gentamicin for synergism [18]. This strategy has been shown to be safe and effective [19]. Without exception, anti-microbial therapy was tailored to sensitivities when these were available.

Echocardiography is recommended in all cases of suspected IE [19]. TTE is followed by TEE, which has higher sensitivity and is better suited at detecting complications than TTE. The timing of echocardiography varied but TTE was undertaken at least once in all patients and was followed by TEE in 89% of cases. Despite there being no data to guide utility of TEE and timing as a 'next test' after TTE in the setting of IE, TEE-performance in 89% of patients likely represents an adequate number.

Previous authors have described embolic phenomenon as the most common expression of infective endocarditis, occurring in 20% to 50% of patients [17]. By contrast, in our study we found a much lower embolic rate of only 14.8%. This highlights the importance of local audits such as ours to better identify the epidemiology endocarditis and potentially allow us to better develop diagnostic and management strategies suitable to our local patient population.

The ESC has recently launched an IE registry to better describe current diagnostic and management practices in IE in Europe and other countries [20]. This is a strategy that would be worth pursuing in the state of New South Wales of Australia as well as the country at large.

The HITH program played a leading role in reducing the overall length of hospital stay. HITH personnel must be commended for the service they provide. They enable anti-microbial therapies to be administered in an out-patient setting. This likely represents a significant financial saving for the local health district of the Central Coast and is likely a reasonable goal for our center and other centers too.

Limitations

The study was a retrospective analysis that relied on accurate case records, by various departments and different groups of health care providers. The accuracy of data collected and its interpretation depends solely on the completeness of this data. This cannot be guaranteed.

There were no age and sex-matched controls. This limits the generalizability and clinical application of the study.

Information was not available on patients transferred to another hospital for further management. Additionally, there was incomplete information on blood samples that were sent to external facilities for further analysis.

Patient aboriginality was not reviewed. Rheumatic Fever and RHD are over-represented in Aboriginal and Torres Strait Islander peoples. These conditions are important risk factors for IE [13]. It would have

been insightful to see what roles they play in Aboriginal and Torres Strait Islander patients.

Patient follow-up was limited to the duration of hospitalization. Data was either incomplete or unavailable for patients transferred to another hospital. Data on timing of surgery and surgical outcomes would have been particularly useful.

Recommendations

Strict adherence to Duke Criteria and appreciating their limitations, e.g., PVE.

Drafting protocols to aid Emergency Department personnel to better identify, investigate and treat suspected IE, e.g., consideration of IE in patients presenting with fever, even when consolidation is present on CXR.

Encouraging adherence to major society guidelines, such as those of the ESC, in the diagnosis, management and follow-up of patients with IE.

Emphasizing the importance of thorough physical examination to not only aid in the diagnosis of IE, but help diagnose other conditions mimicking IE.

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