Infective Endocarditis

A Multidisciplinary Team Approach to a Complex Disease

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Foreword

The history of managing infections of the cardiovascular tree is punctuated by mystery, resistance by the medical community, and slow advances in multiple potential options of treatment, based on the underlying etiology, accidental or self-induced infections, site, organism, and the patient's status at presentation. While Ignaz Semmelweis proved in 1847, although a skeptical medical community, including the celebrated Rudolf Virchow would not believe him, the importance of what we now know as bacteria, "cadaverous particles," in causing infections, it was only later in 1885 that William Osler, ironically a pupil of Virchow, elucidated the field of "mycotic" and endocarditis mushroom-like vegetation infections. Actual mycotic fungal infections are uncommon, but difficult to manage, especially organisms such as *Aspergillus*, and most infections are related to bacteria, hopefully responsive to antimicrobials. But even among bacterial organisms, the response to antimicrobials is variable. Cardiovascular infections caused by *Streptococcus pneumoniae* respond very differently to vancomycin or methicillin-resistant *Staphylococcus aureus*, confounding our treatment options. As Chairman for Guideline Documents for the American Association for Thoracic Surgery (AATS) many years ago, I urged Gösta Pettersson, MD, to put together our collective thoughts on managing cardiovascular infections, and with the help of Joseph Coselli, MD, and input from our excellent Infectious Disease department, who had seen many varieties of cardiovascular infections and endocarditis, and in particular Stephen Gordon, MD, the document was written. The landmark AATS Consensus Guidelines on managing endocarditis did much to demystify the treatment of endocarditis and the follow-up multidisciplinary Master Class in Endocarditis meeting in April 2018 further added to our knowledge.

In this book, the authors masterfully summarize current knowledge of endocarditis, demystify treatment options, and make recommendations based on data that give the best options for treatment. It is a major contribution that I have no doubt

will be extensively quoted, and on behalf of our patients and those of you who read it, I thank them for their tireless efforts in pursuing this noble cause of preventing and finding solutions to treating what has been a vexing cardiovascular disease for centuries!

Chairman of Heart, Vascular,
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August 31, 2023

Lars G. Svensson

Preface

This book about infective endocarditis was initiated in 2020 by the group of coeditors. The book was based on the same idea as our multidisciplinary master class in endocarditis and other cardiac infections we held in April of 2018. This book emphasizes the multidisciplinary approach to management of infective endocarditis and other cardiovascular infections and their complications. Consequently, anyone who has something to contribute to the management team should be interested in this book. All aspects of this serious disease are covered: pathophysiology, virulence factors, diagnosis, and medical and surgical management as well as management of complications, specifically cerebral complications caused by embolism.

The book summarizes current knowledge of pathophysiology, histopathology, and pathogens of infective endocarditis. The current guidelines on surgical treatment of infective endocarditis are critically reviewed and appraised and their implications for clinical practice interpreted. We cover epidemiology, risk factors, and diagnostic criteria and describe strategies for the medical management, especially use of antimicrobials, and discuss the signs and symptoms that indicate a need for surgery. Preoperative evaluation and imaging and timing of surgery are important chapters, particular in relation to the common neurologic complications associated with infective endocarditis.

The role of surgery is discussed in depth, the pros and cons as well as the performance of surgery including when and how to repair valves, choice of prosthesis evaluation, and procedures for advanced disease. We debate issues associated with prosthetic valve infections, should all these patients be treated surgically?

We have a chapter on cardiac rhythm device infections, prevalence, diagnosis, management, and prevention.

Aortic infections, infections of ventricular assist devices, sternal wound infections, and decision-making and treatment approach are discussed.

The serious impact of the still growing opioid crisis on the incidence of infective endocarditis and management has not been forgotten.

Infectious disease specialists, cardiologists, and cardiac surgeons along with general practitioners, internists, neurologists, neurosurgeons, orthopedic surgeons, vascular surgeons, nurses, physician assistants, and other allied health professionals

who care for patients with these infections, take care of manifestations of complications, and encounter patients before the cardiac infection has been diagnosed should all find something of interest in this book.

