Infective Endocarditis

Management in the Era of Intravascular Devices

edited by

John L. Brusch

Infective Endocarditis

INFECTIOUS DISEASE AND THERAPY

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Infective Endocarditis

Management in the Era of Intravascular Devices

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John L. Brusch

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This book is dedicated to my beloved wife,
Patricia Brusch, whose support makes
all things possible. She is my heart and soul.

To my children Amy Claire, Meaghan, and
Patrick, who have accomplished so much
at an early age.

A special acknowledgment of my gratitude
for the prodigious efforts of my friend,
Fred Centanni, who ensured that the layout of the book and
the tables and figures are of the highest quality.
He has become a virtual author.

Preface

My experience with infective endocarditis extends back to my third year in medical school when I was assigned to present a case on endocarditis on teaching rounds to Dr. Louis Weinstein the next day. To prepare, I read Dr. Weinstein's three-part *New England Journal of Medicine* article, "Infective Endocarditis in the Antibiotic Era." Because of the lateness of the hour and the encyclopedic nature of Dr. Weinstein's review, the only thing I was able to comprehend was that I, a third-year medical student, was presenting to a world's expert on the subject. This unnerved me to the point that when I opened my mouth really nothing came out. Dr. Weinstein calmed me down and I managed to get through the presentation. Despite this less than auspicious beginning, I persevered in learning as much as I could about endocarditis. I became one of Dr. Weinstein's fellows. In the early 1990s, he asked me to co-author a text on infective endocarditis. It was a wonderful opportunity. I had access to his case files, library, and his unique experience. His generation was the one that saw the disease before and after the advent of antibiotics. Our book (*Infective Endocarditis*, Oxford University Press, 1996) presented the disease from its first recognition through the onset of AIDS.

This new volume covers the recent profile of this disease. Classic subacute valvular infections still exist. However, *Staphylococcus aureus* and coagulase-negative staphylococci have become the prominent pathogens. They have assumed this prominence not simply because of their increasing resistance to antimicrobial agents. The major reason for the increasing involvement of the staphylococci in valvular infections is the proliferation of intravascular devices.

This realization inspired the title, *Management of Infective Endocarditis in the Era of Intravascular Devices*. Subacute disease is thoroughly presented. However, the dominant theme throughout this book is the ability of the staphylococci and other bacteria to infect prosthetic material. I have attempted to cover this topic from the perspective of the pathogenic properties of the organisms as well as of the defects in the defenses of the hosts who require these intravascular devices.

Because of the specialized nature of many of the areas to be covered, I called upon Drs. Cunha, Picard, Jassal, and Kradin to contribute their extensive knowledge and experience to the book. I am deeply grateful for their efforts.

John L. Brusch

Acknowledgment

John L. Brusch, MD, and Louis Weinstein, MD

In grateful acknowledgment of the many contributions to the study of infective endocarditis made by the late Louis Weinstein, M.D.

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1 Epidemiology

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INCIDENCE

Infective endocarditis (IE) is an infection of the endocardium of one or more valves. Rarely, it may involve the mural endocardium. It currently is classified into one of the four major types: native valve endocarditis (NVE), prosthetic valve endocarditis (PVE), intravenous drug abuser IE (IVDA IE), and healthcare-associated IE (HCIE). Classically, this infection has been categorized as either acute or subacute. The clinical courses were quite different with the pathogens that were highly associated with one type or another. Acute IE was, and still is, a rapidly progressive disease that can be fatal in a few days. Without treatment, subacute IE may smolder for months or even longer than a year (Chapter 6). Until the 1980s, the vast majority of cases were subacute, caused by viridans streptococci. In this era of IE of intravascular devices (Table 1), there has been a dramatic reversal of this pattern. At times, the differences between these two may be blurred by indiscriminately prescribed antibiotic therapy. Infective endocarditis, caused by *Staphylococcus aureus*, may assume an indolent course when exposed to inadequate dosage regimens of antibiotics that are given on the basis of faulty diagnoses. This situation could be labeled as "muted endocarditis." Nonetheless, the clinical classification of acute and subacute disease remains useful, as it still retains a good amount of clinical predictive value.

An accurate rate of new cases of IE is difficult to determine. This is attributed partly to the intermittent courses of antibiotics given because of failure to make the correct diagnosis. The recognition of IE often may be very challenging, especially when its signs and symptoms are noncardiac. Five to 10 percent of the cases of IE have negative blood cultures. In the past, only postmortem examination reliably differentiated uncomplicated bacteremia from that caused by cardiac infection. The declining rate of autopsies has only worsened this situation. In 1981, von Reyn et al. published strict case definitions for diagnosing IE (1). The Duke Endocarditis Service combined echocardiographic findings with various clinical measures to improve the accuracy of diagnosis (2). These criteria have positive and negative predictive values of at least 92%. The International Collaboration on Endocarditis is an initiative to establish a global database of IE patients who have been studied with standard methodology (3).

Based on the studies conducted within the last 25 years, the incidence of IE throughout the world varies from 1.5/100,000 to 6/100,000 per population per year (4–7). There are marked variations in the incidence of IE among nations and even within a given country. This probably is related to the proportion of urban versus rural populations (8,9), and their differences in socioeconomic class and intravenous drug abuse.

