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Update on Infective Endocarditis: New Insights into an Old Disease

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It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future.¹

With these words, William Osler began the first of three seminal lectures on endocarditis to the Royal College of Physicians of London in 1885. In the last 120 years, much has been learned about the pathophysiology and clinical course of infective endocarditis (IE), and dramatic improvements in patient outcomes have been realized with the development of antibiotic therapy in the 1940s and surgical therapy in the 1960s. Disappointingly, despite rapid advances in many areas of health care in the last 30 years, there has been little improvement in the prevention of endocarditis or in serious sequelae, such as valvular destruction or death.^{2,4} As modern medicine moves into the 21st century, it is once again appropriate to “take stock” of our current understanding of IE and look to the future for possible “fruitful investigations.”

This article will focus on key recent advances in several areas concerning IE, including epidemiology, imaging, risk classification, and surgical decision-making. Looking to the future will help in understanding methodologies that can be employed to study this uncommon disease, with a specific examination of investigations by a newly constituted multinational consortium, the International Collaboration on Endocarditis (ICE).

Epidemiology

The incidence of IE is difficult to estimate because true population characteristics, including both cases and the total population at risk, are difficult to obtain. Over the past 10 years, several well-designed epidemiologic studies have provided both data on the incidence of endocarditis and insight into populations at risk. For instance, Hogevis and colleagues conducted an epidemiologic study of IE in Göteborg, Sweden from 1984-1988. During this study period, the incidence was calculated to be 6.2 episodes/100,000 person-years.⁵ After adjusting for both age and gender, the investigators calculated the incidence for the total population of Sweden to be 5.9 episodes/100,000 person-years.⁵ During a similar time period, investigators in Philadelphia, United States (US) conducted a study of the Philadelphia metropolitan statistical area where they calculated the total incidence to be 9.29 episodes/100,000 person-years.⁶ If cases of intravenous drug users were excluded, this incidence fell to 5.02 episodes/100,000 person-years.⁶

These two studies focused on the incidence of IE in a relatively urban setting. In 1991, investigators in France performed an epidemiologic survey that focused on three regions of France (Ile de France, Lorraine, and Rhône-Alpes) that contained both rural and urban populations and overall, represented 18,545,160 inhabitants or nearly 33% of the entire population of France.⁷ The crude incidence in this study was 2.24 episodes/100,000 person-years that increased to 2.43 episodes/100,000 person-years after adjustment for age and gender.⁷

As a follow-up to this important epidemiologic survey, the French investigators repeated this study in 1999. Notably, in this study, the crude incidence was 3.0 episodes/100,000 person-years with a



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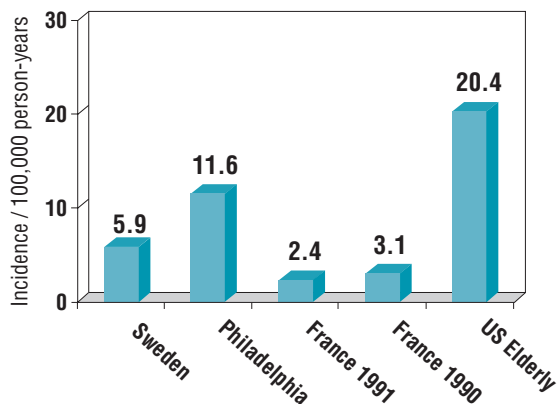
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Figure 1: Incidence of endocarditis



slight increase to 3.1 episodes/100,000 person-years after age and gender adjustment.³ Importantly, the French investigators found that the incidence of IE in young patients was very low and increased dramatically with age, with a peak incidence of 14.5 episodes/100,000 person-years in patients between 70- and 80-years-old.

In a similar fashion, there is preliminary evidence from the US that elderly patients have a 2- to 3-fold increase in the incidence of IE compared to the general population. A study of US Medicare patients found that the overall incidence of IE in 1998 was 20.4 episodes/100,000 person-years and this was a 13.7% relative increase from 1986.⁸

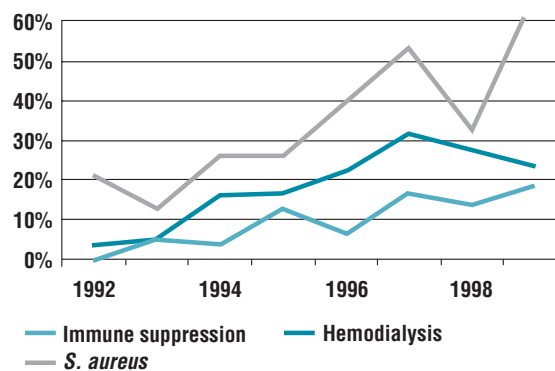
It is clear from each of the studies that there is variation in the incidence of IE (Figure 1). This variation in incidence may be explained by several factors, including year of study, rural/urban mix of patient populations, statistical adjustment, and inclusion of high-risk groups, such as injection drug users or the elderly.

