Title: Infective Endocarditis in Low- And Middle-Income Countries

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Key Points

- Staphylococcus is an increasingly important cause of IE in LMICs, and is the leading cause of IE in UMICs
- RHD remains the major underlying cardiac pathology of IE in LMICs, identified in almost half of reported cases
- The rate of microorganism non-identification is high, reaching up to 60% of IE cases in LMICs, and hampering diagnosis and treatment
- Rates of access to surgery in UMICs for complicated IE are as high as in HICs, but remain dismal in lower-middle income countries

Synopsis

Infective endocarditis (IE) is a rare, life-threatening disease with a mortality rate of upto 25% and significant debilitating morbidities. Although much has been reported on contemporary IE in high income countries, conclusions on the state of IE in low and middle income countries (LMICs) are based on studies conducted before the year 2000. Furthermore, unique challenges in the diagnosis and management of IE persist in LMICs. This article is a review of IE studies conducted in LMICs documenting clinical experiences from the year 2000 to present. We present the causes of IE, management of patients with IE and the prevailing challenges in diagnosis and treatment of IE in LMICs.

Infective endocarditis in low-and middle-income countries

Introduction

Infective endocarditis (IE) is a rare, life-threatening disease with a significant mortality and morbidity burden. In-hospital mortality approaches 25%, increasing in patients with cardiac or extracardiac complications.[1-3] IE also frequently causes debilitating morbidities, such as heart failure, stroke and renal failure requiring dialysis, which contribute to increased mortality and disability adjusted life years (DALYs).[3-7]

The spectrum of causative microorganisms and underlying risk factors for IE has shifted dramatically in high income countries (HICs).[8,9] Staphylococcal IE now predominates. Degenerative valve disease (DVD), prosthetic valves and other intracardiac devices are the leading underlying cardiac conditions, with little contribution from rheumatic heart disease (RHD) and congenital heart disease (CHD).

IE in low and middle-income countries (LMICs) has been said to resemble that seen in HIC-based studies from the mid-20th century which reported a predominance of IE due to streptococcal infection, RHD and CHD as the leading risk factors, and minimal rates of surgical intervention.[9] Reports from LMICs that mirror this epidemiology and treatment patterns are predominantly from before the turn of this millennium and consequently, may not reflect the current state of IE in LMICs. [10-14]

The prevalence of RHD remains disproportionately high in LMICs, while uncorrected CHD persists in the poorest of these settings due to limited access to cardiac surgery.[15,16] It is therefore expected that RHD and CHD remain significant underlying cardiac conditions for IE; however, economic improvement in lower-middle income and upper-middle income

countries has led to medical progress which may have introduced additional IE risk factors for these populations, and altered the spectrum of causative microorganisms.

In this review, we present the causes and treatment of IE in LMICs as reported in contemporary studies, defined as studies which primarily report findings from the year 2000 and after. We also discuss the prevailing challenges to the diagnosis and management of IE in LMICs, and suggest future directions in research.

Methods

We searched PUBMED and EMBASE using the keywords: endocarditis, infective endocarditis, low income, middle income, and developing country. LMICs and HICs were based on 2016 World Bank Income groups classification.[17] Articles were considered relevant if they were original research that described IE epidemiology and management experiences from LMICs from the year 2000 and after. We also screened the reference list of the retrieved articles for additional relevant studies.

CAUSES OF IE

Degenerative valve disease (DVD), prosthetic valves, and intracardiac electronic devices have replaced RHD as the major underlying cardiac risk factors for IE in HICs.[1] Comorbidities such as diabetes mellitus (DM), renal failure requiring dialysis, and malignancy contribute substantially to a growing burden of healthcare-associated IE (HAIE).[2,18] Consequently, growing use of long-term intra-vascular access devices has led to skin bacteria in the form of Staphylococcus being the leading cause of IE in HICs.[1,2,18]

In this section, we review the prevalent underlying cardiac conditions, place of acquisition and microbial etiology of IE in LMICs. A summary of our findings is presented in Table 1.