In 1940, Hedley estimated that there were approximately 5000 cases of IE in the United States, at a rate of 4.2/100,000 per population per year (10). Overall, the

TABLE 1 The Eras of Infective Endocarditis

The preantibiotic era (1725–1943):
1885—William Osler presented the first comprehensive account in English of infective endocarditis
The antibiotic era (1943–1980s):
1966—Louis Weinstein presented an in-depth review of the pathophysiology, clinical presentation, diagnosis, and treatment of infective endocarditis
1980s—Infective endocarditis in the era of intravascular devices

availability of antibiotics does not appear to have made a significant decrease in the incidence of this disease (10,11). There might have been a transient decrease during the early days of antimicrobial therapy (12). This could be attributed to several factors, including (*i*) widespread use of antibiotics that decrease the rate of sustained bacteremia, originating from many types of extracardiac infections; (*ii*) antibiotic prophylaxis in patients with significant underlying heart disease; and (*iii*) admission of patients with endocardial infection to referral hospitals. The increase in the resistance of bacteria to various types of antibiotics and the increase in cardiovascular surgery and intravascular devices have blunted this advantage. These same factors have changed the clinical profile of IE from a predominantly subacute disease to an acute one. Newsom reported that the incidence of IE had changed little since the 1930s (3.8/100,000 per population per year between 1950 and 1981) (13). Currently, there are approximately 2000 to 15,000 new cases of IE yearly in the United States (14).

The incidence and type of IE in any given hospital is dependent on the types of patients it serves (15,16). Institutions that have a large population of IVDA, congenital heart disease or patients with prosthetic valves, have a higher rate of IE than a community hospital. The IE owing to *S. aureus* occurs more often than those admitted to a community hospital, whereas enterococcal disease is cared for more frequently in tertiary-care hospitals (1).

AGE AND SEX

The age distribution of IE has changed considerably since the 1940s. This was formerly a disease of young adults. In 1920s, the patients were usually <34 years of age (17). The mean age of those with subacute IE has increased from 36 (1923) to 32 (1930s and 1940s) to 46 (1950s), and to 56 years (1960s) (18–20). The current median age is 58.0 (3). Gladstone and Rocco observed that the elderly are more susceptible to IE. Older patients present with more subtle clinical manifestations than younger ones to the degree that the correct diagnosis was missed in two-thirds of them early in the course of disease. They postulated that their vulnerability is related to a decrease in the activity of their immune system and to the dysfunction of the heart and other organs that marks the aging process (21). Other proposed causes of this "graying trend" include (22): (*i*) a heightened susceptibility of the endocardium to infection during a transient bacteremia because of an increase in calcific valvular disease; (*ii*) a marked increase in cardiac surgery and intravascular devices among the elderly; (*iii*) 67% of those with nosocomially acquired staphylococcal bacteremia are elderly compared with the 30% of those with community-acquired staphylococcal infections (23); (*iv*) almost complete disappearance of

rheumatic fever and rheumatic heart disease (RHD) in the United States (24); (*v*) individuals with congenital heart disease live longer and often require valvular replacement; and (*vi*) people, in general, are living longer (25). In adults, the major exception to this aging pattern is IVDA IE. The median age of these patients is approximately 30 (26).

Pediatric IE is quite uncommon. Infective endocarditis accounts for 0.55 per 100,000 admissions to tertiary-care pediatric hospitals (27). As would be expected, most cardiac infections are attributed to congenital abnormalities in children more than two years of age. In the very young, pediatric IE more commonly occurs in the setting of normal cardiac structures, and is usually secondary to a catheter-related bloodstream infection (BSI) (28).

Infective endocarditis occurs at least twice as often in men as in women (11,26). This ratio increases to 9:1 in patients 50 to 60 years of age and to 6.5:1 in individuals 61 to 70 years of age. This sexual distribution generally is not dependent on the specific infecting organism. However, women <35 years of age are disproportionately involved in cases of enterococcal endocarditis (29).

PREDISPOSING CARDIAC LESIONS

Approximately 40% of cases of IE affect the mitral valve alone, and 5% to 36% affect the aortic valve alone. Infection of both of these valves occurs less often (30). The pulmonic valve is seldom infected. Cases of right-sided endocarditis occur primarily in IVDA and HCIE owing to intravascular lines.

Almost any structural lesion of the heart may give rise to IE as long as it can result in the formation of a sterile platelet/fibrin thrombus, the indispensable precursor of all types of IE (Chapter 5). The specific type of cardiac abnormality underlying a given case of IE is closely associated with certain characteristics of the patient (age, history of drug abuse, or immunosuppression) and the nature of the infecting organism. Bacteria, such as *Streptococcus viridans*, with a low invasive potential, opportunistically infects abnormal valves. *Staphylococcus aureus* has the ability to infect normal valvular structures. Cabell and Abutyn commented that "there are studies available to quantify the risk of developing IE for patients with specific cardiac conditions. It is more clear which conditions, when associated with active IE, are more likely to be associated with complications and death" (31). For certain cardiac conditions, the risk of developing IE is better established. In the case of mitral valve prolapse (MVP) with significant regurgitation, it is increased 10- to 100-fold (32), whereas for prosthetic valves and for patients with prior IE, the risk for valvular infection may be increased >100-fold (33,34).

Durack and Petersdorf (22) have concluded that the advent of antibiotics has made no change in the contribution of congenital heart disease to the development of IE. Overall, congenital heart disease is the underlying factor in 5% of adult IE. Bicuspid aortic valves may account for up to 20% of the cases of IE in individuals older than 60 years. Among congenital heart diseases, the tetralogy of Fallot exhibits the greatest incidence of IE. Even when surgically corrected, it remains a significant factor for the development of endocardial infection. Approximately 25% of tetralogy patients, who undergo an anastomotic correction develop infection at the surgical site. This is attributed to the turbulent blood flow at the point where the vessels are joined. Lesser, but still significant, risk factors for IE include coarctation of aorta, ventriculoseptal defect and bicuspid aortic valve. Secundum atrial septal

defect and congenital pulmonic stenosis pose negligible risks for IE, probably because of the minimal pressure gradient across these lesions (35,36). The risk of congenital aortic stenosis becoming infected is directly proportional to the pressure gradient across the valve (37).