Cleveland, OH, USA

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Epidemiology and Team-Based Care

Chapter 1
Introduction

Paul C. Cremer, Steven Gordon, Brian P. Griffin, Gosta B. Pettersson, Nabin K. Shrestha, and Shinya Unai

The first good description of infective endocarditis (IE) was provided by William Osler in his Gulstonian Lectures on malignant endocarditis 1885 [1]. IE at that time was an almost uniformly deadly disease; acute endocarditis caused by *Staphylococcus aureus* killed the patient within 2 months while subacute or chronic endocarditis, mostly caused by viridans group streptococci, bacteria that are commensal oral flora, could allow the patient to live up to a year. Osler realized that IE manifestations were not only cardiac but systemic with primary and secondary infectious manifestations and embolic events affecting any organ and part of the body. Osler's description and understanding of the etiology, pathology, complications, and prognosis were detailed and accurate, and his papers are still very much worth reading.

The number of patients at risk of developing IE is increasing and the epidemiology is changing. Patient presentation is dependent on original cardiac pathology, microorganism, location—affected valve, stage, embolic complications, and primary and satellite infectious foci. Today we have an even better understanding of the infectious process, the causative microorganisms, and their virulence factors. Although the virulence factors and related aggressiveness and host response differ between microorganisms, the pathologies, in the end, however, look fairly similar,

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irrespective of the pathogen. The diagnostic tools are constantly improving, echocardiography technology is better and includes 3D, and so are the other imaging technologies. Identifying the causative pathogen no longer relies completely on microscopy and culture but we have molecular techniques to identify microorganisms, alive or dead, by their nucleic acid content.

It was not until penicillin, discovered by Fleming 1928, was ready for clinical use in the mid-40s that a cure was possible. It was, however, soon recognized that endocarditis was difficult to cure and that much higher doses and longer durations of treatment than for other infections were required. Despite many new effective antimicrobials and regimens, cure by antibiotics was still only possible assuming infected valves were not destroyed, and the integrity of the heart was not compromised. With the development of cardiac surgery, it became possible to treat these complications, and to repair the heart and valves. The role of cardiac surgery has increased, and its value is no longer disputed. More than half of the patients with native valves and the majority of those with prosthetic valve endocarditis eventually require surgery. However, indications for and optimal timing of surgery are still evolving. Noncardiac manifestations must be taken into consideration and other specialties, like neurology and neurosurgery, interventional radiology, vascular and general surgery, nephrology, are consulted as relevant for the diagnosis and management of these complications. Early diagnosis is key to a good outcome, the diagnosis must be recognized and established before too much damage has occurred and the patient is too sick and has suffered devastating embolic complications. IE in persons who inject drugs (PWID) has come to constitute an increasing proportion of the IE population over the last decade. PWID with IE present two deadly problems, the IE itself and the addiction, both of which have to be adequately treated for long-term success.

Although the understanding of the disease, diagnostic tools, and management has much improved, IE remains a very serious disease with significant morbidity and mortality. The purpose of this book is to emphasize that proper management of patients with IE requires a TEAM and to give involved clinicians an up-to-date understanding of the many aspects of this disease. We have asked different specialists who are part of our IE TEAM or are regularly consulted to give us their angle and perspective.

We like to thank all the contributors for the time and effort invested in helping us realize this project!

Cleveland November 2024
Gosta B. Pettersson, Paul Cremer, Steven Gordon, Brian Griffin, Nabin Shrestha, and Shinya Unai

Reference

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Chapter 2
Natural History and Evolution of Treatment of Infective Endocarditis

Eugene H. Blackstone

Natural History of Infective Endocarditis

Natural History Framework for Therapeutic Decision-Making

Estimating the natural history of progression and prognosis of disease for an individual patient is central to rational therapeutic decision-making, recommendation for a specific therapy among alternatives, and informed patient consent. It became the central organizing structure of chapters in the Kirklin/Barratt-Boyes text *Cardiac Surgery: Morphology, Diagnostic Criteria, Natural History, Techniques, Results, and Indications* [1]. Notably, the order of subtitle elements in that textbook is not random but reflects an orderly framework. Following morphology and diagnosis of a disease, one considers its natural history, enumerates applicable therapeutic options (including no treatment), compiles results related to both benefits and risks, early and late, of each option, and arrives only then at the indication for a therapy whose benefit best outweighs risk.