To many, the fact that the incidence of IE has not decreased over the past 30 years may seem surprising. It is well-established that diseases such as rheumatic heart disease, which has typically placed patients at risk for diseases such as endocarditis, has decreased dramatically in the western world. In addition, progress in dental care and attention to prophylactic guidelines would seemingly have made a difference in the incidence of IE. There are several potential explanations for these observations. First, endocarditis is a constantly changing disease and in recent years, it is less a disease of poor dentition and rheumatic heart disease and more a disease of an aging population and medical intervention.³⁻⁹ For instance, recent work has shown a dramatic increase in the proportion of cases attributed to *Staphylococcus aureus* and a concomitant rise in patients with IE that have been exposed to chronic IV access such as hemodialysis (Figure 2).⁹ In addition, prophylaxis regimens have never been shown to be effective in human studies¹⁰⁻¹² and recent data have shown that more cases of IE are related to other types of medical procedures than are related to antecedent dental work.¹³

Imaging

Since the advent of 2-dimensional transthoracic echocardiography (TTE) in the 1970s and transesophageal

Figure 2: Changing patient characteristics of endocarditis 1992-1999



Adapted from Cabell CH, et al.⁹

echocardiography (TEE) imaging in the 1980s, echocardiography has become a standard diagnostic tool in patients with suspected IE. It is now well-established that echocardiography is the technology of choice for the diagnosis of IE,¹⁴ and that echocardiography can detect cardiac involvement in a significant proportion of patients with clinically occult IE.^{15,16} Characteristics of endocarditis by echocardiography include vegetations (Figure 3), abscess, valvular perforations, and other complications, such as prosthetic valve dehiscence.

Because IE is a lethal infection that can be difficult to clinically diagnose, clinicians who care for patients at risk for IE often have a low threshold for employing echocardiography. While echocardiography can often provide a rapid diagnosis, its optimal use is predicated on appropriate pre-test probability of disease.^{17,18} Echocardiography is not only critical to the timely diagnosis of IE, but findings from these studies have important implications for prognosis and therapeutic decision-making. For instance, Sanfilippo and colleagues found that the risk of embolization was directly related to vegetation size. In fact, for vegetations > 6 mm in size, the risk of subsequent embolization was linearly related to an increase in vegetation size (Figure 4).¹⁹ These findings have been verified by several investigators.^{20,21} Importantly,

Figure 3: Mitral valve vegetation by echocardiogram

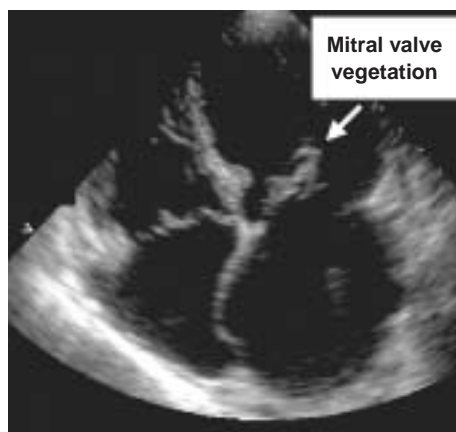
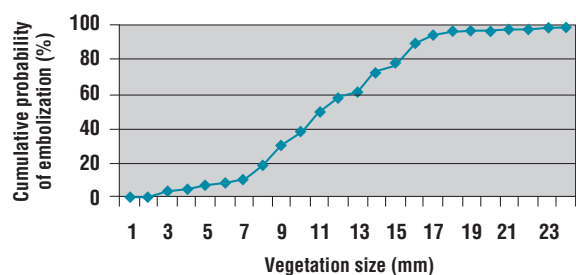


Photo courtesy of Christopher H. Cabell, MD MHS.

Figure 4: Risk of systemic embolization by size of vegetation



Adapted from San Fillipo AJ, et al¹⁹

Di Salvo and colleagues have extended these findings by studying both clinically-apparent thromboembolic events, as well as clinically-silent embolic events diagnosed by standard imaging in all patients.²² The investigators found that both vegetation size and mobility were predictive of embolic events. Specifically, 70% of the embolic events were in patients with large (>15 mm) vegetations. In addition, vegetation mobility was also related to embolic risk; in the 73 patients with moderate-severe mobility in the vegetation, 45 (62%) had a subsequent embolic event.