Although RHD has become a negligible predisposing factor for IE (38,39) in the developed world, it remains the largest cardiac risk factor for IE in the developing countries (50% of cases). The lifetime risk for patients with RHD to develop endocardial infection is 6% (39). The majority of cases of RHD IE occur in females (67% of cases), and involve the mitral valve (85% of cases).

Mitral valve prolapse accounts for up to 30% of cases of NVE. It has supplanted RHD as the chief underlying condition for the IE of younger patients (32,40,41). Mitral valve prolapse is found in approximately 5% of the population. It is inherited in an autosomal dominant fashion. It may be a part of a syndrome (von Willebrand's disease, ophthalmoplegia, and distinctive female habitus) that is associated with an abnormality of chromosome 16p (42). Cases of MVP that do not exhibit any significant regurgitation are at little increased risk of IE (43). Thickened anterior mitral leaflets and male sex >45 years of age are additive risk factors for the development of IE in MVP (40,44). On the whole, the cases of IE of MVP have relatively lower rates of morbidity and mortality (45) than do other types of valvular infection.

The term degenerative cardiac lesions represents a wide range of entities, including degenerative valvular disease (DVD), calcified mitral annulus, and atherosclerotic calcifications of the endocardium. They all have in common a roughened endocardium that enhances thrombus formation. Often there is no significant pressure gradient across these valves (40,46–48). If a murmur is present, it usually is classified as innocent. Thirty-three to fifty percent of people >60 years of age have evidence of wear-and-tear aortic valve disease. Degenerative valvular disease accounts for approximately 50% of IE in elderly patients (25). It coexists with a number of other significant medical conditions in >50% of patients. These include diabetes mellitus, renal failure, current artery disease and chronic lung disease. Their presence accounts for the increased fatality rates in these patients.

An underappreciated predisposing cardiac lesion for IE is asymmetric septal hypertrophy. The risk of developing IE is directly related to the level of obstruction—the higher the peak pressure, the greater the chance of infection (49,50). The lifetime risk of developing IE in these patients is 5%. Most cases involve the mitral valve, and rarely the aortic valve. This distribution is attributed either to displacement of the anterior leaflet of the mitral valve by the abnormal contractions of the septum or by the jet stream affecting the aortic leaflets distal to the obstruction. *Streptococcus viridans* is the causative organism in 75% of cases. The outcomes of valvular infection are worse among the one-third of patients who clinically develop a new murmur.

Infective endocarditis occurs in approximately 5% to 10% of prosthetic valves (51). The greatest risk of infection occurs within two months of implantation (early PVE). Initially, mechanical prosthetic valves were most vulnerable. With time, the rate of infection of bioprosthetic valves equals or exceeds that of mechanical ones. After the first year, the rate of infection averages about 0.3%. Over time, the process of endothelialization partially protects prosthetic valves from being infected by transient bacteremias. However, it is important to emphasize that no matter how old the valve is, it will always be at some risk (52). Prosthetic valve endocarditis accounts for 7% of the total cases of IE (8,14). Similar in nature to PVE is IE of pacemakers

and other intracardiac devices (53). Most become infected within a few months of implantation.

EXTRACARDIAC PREDISPOSING FACTORS

The incidence of IE in IVDA ranges from 1% to 5% per year (54). Those who inject cocaine are at the highest risk of developing valvular infection (55). Intravenous drug abuser IE might be decreasing in certain populations because of the increased use of sterile needles and syringes in an effort to decrease HIV transmission (56). Intravenous drug abuser IE is a disease of urban areas with few cases seen in rural ones. The male to female ratio is 9:1 (57). In certain areas of the country, up to 90% of patients with IVDA IE are HIV-positive (58). Those suffering from advanced AIDS do significantly worse with their valvular infections (59). Pure right-sided IVDA IE occurs in >50% of cases, usually involving the tricuspid valve. The aortic valve is involved in 25%, with the mitral valve in 20%. Polymicrobial IE is seen most frequently in IVDA. Of all the types of IE, the chance of recurrence is highest among IVDA. Most likely, this is the result of the persistence in the use of injectable drugs by those who have already had an attack of IE (20–40% of cases).

The shift from the use of the term nosocomial IE to HCIE reflects the fact that healthcare is increasingly delivered outside the walls of the hospital. In the 1970s, von Reyn (1) was one of the first to recognize that hospitalization itself could be a major risk factor for acquiring IE. In his study, 20% of the patients acquired IE on being hospitalized for some other condition. HCIE is defined as a valvular infection that occurs within four weeks of an invasive procedure or the development of signs and symptoms of IE 48 hours or longer, following admission to a healthcare facility (1).

Finland and Barnes (60) associated the rise in the cases of IE, caused by *S. aureus*, enterococcal sp., *S. epidermidis*, and gram-negative bacilli with the institutalization of the patient. Friedland et al. characterized patients with HCIE as being older, with a higher rate of valvular disease, and whose bacteremias are related to various intravascular procedures (61). The mortality rate of HCIE is approximately 50%.

The cases of HCIE appear to be on the rise, accounting for approximately 30% of the cases in many hospitals (61). It correlates with the escalating employment of intravascular devices, such as hyperalimentation lines, dialysis catheters and pacemakers. Much of this is related to the increase in staphylococcal bacteremia, associated with the infection of intravascular catheters and other devices (62–66). Staphylococci followed by enterococcal species, are the predominant organisms. They usually originate from the skin or urinary tract. There appears to be a close association between particular healthcare procedures and the risk of IE. A particularly strong connection exists between bacteremias associated with hemodialysis and the development of *S. aureus* IE (66). Thirteen percent of staphylococcal bacteremias acquired in the hospital result in HCIE.