Classic (Unconditional) Natural History Paradigm

This natural history framework is particularly well suited to settings in which natural history can be traced from a single point in time and progresses predictably and unidirectionally from that point, such as for congenital heart disease [2]. For infective endocarditis, this point in time would be when organisms adhere to the endocardial surface and start developing colonies. The optimal timing of a therapeutic

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intervention is the point in the natural history at which the benefit of an indicated therapy exceeds the risks.

Conditional Natural History Paradigm

Kirklin and Barratt-Boyes emphasized that this framework is also applicable to acquired heart disease. The difference is that each patient presents at a different point in the natural history of his or her heart disease. This we will call "conditional natural history," meaning that the patient has survived to presentation, so the patient's subsequent natural history is conditional on surviving.

A well-recognized example may help the reader understand this. Consider cancer. Cancer onset is rarely if ever known. Instead, when a patient is initially diagnosed with cancer, the first thing oncologists ascertain is cancer stage. This is a shorthand way of assessing crudely the point this patient is at in the natural history of that type of cancer. It is based on anatomic cancer categories (tumor size or depth [T], extent of lymph node involvement, if any [N], and metastatic cancer spread [M], TNM). These multiple variables have been assembled into a cancer staging system based on prognosis (prognostic stages) [3, 4]. At clinical diagnosis, a patient might be said to be at an early stage of the disease, or a later stage, and prognosis and treatment decisions are based on stage and knowledge of disease progression conditional on that stage: conditional natural history.

To date, a staging system for infective endocarditis based on clinical, microbiologic, and immunologic factors, location, stage of invasion, and other factors that affect prognosis has not been devised. However, the idea that prognosis is conditional on certain features of the disease at a given time in its course is intellectually understood. What is less well recognized is that many of the therapeutic dilemmas in managing patients with infective endocarditis, and many of the debates in the literature about therapeutic options, can be traced to failures to take the stage of the disease into account.

Challenge of Defining the Classic Natural History of Infective Endocarditis

Defining the unconditional natural history of infective endocarditis is challenging for these reasons:

First, the time of disease onset is often uncertain. This is unlike experimental animal studies of infective endocarditis in which the time of injection of pathogens is controlled. For example, Weinstein and Brusch [5] reported that in 1886, Wyssokowitch [6] and Orth [7] had designed an experimental model for infectious endocarditis in which aortic valve cusps of animals were traumatized and the animals subsequently injected with bacterial suspensions from patients with

endocarditis. The animals developed murmurs, embolic complications, and exhibited valve lesions at autopsy.

Second, infectious endocarditis can be asymptomatic, unrecognized, and untreated. The prevalence of unrecognized infective endocarditis is unknown and will probably never be known. Evidence for this is found in reports of both pathologic human valves and apparently normal explanted human valves from individuals who are not suspected to have endocarditis but have footprints of pathogens detected by histochemistry and bacterial polymerase chain reaction methods [8, 9].

Third, multiple aspects of infective endocarditis modulate its progression and prognosis. These include characteristics of the infecting organism, valve abnormalities of the infected patient (host) [8–10], and response of the host to the disease [11, 12].

Fourth, endocarditis progression may be nonlinear. Pathophysiology, and with it prognosis, may change abruptly when valvular vegetations embolize to the brain, valve cusps perforate causing hemodynamically important massive regurgitation, or overwhelming systemic sepsis develops.

Conditional Natural History of Infective Endocarditis

Given this information, we cannot construct an unconditional natural history of infective endocarditis. This is not an insurmountable limitation, however, because we can define many aspects of its conditional natural history.