Although multiple studies have shown that echocardiography is central to both diagnosis and prognosis in IE, it is evident that imaging technologies can be overused in certain clinical scenarios. For instance, Kuruppu and colleagues have shown that 53% of echocardiograms could be avoided without loss of diagnostic accuracy by using a simple algorithm in patients with a low pre-test probability of disease.²³ In addition, Greaves and colleagues have shown that the collective absence of 5 simple clinical criteria indicated a zero probability of a TTE showing evidence of endocarditis.²⁴ Collectively, these studies have shown that echocardiography may be avoided without the loss of diagnostic accuracy in patients with a very low pre-test probability of disease.

Although current guidelines highlight the use of TTE and/or TEE imaging depending on the clinical scenario,²⁵ studies have shown that TEE imaging is the most cost-effective imaging tool in the majority of clinical situations. For instance, Heidenreich and colleagues have demonstrated that in most situations of suspected endocarditis, a diagnostic strategy that focuses on TEE as the initial imaging modality is the most cost-effective approach.¹⁸

For a variety of reasons, it is important to limit the indiscriminate use of diagnostic technologies. From a safety standpoint, low-risk procedures such as TEE may have an unacceptable risk-benefit ratio as the diagnostic yield approaches zero. In addition, in the era of rapidly rising medical costs, excessive procedures lead to substantial financial waste. For instance, it has been estimated that the appropriate use of TEE to establish the length of therapy in catheter-associated *S. aureus* bacteremia could save over 120 million dollars US annually.²⁶

Risk classification

Despite advances in the diagnosis and management of IE, endocarditis remains a disease with unacceptably high

Table 1: Predictors of early mortality in patients with IE

| Variable | OR | 95% CI | P-value |
|-------------------|------|-----------|---------|
| Male gender | 0.58 | 0.28-1.13 | 0.110b |
| Diabetes mellitus | 2.48 | 1.24-4.96 | 0.010 |
| <i>S. aureus</i> | 2.06 | 1.01-4.20 | 0.046 |
| APACHE II | 1.07 | 1.01-1.12 | 0.021 |
| Embolic event | 2.79 | 1.15-6.80 | 0.024 |

Adapted from Chu V, et al²⁷

morbidity and mortality. Over 50% of patients with IE suffer some type of serious complication including heart failure, stroke, and perivalvular extension, while the in-hospital mortality rates (15%-20%) and 1-year mortality rates (30%-40%) have changed little over the past 20 years.²⁴

Unfortunately, very little data exist to help clinicians identify patients that are at the highest risk for complications and death. Risk classification, in terms of both short-term and long-term risk, is necessary to identify patient populations that may benefit from the most aggressive treatment strategies. Recently, two important studies have provided important insights into risk classification in patients with IE.

Chu and colleagues at Duke recently examined 267 consecutive patients with acute IE to determine factors early in the course of IE that were independently associated with mortality.²⁷ Controlling for severity of illness with APACHE II scoring (Table 1), they found that the independent predictors of early mortality were the presence of diabetes mellitus (OR 2.48, 95% CI, 1.24-4.96), *S. aureus* infection (OR 2.06, 95% CI, 1.01-4.20), and an embolic event (OR 2.79, 95% CI, 1.15-6.80).²⁷

In a similar fashion, Hasbun and colleagues set out to understand how clinical factors at the time of presentation with IE may be related to prognosis at 6 months.²⁸ They examined 513 cases of IE in Connecticut over a 10-year period to derive and externally validate a prognostic classification system for adults with complicated left-sided native valve IE. They included 259 patients in their derivation cohort and 254 patients in the validation cohort. The focus of the study was on risk factors related to mortality at 6 months. They found that 5 baseline features were independently associated with mortality: abnormal mental status, co-morbidities, moderate-severe congestive heart failure, *S. aureus* infection, and medical therapy without the use of surgery. Based on these findings, they were able to create a point-based classification system that accurately risk-stratified patients with IE. Based on this system, they found that patients with ≤ 6 points had a 6% mortality at 6 months, while patients with >15 points had a 63% mortality (Table 2).²⁸

Surgical decision-making

Based on the observation by Hasbun et al, in the aforementioned study, that medical therapy alone may be associated with an increase in mortality at 6 months, Vikram and colleagues used the same data to determine whether valve surgery reduced mortality in adults with complicated, left-sided IE.²⁹ In this study, propensity modeling was used to