There are two varieties of HCIE (67). Type 1 is attributed to various traumatic types of injury to the endocardium of the right ventricle produced by various types of intravascular lines. Type 2 is produced by bacteremias that infect the left ventricular structures. At least 50% of the cases of either type occur in the setting of normal valves. This most likely reflects the predominant role of *S. aureus* and its potential to invade healthy cardiac structures. Friedland pointed out the importance of recognizing the risk factors for developing HCIE (68). He stated "nosocomial endocarditis occurs in a definable subpopulation of hospitalized patients and is potentially preventable."

TABLE 2 Changing Patterns of Infective Endocarditis Since 1966

Marked increase in the incidence of acute IE
Rise of nosocomial, IVDA, and prosthetic valve IE
(a) Change in the underlying valvular pathology: rheumatic heart disease, <20% of cases
(b) Mitral valve prolapse, 30% of cases
(c) Prosthetic valve endocarditis, 10–20% of cases
(d) 50% of elderly patients have calcific aortic stenosis
These changes are attributed to:
(a) The "graying" of patients (excluding cases of IVDA IE, 55% of patients >60 years of age)
(b) The increased numbers of vascular procedures

Abbreviations: IE, infective endocarditis; IVDA, intravenous drug abuser.

The definable sets of hospitalized patients are those that are at risk of developing bacteremias, especially those caused by *S. aureus*.

Dental procedures have been inextricably linked to the development of endocarditis in the susceptible patient. Recently, several human studies have failed to support this connection (69,70). The risk may be as low as 1 in 115,000 patients with predisposing cardiac lesions (71). The risk is much greater for patients with prosthetic valves in place (1–2%) (72).

Various types of immunodeficient states have been identified as risk factors for the development of IE (73). These include diabetes mellitus renal failure, liver disease, pregnancy, many types of neoplasms and organ transplants (Chapter 11) (74).

Table 2 summarizes the current major underlying abnormalities for the development of valvular infection.

MICROBIOLOGY

The organisms that are involved in NVE differ somewhat from those that produce PVE or IVDA IE. Gram-positive cocci predominate in all types of IE. *Staphylococcus aureus* accounts for 30% of cases overall—coagulase-negative staphylococci (CoNS) 16% and *S. viridans* 16%. The frequency of *S. viridans* IE has lessened by 35%, whereas that of *S. aureus* has increased by 50%.

Non-*S. viridans* streptococci, such as nutritionally variant streptococci (currently classified as Abiotophia), have also become more common. They also have become increasingly more resistant to penicillin-culture-negative endocarditis, and currently account for approximately 5% of cases. Tables 3, 4, and 5 summarize the microbiological and clinical correlates of IE.

TABLE 3 Microbiology of Infective Endocarditis in Different Risk Groups

Microorganism recovered (% of cases)	Native valve endocarditis	Intravenous drug users	Prosthetic valve endocarditis	
			Early	Late
Viridans-group streptococci	50	20	7	30
Staphylococcus aureus	19	67	17	12
Coagulase-negative staphylococci	4	9	33	26
Enterococci	8	7	2	6
Miscellaneous	19	7	44	26

TABLE 4 Epidemiological Characteristics of the Four Major Types of Infective Endocarditis

	NVE	PVE	IVDA IE	HCIE
Mean age	50 (15% >70)	50 (15% >70)	30–40	50 (15% >70)
Underlying abnormalities	Congenital heart disease 13% RHD 6% MVP 30% Degenerative valvular disease 21% (especially calcific aortic stenosis) Hypertrophic cardiomyopathy 5%	Prosthetic valve	75% have no underlying pathology	45% involve prosthetic valves
Total cases of IE (%)	>40	10	15	30

Abbreviations: HCIE, healthcare-associated IE; IVDA IE, intravenous drug abuser infective endocarditis; MVP, mitral valve prolapse; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; RHD, rheumatic heart disease.

TABLE 5 Clinical Characteristics of Organisms Commonly Involved in Infective Endocarditis

Organism	Comments
Staphylococcus aureus	The most common cause of acute IE, including PVE, IVDA, and IE related to intravascular infections. Approximately 35% of cases of *S. aureus* bacteremia are complicated by IE.
Streptococcus viridans (*S. mitior*, *S. sanguis*, *S. mutans*, *S. salivarius*)	70% of cases of subacute IE. Signs and symptoms are immunologically mediated with a very low rate of suppurative complications. Penicillin resistance is a growing problem, especially in patients receiving chemotherapy or bone marrow transplants.
S. milleri group (*S. anginosus*, *S. intermedius*, *S. constellatus*)	Up to 20% of streptococcal IE. Unlike other streptococci, they can invade tissue and produce suppurative complications.
Nutritionally variant streptococci (NVS)	5% of subacute IE. Isolates require active forms of vitamin B6 for their growth. Characteristically, they produce large valvular vegetations with a high rate of embolization and relapse.
Enterococci	Third most common cause of IE. They may produce alpha, beta, or gamma hemolysis. Source is GI or GU tracts, associated with a high rate of relapse. Growing problem of antimicrobial resistance. Most cases are subacute.
Nonenteroccocal group D streptococci (*S. bovis*)	50% of group D IE; associated with lesions of large bowel.
Coagulase-negative *S. aureus*	30% of PVE; <5% of IE of native valves; subacute course that is more indolent than that of *S. viridans*.
Pseudomonas aeruginosa	Most commonly acutely seen in IVDA IE (right-sided disease is subacute) and in PVE.
HACEK organisms (*Hemophilus aphrophilus*, *Actinobacillus actinomycetocomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*)	Most common gram-negative organisms in IE (5% of all cases of IE); presents as subacute, culture-negative IE. Part of normal flora of the GI tract. Intravenous drug abuser is a major risk factor. Complications are arterial macroemboii and congestive heart failure. Cases usually require the combination of ampicillin and gentamicin, with or without surgery, for cure.