Early reports of the disease, such as that of Jean-Baptiste Bouillaud in the nineteenth century [13], labeled it as "acute endocarditis," and its conditional natural history was rapidly fatal (Fig. 2.1). Then for many years, beginning in 1912 [14], the disease usually seen was characterized as "subacute bacterial endocarditis" (SBE; see Fig. 2.1). However, even Osler and others recognized a chronic (and even healed) stage of endocarditis [15, 16]. Although tied to the causing organism, acute to *Staphylococcus aureus* and subacute to viridans group streptococci, the value of these characterizations of the conditional natural history of infective endocarditis was that they defined three broad categories of rapidity of disease progression. Today, endocarditis is simply dichotomized as "active" and "healed or remote," but with the recognition that organisms differ with regard to virulence factors and aggressiveness.

Understanding how infective endocarditis primarily disintegrates and extends into connective tissue, sparing cardiac muscle [10–12], has led to the disease being characterized as noninvasive vs. invasive, implying a temporal stage of disease progression. Invasive disease has been further characterized by a series of stages: the presence of acute inflammation, abscess formation, abscess cavities, and pseudoaneurysm formation (although there may be a mix of these invasive stages in different areas of the same heart) [17].

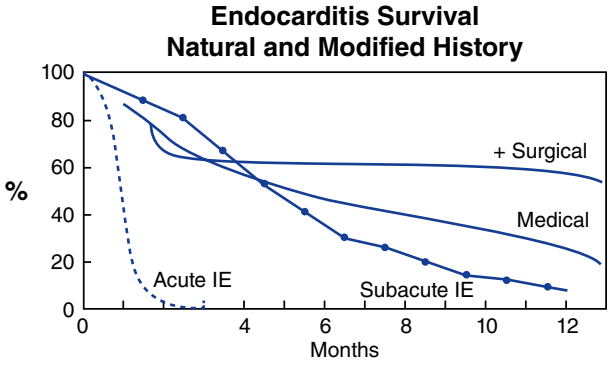

Fig. 2.1 Freehand estimate of natural and modified natural history of infectious endocarditis (IE) compiled from literature sources: acute infectious endocarditis in the pre-antibiotic era, subacute endocarditis in the pre-antibiotic era, medically treated infectious endocarditis in the antibiotic era (note the delay in treatment is assumed to follow the combined trajectory of acute and subacute endocarditis), and surgically treated infectious endocarditis (after medical treatment). Many of these differences are due to what we term "conditional natural history." That is, survival for subacute IE is conditional on surviving acute IE, and survival after surgery is conditional (as is depicted) on surviving medical therapy

Other factors modulate the conditional natural history, such as causative organism and its virulence factors, disease location (e.g., aortic, mitral, or tricuspid valve; left- vs. right-sided), invasion of the conduction system, native vs. prosthetic valve endocarditis, fistulae formation, and so on. These are described in later chapters. All affect a patient's conditional natural history.

If we are to select the right therapy at the right time for the right patient with infective endocarditis, heterogeneity of the clinical condition of patients at presentation, which determines the specific point where each is on their conditional natural history curve, must be taken into account. One patient may present with a nonspecific fever, another with an unexplained stroke, and a third with acute onset of fulminant life-threatening heart failure. The diagnostic work-up, treatment strategy, and therapeutic urgency will be different for these three patients—as will the response to changes as their endocarditis evolves and treatment intervenes. At one end of conditional natural history, the stable patient with fever traced to infective endocarditis may be cured with antibiotics; at the other end of the spectrum, the patient in fulminant heart failure with acute, severe aortic regurgitation, and aortic root abscesses needs emergency, life-saving extensive debridement and aortic root replacement [17].

Alteration of Natural History by Therapy

What can be said definitively is that the natural history of infective endocarditis has been profoundly altered by therapy. Prior to the antibiotic era, complete cure of acute infective endocarditis occurred in less than 5% of cases [5]. High-dose,