Table 2: 6-month mortality by prognostic group

| Prognostic group | 1 | 2 | 3 | 4 |
|-------------------|-----|------|-------|------|
| Points | ≤ 6 | 7-11 | 12-15 | > 15 |
| Total cohort | 6% | 17% | 31% | 63% |
| Derivation cohort | 5% | 15% | 31% | 59% |
| Validation cohort | 7% | 19% | 32% | 69% |

Scoring system:

| | |
|--|-------------|
| Mental status: lethargy or disorientation | (4 points); |
| Charlson comorbidity scale: ≥ 2 | (3 points); |
| Congestive heart failure: moderate to severe | (3 points); |
| Microbiology: <i>Staphylococcus aureus</i> | (6 points); |
| Other non- <i>viridans</i> infection | (8 points); |
| Therapy: medical therapy only | (5 points). |

Adapted from Hasbun R, et al²⁸

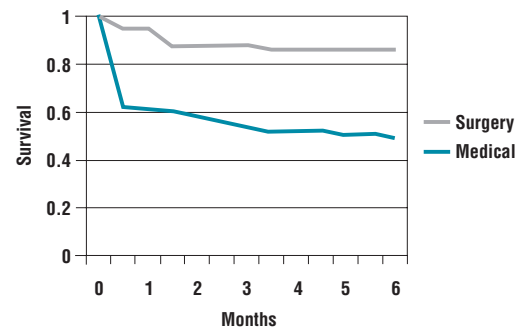
create a matched case-control study. Utilizing this statistical strategy, the authors found that valve surgery was strongly associated with improved survival (OR 0.40, 95% CI 0.18-0.91) at 6 months compared to matched controls. Importantly, almost all of the benefit was realized in patients who had moderate-to-severe heart failure (Figure 5). In these patients, the mortality at 6 months in the medical group was nearly 50%, while the mortality in the surgical group was only 15%. In patients with none-to-mild heart failure, there was no difference between the medical and surgical groups, with 6-month mortality at 15%.²⁸ From this work, it is clear that in patients with acute IE and at least moderate heart failure, surgical therapy should be strongly considered. In all other patients, it is less clear if surgery is of any benefit.

How to study a rare disease

Definitive studies of IE have been difficult to perform due to the low incidence of disease, a limitation that is compounded by the heterogeneous nature of the populations at risk, the variable underlying risk factors, and the wide array of infecting organisms. Out of necessity, most studies are derived from case reports or series of cases collected at a single clinical site. There have been few case-controlled studies or large, prospective cohort studies, and even fewer randomized controlled trials. Most of these small studies are not adequately powered to examine important groups of patients with IE, such as those with specific cardiac risk factors, affected anatomic sites, or particular microorganisms. These are serious limitations in a heterogeneous disease that affects at least 15,000 patients per year in the US³⁰ and has a 1-year mortality approaching 40%.^{9,30,31}

To further understand endocarditis and to definitively study therapeutic choices, a shift in approach is necessary. Establishing a multicenter study group has the potential to overcome some of the limitations that plague IE investigations.

As a result of these considerations, a group of investigators formed a collaborative study consortium, the *International Collaboration on Endocarditis* (ICE). ICE was formed to:

Figure 5: Six-month survival in patients with endocarditis and moderate-severe heart failureAdapted from Vikram HR, et al²⁹

- establish a group of investigators who would work together and be dedicated to further the understanding of endocarditis
- combine existing databases to study regional differences in IE
- begin a large prospective cohort study of IE
- develop a network of investigators to perform randomized clinical trials.

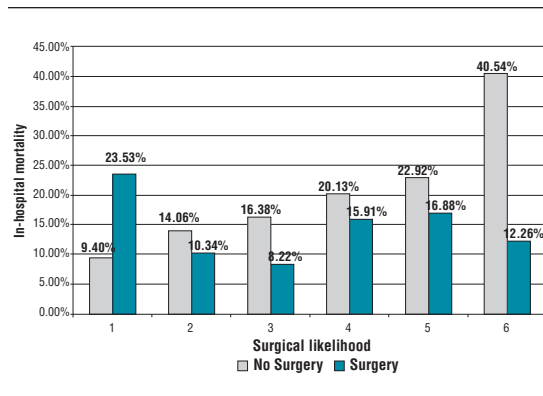
ICE working group: The ICE investigation was launched at the 5th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections, Amsterdam, Netherlands, July 1999. Since its inception, 50 sites in 19 countries have become involved in the project. An International Steering Committee charged with promoting collaboration and discovery governs the working group. The Steering Committee directs the activities of the ICE consortium and coordinates research activity by member investigators and institutions.