(*Continued*)

TABLE 5 Clinical Characteristics of Organisms Commonly Involved in Infective Endocarditis (*Continued*)

Organism	Comments
Bartonella species (*Bartonella quintana*, *Bartonella henselae*, *Bartonella elizabethae*)	*B. quintana* is the most common isolate. Culture-negative, subacute IE in a homeless male should suggest the diagnosis. Usually treated with a combination of a beta-lactam antibiotic and an aminoglycoside.
Fungal IE	An increasing problem in the ICU and among IVDA. *Candida albicans* is the most common example (especially in PVE) as compared with IVDA IE, in which *Candida parapsilosis* or *Candida tropicalis* predominate. *Aspergillus* species recovered in 33% of fungal IE. Most cases of fungal IE follow a subacute course.
Polymicrobial IE	Most common organisms are *Pseudomonas* and enterococci. It occurs frequently in IVDA and cardiac surgery. It may present acutely or subacutely. Mortality is greater than that of single-agent IE.

Abbreviations: GI, gastrointestinal; GU, genitourinary tract; ICU, intensive care unit; IE, infective endocarditis; IVDA, intravenous drug abuser; PVE, prosthetic valve endocarditis.

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2 Microbiology of Infective Endocarditis and Clinical Correlates: Gram-Positive Organisms

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INTRODUCTION

This chapter, along with the following one, presents the distinctive properties of the principal organisms that are involved in infective endocarditis (IE) in the era of intravascular devices. In the last 10 years, there has been a significant increase in our knowledge of the pathogenesis of IE. Much has been learned of the manner in which pathogens infect both native tissues and prosthetic devices of all types. Much remains to be discovered. Hopefully, this expanded knowledge base will provide targets for antimicrobial therapy that were not even dreamed of about a decade ago. Later chapters examine the interaction of specific pathogens and the host that results in varied presentations of native and prosthetic valve endocarditis.

Gram-positive cocci have remained the premier pathogens of IE. The advent of intravascular devices, cardiac surgery, antibiotics, potent immunosuppressive agents, and the increase in intravenous drug abuse have led to the decline of *Streptococcus viridans* and to the ascendency of both coagulase-positive and negative staphylococci in IE (Chapter 1). Although the target of these organisms is the same—native or prosthetic materials, the manifestations of each can be markedly different. *Staphylococcus aureus* typically produces an acute type of valvular infection, whereas *S. viridans* and coagulase-negative staphylococci (CoNS) an indolent/subacute one. Unusually, the course of *S. aureus* IE may be subacute. This reversal of clinical course is often attributed to the administration of suboptimal doses of antibiotic (1). Much less frequently, *S. viridans* results in acute disease. These organisms differ greatly among themselves as to their pathogenic factors. What they have in common is the ability to resist decolorization by alcohol during the process of Gram staining. This is attributed to their thick peptidoglycan layer with extensive teichoic acid cross-linkages (2) compared with the far thinner peptidoglycan structure of the gram negatives that completely lack teichoic acid. Exposure to antibiotics may lessen the ability of gram positives to retain the crystal violet stain. Some cells will appear pink and others purple. This state is classified as Gram variable. Characterization by their gram-staining properties and morphology of organisms, isolated in blood cultures, remains clinically useful. It is usually the first "hard" information that the clinician receives regarding the nature of the suspected case of IE. There is no diagnostic technique on the horizon that usurps this role of the Gram stain. Figure 1 presents an algorithm for the identification of gram-positive organisms.

THE STAPHYLOCOCCI

Staphylococci are members of the Micrococcaceae family. The genus *Staphylococcus* consists of 31 species. They are gram-positive cocci that cluster irregularly.

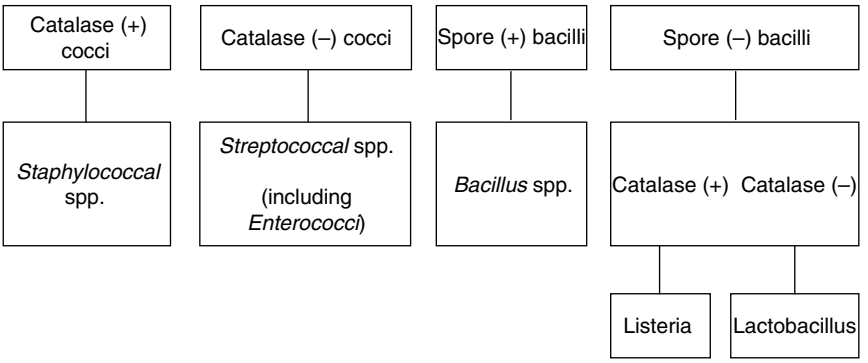

FIGURE 1 Gram-positive organisms.

All examples are anaerobic/facultatively anaerobic and catalase positive. Only *S. aureus* is coagulase positive.

Staphylococcus aureus

Finland and Barnes observed that *S. aureus* caused approximately 6% of IE in the decade prior to the widespread use of penicillin (3). From 1944 to 1966, the frequency of IE, caused by this organism, increased to 16% (4). Currently *S. aureus* produces greater than 30% of cases of IE. In the past, most cases of staphylococcal IE originated in the community; 4% of these at present are cases of healthcare-associated IE (HCIE) (5,6). As early as 1982, it was recognized that staphylococcal IE is "… part of what is to be called a staph pandemic which was presumably reflected in large hospitals and all the highly developed countries" (7).