Underlying cardiac conditions

Rheumatic heart disease (RHD) is identified as the underlying cardiac pathology in a majority of IE cases, ranging from 28-45% in most of our reviewed studies.[19-24] Nel et al.[25] however, reported a much higher (78%) prevalence of underlying RHD in their study in South Africa, a country where RHD is endemic.[26]

Overall, this range of underlying RHD in IE represents a decline from the 45-80% reported in earlier (pre-2000) LMIC studies.[10,11,13,27,28] Compared to HICs however, these findings are remarkable in that RHD is identified in only 3% of IE cases.[1] This is likely because the prevalence of RHD is disproportionately high in LMICs,[29,30] which bear 79% of the global RHD burden.[15]

Underlying CHD accounts for 5-23% of reported IE cases.[19,21,23-25,31,32] Math et al.[20] reported CHD as the leading cause of IE (39%) in northern India. This study was conducted in a cardiac surgery centre and included a large paediatric population which may account for the higher findings of CHD.

Prosthetic valve IE (PVE) and pacemakers/intracardiac defibrillators is reported in 17-44% and 6-19% of IE cases in LMICs respectively.[19-23,31,32] UMIC studies account for the higher figures in these ranges, which reflects advances in medical technology and higher access to cardiac surgery.[21,22] Indeed, the largest report of PVE cases from a LMIC comes from Simsek-Yavuz et al.[21] who reported findings from a referral centre in Turkey (an UMIC) in which 141 patients (44%) among 325 IE cases had PVE. 52% of the total patient cohort received surgical intervention, closely approximating the rate seen in HICs.[2]

Degenerative valve disease (DVD) contributes little to the IE epidemiology in LMICs, accounting for less than 10% of cases.[19,21,23,32] Elbey et al.[31] however, reported a high rate of

DVD (23%) in a multicentre retrospective study in Turkey. Mean patient age was 47 years, higher than that typically seen in LMIC studies, which may explain the higher rate of DVD. Overall, unlike in HICs where DVD is the major underlying cardiac disease in native valve IE (NVE), a lower aged mean patient population in LMICs limits its contribution.[1,8,9,18]

Place of infection acquisition

The burden of HAIE is growing in HICs, reported in 30% of IE in recent studies.[1,2,18] Advances in medical technology, increased indwelling intravascular device use and increased prevalence of comorbidities such as end-stage renal disease contribute to this burden.[33]

Two LMIC studies reported on the site of acquisition of IE. Simsek-Yavuz et al.[21] characterized 23% of IE cases as HAIE at a referral centre in Turkey, while Damasco et al.[34] reported predominantly HAIE (56%) in two centres in Brazil. In the latter study, an indwelling intravenous catheter was the main source of infection in the entire patient cohort, while among HAIE cases, 55% had chronic renal insufficiency as a comorbidity. The authors attributed the higher HAIE rates to advances in medical practices in Rio.

Microbial etiology

Staphylococcus is now the leading causative microorganism of IE in HICs, followed by Streptococcus and Enterococcus. Together, these microorganisms account for >80% of the microbial etiology of IE in HICs.[1,2,18]

Describing the microbial etiology of IE in LMICs is extremely challenging as limited data exists on IE as it is, and one's ability to make conclusions from the available data is further curtailed by a high rate of non-identified microorganisms. From available data however, Staphylococcus and Streptococcus are the leading causative microorganisms.

Staphylococcus

Staphylococcus is increasingly common, and in some instances is the leading cause of IE in LMICs (Table 1). Staphylococcus accounts for 15-50% of cases with *Staphylococcus aureus* more common than coagulase negative Staphylococcus (CoNS).[19-23,25,31,32,34] Comparison with pre-millennial ranges shows an increase in Staphylococcus which was previously reported in less than 20% of cases.[11,13,28]

The emergence of Staphylococcus as a leading cause of IE in LMICs, a trend that was also previously noted in HICs, may reflect medical technology advances, increased hospital contact and increasing comorbidities.[9,34,35] Consistent with these factors, it is noteworthy that only UMIC studies reported Staphylococcus as the leading cause of IE, accounting for up to 50% of cases.[21,22,25,31,32,34] In lower-middle income countries however, Streptococcus still predominates.[19,20]

Streptococcus

Streptococcus causes 18-54% of IE cases, with viridans group streptococci predominating.[19-23,25,31,32,34] Streptococcus is common among younger patients, patients with community-acquired IE and patients with rheumatic or congenital NVE.[19,20,34] This finding was highlighted by Simsek-Yavuz et al.[21] in a study in Turkey where although Staphylococcus was the leading cause of IE in the entire cohort, Streptococcus was significantly more prevalent among patients with a native valve, patients less than 40 years of age, and patients with community-acquired IE.