ICE database merger: The initial project of the ICE investigation involved the merger of existing databases from throughout the world. The purpose of the database merger project was to evaluate regional differences in endocarditis and to provide a large sample of IE patients that would permit subgroup analyses.³¹

The promise of this data resource (to more completely understand IE and to generate testable hypotheses) has already been realized. For example, similar to Vikram and colleagues, the ICE-MD investigators have also examined the role of surgery in the treatment of IE. The ICE-MD database was used to better understand the relationship between patient characteristics, surgical intervention, and outcome in a large, unselected, multicenter cohort of patients with definite endocarditis. The authors specifically sought to characterize native valve IE patients relative to surgery and to determine if patients could be identified who would benefit from early surgical intervention.

This analysis has shown that patients treated with surgical therapy are quite different than those treated with medical therapy alone, which is not surprising from a clinical standpoint. Important differences included age, gender, diabetes, intravascular catheters, a history of cancer, referral to a tertiary-care hospital, microorganisms, and

Figure 6: In-hospital mortality within groups of similar patients



valvular location. Importantly, the rates of in-hospital mortality were similar between groups: 13.6% in the surgical group vs. 13.6% in the medical-therapy group ($p=0.140$). When this mortality was examined more closely using propensity techniques, it became clear that surgery definitely had an impact on mortality, particularly in those patients with the most indications for surgery. Interestingly, in the group with the fewest indications for surgery, there appeared to be a survival disadvantage with surgery (Figure 6). It is intriguing that in patients with moderate indications for surgery, there was no significant advantage with surgery. It is in these patients that further work is necessary to understand and refine indications for surgery.

ICE prospective cohort study: The prospective cohort study began on June 15, 2000. This observational study aims to collect data on IE cases as they are identified, using a standard case-report form and definitions. To date, over 40 sites have enrolled patients in the prospective cohort study and the study now contains over 2200 prospectively identified and collected cases.

Several advantages in this study can be identified.³¹ The prospective design will minimize ascertainment and sampling bias from any individual site, but clustering will need to be evaluated. The registry should also provide rapid accrual of patients that can limit the effect of changing demographics of disease over time. The large sample size provided by the registry will provide the power necessary for detailed analyses and the study of rare IE characteristics. Because valid data can be accrued rapidly, the ICE should also have the capacity to answer questions about IE soon after the need for specific data is identified. Finally, the multicenter design will afford the opportunity to analyze natural experiments regarding practice variation and associated patient outcomes.³¹

Future directions

Although retrospective data analyses and observational studies provide important information and insights into disease processes, these study designs are of limited use in testing treatment strategies. Randomized clinical trials provide the opportunity to test treatment strategies

and maximally control for other factors affecting outcome. Without randomized trials, it is not possible to fully control for all potential confounding factors and accurately assess the full impact of therapeutic decision-making. There are many examples of treatment strategies thought to be beneficial based upon observational data (eg, hormone replacement therapy in women at risk for cardiovascular events) that have later been found to be of no benefit in randomized controlled trials.

In diseases of high morbidity and mortality, such as IE, randomized trials are necessary to definitively improve the outcomes of patients. Networks of investigators are needed to study these diseases; the ICE investigators have developed a network of dedicated scientists and an established infrastructure from which clinical trials will be possible.

Conclusion

Since Osler's important description of endocarditis in the 1880s, much has changed with this disease; yet, the improvements that we have seen in many facets of cardiology have not been fully realized in endocarditis. Over the last several years, as highlighted in this article, there have been many new developments that have expanded our knowledge of IE. We know that the epidemiology is changing, with an incidence that may be increasing and that new characteristics, such as device infections, have become important. In addition, studies have shown that echocardiography is central to the diagnosis and management of IE and that TEE is a cost-effective diagnostic strategy in a variety of situations. Moreover, recent studies have shown that risk classification is possible and that the use of surgery in certain patient populations, particularly those with significant heart failure, may have a dramatic benefit on survival. These studies have also provided data suggesting that the benefit of surgery is less clear in other patient groups; therefore, standard indications for surgery may need refinement.

Finally, a change in the approach to this disease is necessary to improve the outcomes of patients with endocarditis. Multicenter collaboration is needed to provide a more precise understanding of the disease, while randomized clinical trials are critical to ultimately discern which therapeutic strategies improve the outcomes of patients with endocarditis.

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Dr. Cabell has reported no relationships with industry relevant to the enclosed CME program.

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