S. aureus is uniquely qualified to take advantage of the aforementioned advances in medical care, especially when used in the treatment of the elderly and immunosuppressed. This section will examine the properties that facilitate *S. aureus* distinctive ability to produce IE. *S. aureus* exhibits three classes of virulence agents (8). The first are those that govern the organism's attachment to a variety of cells and extracellular material. As an initial step, staphylococci must be able to bind to the integument or mucosa of the host to establish a "beach head" from which to invade the bloodstream. Teichoic acid is a phosphate-containing polymer that has been implicated in the ability of the bacteria to attach to the nasal mucosa (9). Mucosal binding is also facilitated by upper respiratory viral infections, intravenous drug abuse, hemodialysis, and diabetes. More recent work indicates that *S. aureus* employs several bacterial surface proteins that interact with the host's extracellular matrix proteins to promote colonization and invasion (10). These are termed "microbial surface components recognizing adhesive matrix molecules" (MSCRAMMs) (11). These molecules are covalently attached to the peptidoglycan layer by a common core of six amino acids, LPXTGX. The LPXTGX has to be cleaved by sortase, which then transfers and attaches the MSCRAMMs to the peptidogycan layer. The expression of these factors is governed by several gene regulators—most important of these is the accessory gene regulator (*agr*) and the staphylococcal accessory regulator (*sag*) (12,13). Attachment factors are expressed only during the exponential phase of bacterial growth (14). Table 1 lists the most significant MSCRAMMs. Of these, those with the best-established role in the pathogenesis of

TABLE 1 Attachment Virulence Factors of *Staphylococcus aureus*

MSCRAMM	Demonstrated pathogenic role in IE
Clumping factor A	Yes
Clumping factor B	No
Coagulase	No
Fibronectin A and B	Yes
Collagen-binding protein	No

Abbreviations: IE, infective endocarditis; MSCRAMM, microbial surface components recognizing adhesive matrix molecules.

IE are clumping factor A and fibronectin-binding protein A and B (15,16). *S. aureus* surface proteins G and H appear to to be highly associated with the the organism's potential for tissue invasion (11).

In addition, *S. aureus* may attach to a prosthetic device by means of its production of a biofilm (17). This extracellular matrix probably is less significant for infection of medical devices by coagulase-positive staphylococci than for CoNS.

At any given time, 10% to 40% of healthy adults are nasal carriers of *S. aureus* (18). From the nares, microorganisms spread to the skin (19). A minor cut, an abrasion, injury to the mucosa or intravascular line placement can serve as an entry point to the vascular system for *S. aureus*. Once the dermal or mucosal barriers are breached, the staphylococci must avoid or overcome the host's defenses. These constitute the second class of virulence factors (Table 2). The pathogen has at its disposal many resources to do so. At the early stages of tissue invasion, the patient's primary defense is the polymorphonuclear leukocyte (PMNL). These cells are summoned to the point of infection by a complex series of events (chemotaxis) (20). Concurrently, the pathogens are opsonized in order to prepare them for phagocytosis by the PMNLs. The process of opsonization involves primarily activated C3 of the classic pathway of complement and immunoglobulin (Ig) G. Occasionally, the alternative pathway and antibodies directly reacting against the peptidoglycan component of the cell wall are involved. The polysaccharide capsule of *S. aureus* interferes with opsonization to a variable degree per given isolate. Antibodies against the *O*-acetyl group of the polysaccharide component are the primary means of opsonizing encapsulated *S. aureus* (21). Paradoxically, Baddour et al. documented that unencapsulated strains were more efficient in producing IE in an experimental model (22).

The other principal means by which *S. aureus* evades opsonization is by its expression of protein A, which takes place primarily during the exponential growth

TABLE 2 Host Defense Evasion Virulence Factors of *Staphylococcus aureus*

Factor	Demonstrated pathogenic role in IE
Protein A	Yes
Lipase	?
V8 protease	?
FAME[a]	?
Leukocidins	No
Antibiotic resistance	Yes

[a]See text.
Abbreviations: FAME, fatty acid-metabolizing enzyme; IE, infective endocarditis.

of the organism. The role of this protein appears to be more important in the beginning stages of infection when there are low concentrations of organisms. By its ability to bind with the the Fc portion of IgG, protein A interferes with successful phagocytosis of the pathogen in three ways. Extracellular protein A may bind with the Fc end of IgG. The resulting aggregates consume complement that is required for phagocytosis. Extracellular protein A also may attach to the Fc portion of antistaphylococcal antibodies that are already attached to the bacteria. This blocks the Fc receptor of the PMNLs. Protein A that remains bound to the staphylococcus may attach to the Fc portion of any IgG molecule, and hence functionally inactivates them (23).

Complement appears to be the most important component of opsonization. There is an increase in staphylococcal infections of all types in individuals deficient in complement. However, there is probably no such extra risk for those with a significant decrease in their immunoglobulins (24,25). It is challenging to separate the intrinsic risk of gammaglobulin deficiencies from the exposure to staphylococci in the nosocomial environment.

Defects in cellular immunity do not appear by themselves to increase the rate of staphylococcal infection. The actual rate of staphylococcal infections in patients with T-cell deficiencies depends on the particular situation. In AIDS patients, *S. aureus* infections probably occur significantly more often than in comparable individuals without AIDS. This augmented rate probably reflects the multiple immunodeficiency components of HIV infection. These include an increased rate of nasopharyngeal colonization and complicating bacteremia with *S. aureus* (26); the frequency of eczema that makes this population susceptible to bloodstream invasion by *S. aureus* (27); the common usage of intravascular lines; and the increased incidence of both neutropenia and decreased phagocytosis in AIDS patients (28) (Chapter 11).

Five percent of *S. aureus* remain viable for at least 30 minutes within normally functioning PMNLs. A few bacteria completely escape intracellular killing. This seems to be strain dependent, and may be associated with a particular coagulase genotype (29). Additionally, strains of *S. aureus* may differ in their susceptibility to being killed by the intracellular oxidants of PMNLs. It is possible that the isolates exposed to sublethal concentrations of H_2O_2 may develop tolerance to this important molecule (30). In comparison, 100% of CoNS are killed within minutes after being phagocytized. Circulating white cells lower the concentration of *S. aureus* that has been injected into the bloodstream of experimental animals, by more than a 1000-fold within 20 minutes. However, the small percentage of staphylococci, which resist intracellular killing, can be released back into the bloodstream upon the death of the PMNL. Their intracellular survival sustains the initial bacteremia and increases the risk of developing IE. The greater the numbers of *S. aureus* in the bloodstream, the greater the chance of developing a sustained bacteremia (31).