Other organisms

Less common causes of IE in LMICs are Enterococcus, gram negative bacteria and true causative agents of blood culture negative IE such as Bartonella and Coxiella.[19-22] This is consistent with reports from HICs, except for Enterococcus which is the third leading cause of IE in HICs after Staphylococcus and Streptococcus.

Prevalence of Enterococcal IE was reported to range between 7-18%[19-22,31,32] in our reviewed studies. Damasco et al.[34] however, reported Enterococcus as the second most common cause of IE, after Staphylococcus, accounting for 27% of cases. Furthermore, among patients aged ≥40 years, Enterococcus was the most commonly isolated microorganism, indicating a predilection for increasing age, a finding supported by Simsek-Yavuz et al.[21] who reported increasing prevalence of Enterococcus in individuals >50 years old.

In summary, conclusions about the microbial etiology of IE in LMICs are hampered by scarce available data and a high rate of unidentified microorganisms due to widespread prior antibiotic use, limited microbiological capacity and inadequate sampling procedures, challenges that are discussed further later. Inconsistent serological testing for atypical microorganisms further limits etiology determination.[36] Existing data, however, highlight a prominent contribution of Streptococcus and a growing contribution of Staphylococcus, particularly in UMICs.

TREATMENT

Prompt and appropriate organism-specific antibiotic therapy is recommended to improve clinical outcomes for IE patients, while surgical intervention is recommended for complicated IE.[37-40] The antimicrobial regimens employed, mean hospital stay and surgical intervention rates are summarised in Table 1 and discussed below.

Medical therapy

Medical therapy remains the most common treatment for IE due to limited access to cardiovascular surgery in LMICs.[16] Setting-specific treatment guidelines are non-existent and subsequently, societal guidelines from HICs are referenced in deciding treatment.[37,41] Determination of the microbial etiology of IE should be the cornerstone of selecting

antibiotic therapy; however, as discussed later, this is hampered in LMICs by high rates of organism non-identification.

In the absence of reliable microbiological findings, antibiotic therapy in a majority of suspected cases remains empirical. The choice of therapy varies because the guidelines for empirical therapy from HICs[42] may not be translatable to settings with different local susceptibility patterns.

In the few cases where microbial etiology is determined, antibiotics are instituted based on standard guideline based regimens.[37,41] Our reviewed studies reveal high usage of combination therapy that typically includes beta-lactams or peptide antibiotics and aminoglycosides, with prolonged duration of therapy ranging between 35-67 days.[20,43]

Mean duration of hospital stay ranges between 16-38 days.[21,22,34,43] Outpatient parenteral antibiotic therapy (OPAT) may be considered in stable patients to decrease hospital stay.[44] OPAT for IE however, may not be possible in most LMIC settings due to a high rate of complications associated with late hospital presentation, and unavailability of required medical services in the outpatient setting. None of our reviewed studies reported on the rates of OPAT.

Surgical management

Due to late presentation and/or diagnosis, patients often present with complications, such as valve abscess, systemic embolization, heart failure and hemodynamic instability, which are indications for emergent surgical intervention. Reviewed LMIC studies reveal that surgical intervention rates remains low, ranging from 0-53% in our reviewed studies.[19-25,31,32,34,43] The higher figures in this range (42-53%) predominantly come from UMICs.[21,22,24,25,32,43] These figures refer to surgical rates among the entire patient cohort in the given study, and not among patients with indications for surgical intervention, it is

therefore difficult to conclude whether intervention rates are optimal. However, in lower-middle income countries for instance, surgical intervention was less than 15%, despite over 30% of IE patients presenting in heart failure, an indication for surgery.[19,20] In a cardiac centre in India however, where access to surgical consult and intervention was prompt, Gupta et al. reported a surgical intervention rate of 49%.[23]

Among patients with complications that require emergent intervention, the optimal timing for surgery remains controversial.[45] Early surgery however, has been shown to decrease the rate of embolic events,[46] in-hospital,[47] and 6-month mortality.[48] Two studies in our review reported on the timing of surgery. Rekik et al.[43] reported a mean delay to surgery of 15 days among 20 patients with PVE and indications for surgery. Similarly, Trabelsi et al.[24] reported a mean time between admission and surgery of 16 days among 68 patients with NVE and surgical indications.

CHALLENGES

The prevailing challenges to the diagnosis and management of IE that co-exist in LMICs are illustrated in Figure 1 and discussed below.

High prevalence of rheumatic heart disease

The prevalence of RHD remains high and accounts for a significant portion of cardiovascular disease (CVD) morbidity and mortality in LMICs.[15,49,50] IE is a common complication of RHD and as highlighted earlier, up to half of IE cases in LMICs are superimposed on RHD. 79% of the 15.6 million cases of RHD in 2005 were from LMICs, driven by poor standards of living, poor nutritional status, and limited access to healthcare facilities and penicillin prophylaxis.[15] With recent estimates projecting that up to 80 million people worldwide have RHD, more LMIC patients are at risk for IE.[50,51]Addressing the high

burden of RHD in LMICs is therefore a key step in decreasing IE related morbidity and mortality.

Late hospital presentation

IE patients in LMICs often present to hospital late. Median time between symptom onset and hospital presentation ranged from 15-36 days in our reviewed studies.[22,24,34] Consequently, patients frequently presented with IE complications such as heart failure and stroke.[19-22] IE complications are associated with higher mortality, and require surgical intervention which is often unavailable in LMICs, furthur worsening clinical outcomes.

High rate of organism non-identification

Identification of causative microorganisms, mainly through blood cultures, is the cornerstone of IE diagnosis and is crucial to the initiation of effective organism-specific antimicrobial therapy.[52]

The rate of organism non-identification in IE from HIC studies is <5%, while this figure is generally >35%, reaching upto 60%, in LMICs.[1,19,20,24,25,31,43] Causes of this high rate are multifactorial. First, widespread use of antibiotics prior to collection of blood samples for culture substantially decreases the likelihood of obtaining growth on culture media. In our reviewed studies, 35-74% of patients reported prior antibiotic use.[20,23,24,32,43]

Second, there is limited capacity for high quality microbiology studies, particularly in lower-middle income and low-income settings. Blood culture infrastructure is underdeveloped and testing reagents are often unavailable.[53] Facilities for serological testing of atypical organisms are also unavailable in the poorest settings.[36] Serological testing increases the rate of organism identification and is particularly useful for organisms responsible for culture-negative IE such as *Bartonella henselae, Brucella melitensis and Coxiella burnetii.*

Third, inappropriate procedures in collecting samples for culture may occur.[54] It is recommended that at least three sets of blood culture samples are collected over a period of 12 hours (or more practically, with the first and last set obtained at least an hour apart).[52] LMIC studies however, reported that a lower number of samples were collected, resulting in few samples fulfilling major IE criteria for blood culture.[20]

Empiric antibiotic therapy

Prompt identification of microorganisms and initiation of appropriate antibiotics decreases IE mortality and morbidities such as stroke.[37,41] In the absence of organism identification in LMICs however, antibiotic therapy in suspected cases is empirical. Choice of therapy varies between regions, hospitals, and physicians. This is because resource poor regions often have little guidance to inform empirical therapy since local data on prevalent microorganisms and antibiotic resistance are scarce.[55]

Additional problems related to antibiotic use include cost limitations in resource poor settings. Physicians and patients have little access to expensive regimens that may be required for drug resistant cases.[56] Although commonly used antibiotics for IE such as gentamicin, vancomycin and most beta-lactam antibiotics, including penicillin and ceftriaxone, are included in the WHO essential medicines list, agents such as daptomycin which may be necessary in drug resistant IE cases are not.[57] Antibiotic stock-outs may also occur during the course of treatment, leading to missed drug doses or unnecessary regimen changes.