Other staphylococcal compounds that interfere with the host's defenses include gamma toxin and Panton–Valentine leukocidin. These are synergistically toxic for PMNLs, macrophages, and monocytes. They probably play little, if any role, in the development of IE (32) that are associated with a type of catastrophic, necrotizing pneumonia in children and young adults. Lipase and fatty acid metabolizing enzyme (FAME) are able to break down the host's fatty acids that can damage the staphylococcal membrane by their surfactant action (33).

S. aureus produces several extracellular proteases. The most studied of these is the serine protease, V8 protease. This substance can inactivate IgG and the neutrophilic antimicrobial peptides (defensins) and platelet microbicidal proteins (8).

The resistance of *S. aureus* to a growing list of antibiotics has to be considered an essential part of its ability to escape the host defenses. A dramatically increasing therapeutic challenge is the proliferation of methicillin-resistant *S. aureus* (MRSA) infections, acquired both in the community and in healthcare facilities (34). A recent meta-analysis indicates that the mortality associated with MRSA IE was significantly greater than that associated with methicillin-sensitive *S. aureus* (35).

A particular isolate of *S. aureus* may exhibit intolerance to a number of antibiotics. When an organism expresses tolerance, it requires much higher concentration of the antibiotic to kill rather than suppressing its growth. The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of penicillin cephalosporin for nontolerance strain are essentially the same, whereas in the intolerance ones, the MBC may be 128 times higher than the MIC. The clinical importance of tolerance still has not been clarified (Chapter 14) (36).

In addition to the loss of dermal and mucosal integrity, other common sources of staphylococcal bacteremia include prostatitis and pneumonia. In these latter situations, the organism usually enters the vascular space by way of lymphatics that drain into the small venules (37,38). *S. aureus* infects the endothelium of the microcirculation (endotheliosis) in a manner similar to that by which *S. aureus* infects normal endocardial cells. Fibronectin both anchors *S. aureus* to the venular endothelium and promotes bacterial aggregation. Clumps of *S. aureus* are then ingested by the endothelial cells. When the capacity of these endothelial cells is reached, a prolonged bacteremia can occur (Chapter 5) (39).

For a bacteremia to develop into IE, it is essential that the circulating pathogens be able to affix to the intact endothelial cell or to the platelet/fibrin thrombus (40). This process is facilitated by the same adhesions, MSCRAMMs, as described earlier (8,11). The complete description of the way *S. aureus* produces IE in both previously normal endocardium and have normal endocardium is described in detail in a later chapter (Chapter 5).

Once *S. aureus* has attached itself to the valve, it must survive long enough to reach the point where it is capable of successfully invading the tissue. It appears that the growth of the platelet fibrin thrombus is vital. On reaching maturity, this complex serves to protect the invading organisms from host defense mechanisms and antibiotic effect. Production of tissue factor (TF) and the aggregation of platelets are key to this. Tissue factor is a membrane glycoprotein which when combined with activated factor VII activates factor X. This latter factor converts prothrombin to thrombin which eventually leads to the production of fibrin. *S. aureus* can induce TF activity (TFA) from a variety of cells. Monocytes are its chief target in early vegetation formation. Eventually, the endothelial cell becomes the chief producer of *S. aureus*-induced TFA (41) and a variety of cytokines. These componds promote both coagulation and local inflammation, thus allowing the fibrin/platelet thrombus to grow.

The platelet has a dual role in the pathogenesis of IE. The ability of *S. aureus* to directly aggregate platelets by utilizing fibrinogen as a bridging molecule is essential to the infectivity of the organism in the immature thrombus (42). Strains of *S. aureus* that lack this ability are up to 100 times less infective than those that possess it. The platelet also may play a role in the defense of the host. Once they are exposed to thrombin, they release a variety of platelet microbicidal proteins (PMPs) that reside in the alpha granules of the intact platelet (43). The PMPs appear to break down the bacterial cell wall, and may work synergistically with certain antibiotics.

TABLE 3 Tissue Invasion Virulence Factors of *Staphylococcus aureus*

Factor	Demonstrated pathogenic role in infective endocarditis
Alpha toxin	Yes
Beta hemolysin	?
Hyaluronidase	?
Metalloprotease	?
Stimulation of tissue factor activity	Yes
Platelet aggregation effect	Yes

When the staphylococci are adequately sheltered by the growing vegetation, they may then start producing the third type of virulence factors (Table 3). Chief among these cytotoxic agents are the hemolysins (43). Although they may injure the membrane of many types of cells, their clinical importance in IE has not been established. The role of other enzymes, such as hyaluronidase and the metalloproteases is even less understood (44).

Persistence of *S. aureus* within the endocardial vegetation may be attributed to small-colony variants (SCV) (45). These isolates have a slower growth rate with lessened hemolytic and coagulase activity that is caused by a decrease in bacterial ATP (46). The SCV of *S. aureus* also produce less alpha toxin. This downregulation promotes the organism's survival within the host cells. Presumably, reversion of the SCV phenotype would be a mechanism for relapsing infection. This topic is further discussed in relationship to CoNS (see later).