Little capacity for therapeutic drug monitoring

Therapeutic drug monitoring (TDM) services are frequently unavailable in LMICs.[58] TDM is recommended for antibiotics used to manage IE, especially vancomycin and aminoglycosides, to ensure adequate drug levels are reached to maximize efficacy, decrease risk of resistance development, and prevent toxicities such as renal failure. Empiric antibiotic

therapy often involves combinational agents which further increase risk of nephrotoxicity.[59,60] Furthermore, among patients with heart failure which commonly complicates IE, the risk of nephrotoxicity is heightened.[61]

Dismal access to surgery

Early surgery decreases mortality among patients with IE complications.[39,47] In HICs, approximately half of IE patients in reported prospective series' undergo surgical intervention,[1,2,62] with up to 75% of patients with indications for surgery receiving it.[62] In our reviewed studies, although UMIC studies reported surgical intervention rates close to HICs, two lower middle-income country studies reported low rates of 0% and 15%.[19,20] We however found no information on the rates of surgical intervention among patients with indications for surgery, however, given the high rate of complications among IE patients in our reviewed studies, we can conclude that this rate was low. Only a few referral facilities in Sub-Saharan Africa (SSA) have the physical and human resource infrastructure to perform cardiovascular surgery,[16,63] and the few with such capacity often have long waiting lists, making emergent intervention difficult. Furthermore, where such opportunities are available, high costs remain an insurmountable barrier for a majority of patients.[14]

FUTURE DIRECTIONS IN RESEARCH

A research agenda is urgently required around IE in LMICs. Our review reveals a scarcity of studies documenting clinical experience since the new millennium. In low-income countries for instance, we found no studies meeting our search criteria. A high RHD prevalence in lower income settings, coupled with medical progress in improving economies where new IE risk factors for the population emerge, implies that IE will remain an important CVD in LMICs. In addition, challenges in IE diagnosis and management result in higher IE related morbidity and mortality in LMICs compared to HICs.[64] Setting-specific data is

therefore required to track the clinical characteristics, diagnostic and management practices, and outcomes for patients with IE in order to foster investment in improving microbiological, echocardiographic and cardiovascular surgery capacity.

We propose the following steps to stimulate research and further understanding of IE in LMICs. First, where there is a critical lack of published data such as in the low-income countries, retrospective reviews should be conducted based on existing records. This would serve as a first step to provide critical expeditious updates on the state of IE, while building capacity in research, and providing preliminary data that can be used to justify larger prospective studies.

Secondly, prospective IE registries in LMICs need to be established. Current studies are limited by few patient numbers in single healthcare centres which hampers generalizability. Experiences from contemporary registries such as the International Collaboration on Endocarditis (ICE) have effectively improved understanding of IE.[1,65] This registry however, has predominantly included sites from HICs and UMICs, and to date has not included a site from a low income country.[1] Experiences from ICE should be leveraged in order to build capacity in LMICs to enable them to form rigorous registries documenting experiences in their settings.

LIMITATIONS OF REVIEW

Our review has several strengths. Our focus on studies reporting findings from 2000-present day provides a contemporary update on the causes of IE in LMICs, and the challenges yet to be addressed. Where possible, we have also described the differences in the IE profile between different LMIC economies.

Our review however, has several limitations. We found few LMIC studies on IE, with a majority of them from UMICs and none from low-income countries. Therefore, this review

may not adequately reflect findings from the lowest resource settings. Available studies have few patients, mostly from single centres, and are heterogeneous in nature, limiting our ability to form generalizable conclusions. Finally, most of the available data comes from referral centres and thus our findings are subject to referral bias.

CONCLUSION

Staphylococcus is an increasingly important cause of IE in LMICs, particularly in UMICs although the rate of organism non-identification is high. RHD remains the major underlying cardiac pathology, with a growing contribution of PVE. Rates of access to surgery in UMICs for complicated IE are as high as in HICs, but remain dismal in lower-middle income countries. Publication of retrospective findings in low-income settings, and the formation of collaborative registries to improve understanding of contemporary IE in LMICs must be encouraged.

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