Coagulase-Negative Staphylococci

Over the last 25 years, CoNS have become an increasingly prominent cause of IE. Formerly, only about 5% of all types of valvular infection were attributed to CoNS. In the past, only 6% of blood cultures, positive for CoNS, were considered to represent true infection. No longer can we assume that the presence of CoNS in a blood culture signifies contamination. Currently 6.6% of cases of native valve endocarditis (NVE) are produced by this group (47). Coagulase-negative staphylococci are also the most frequent cause of prosthetic valve endocarditis (PVE) occurring within one year of valve implantation (48). It is also the most commonly found organism in healthcare-associated bloodstream infections (HCBSI) (49). This change in the profile of CoNS infections is understandable in the light of the increased use of intravascular catheters. Fifty percent of hospitalized patients receive some type of intravascular catheter (50). Up to 18% of these devices are associated with a primary BSI and 31% with CoNS (51).

There are at least 15 species of CoNS that are part of the resident flora of humans. Fifty to seventy percent of these belong to the *Staphylococcus epidermidis* group (*Staphylococcus epidermidis*, *Staphylococcus hemolyticus*, *Staphylococcus hominis*, and *Staphylococcus capitis*) (52,53). As compared with particular areas of skin and mucus membranes inhibited by other species of CoNS, *S. epidermidis* is widely distributed throughout the body. Because of this, it is important to identify particular strains of *S. epidermidis* both in order to verify the presence of a true bacteremia and to rule out common sources of nosocomial transmission. Several commercial kits are available to identify subspecies. Biotyping system and the use of antibiogram of an isolate is the most commonly employed approach to accurately characterize an organism retrieved in blood culture (54).

However, it appears that the predominant role played by *S. epidermidis* goes beyond its dominance of the flora of the human skin. This species appears to have intrinsic pathogenic mechanisms. In an experimental model, IE was produced in all animals infected with *S. epidermidis*, but only in 12.5% of those given *S. hominis* (55). Coagulase-negative staphylococci possess several virulence factors that are analogous to those of *S. aureus*. They often show variation in their colony morphology. This has been described in cases of both NVE and PVE (56). These observations have given rise to the possibility that this phenotypic variation may contribute to the pathogenesis of CoNS infections (57). The small cell variation (SCV) of *S. epidermidis* were found within the endothelial cells of rats after the establishment of experimental IE. However, the small colony type is less able to initiate infection than the usual type. The significance of these findings is not clearly known. Extrapolating from the situation of the SCV of *S. aureus*, one can speculate that this is a type of survival mechanism. The phenotypic conversion permits the organism to enter and persist within the endothelial cell. There they are safe from phagocytosis by PMNLs (58). Most SCV have defects in hemin or menaquinone synthesis (59) that are attributed to a disrupted electron transport chain. Downregulation of the electron transport system leads to overall decreased metabolic activity.

The primary virulence factor of CoNS is its distinctive ability to attach and adhere to a variety of prosthetic materials, and then use the medical device as a part of a multifactorial shield against the defenses of the host and most antibiotics (60).

The infection of prosthetic material by CoNS is a two-step process. The first phase is an initial rapid attachment, brought about by electrostatic forces (61) and a capsular polysaccharide adhesion, PS/A (62). Some CoNS isolates possess a fibrinogen-binding protein (Fbe) that promotes the adherence of the organism in a manner similar to that of *S. aureus* (63). Fbe may explain in part the ability of some CoNS to infect native valve tissue. The second step is intercellular adhesion of the individual CoNS bacteria to one another. This is the result of several cellular antigens. Probably, the most important of these is polysaccharide intercellular adhesion (PIA) factor. It is a very complex *N*-acetyl glucosaminoglycan polysaccharide that imbeds the bacterial cells in a thick matrix of slime (biofilm) (64). It appears that PIA and PS/A share many similar antigenic components, and may be identical (65). Norepinephrine and certain types of antibiotics (suprainhibitory levels of vancomycin) increase the production of slime. Subinhibitory concentrations of vancomycin and cefazolin decrease its formation (66). In general, slime producing CoNS have a higher MBC to most antibiotics than nonslime-producing examples. The MIC is not affected.

Biofilm formation is the major virulence factor of CoNS, because it both enables the infection of prosthetic material and protects the bacteria from the host's defenses and many types of antibiotics. Slime interferes with the migration of PMNLs, opsonization, and T-cell activation (67). Isolates of CoNS, which are imbedded in the biofilm, are more resistant to antibiotic action than the same strain tested outside this envelope (68). This resistance is not intrinsic but reflects the fact that bacteria in slime multiply much more slowly (69). This decreased reproduction rate reflects the cellular adherence phenomena and not deficiencies of nutrition.

Within the biofilm, CoNS downregulates genes that control the production of adhesion factors and aerobic metabolism (70). Poly-D,L-glutamic acid (PGA) is secreted by CoNS. It aids in the resistance of the bacteria at high salt concentrations (71). Currently, it appears that PGA is an extremely important part of the infectious process. Conversely, CoNS upregulates genes that control osmoprotection and an

antibiotic resistance determinant (Drp 35). This upregulation process may indicate that the bacteria perceive the slime cocoon as hostile.

Hemagglutinins of CoNS may play a role in infecting prosthetic material in humans (72). DNAse, fibrinolysins, hemolysins, and proteases have been named as potential virulence factors of CoNS (73). Eighty percent of CoNS, which are retrieved from nosocomial infections, are resistant to the beta-lactam antibiotics (74). Their methicillin-resistant gene (mecA) is the same as that found in *S. aureus*. Because of the high rate of heterotypy among CoNS, methicillin resistance was not clinically evident until the patient was given antibiotics either for therapeutic or prophylactic reasons (75). More than 50% of these isolates are resistant to multiple antibiotics, including macrolides, trimethoprim/sulfamethoxazole, and gentamicin. This may well be attributed to the high rate of resistance plasmids among CoNS. Studies that show that the carriage of these plasmids by the hands of nurses gave rise to the spread of multiple antibiotic resistance in a cardiac thoracic intensive care unit (76).

It would be appropriate now to discuss *Staphylococcus lugdunensis*, as it produces an extremely aggressive type of IE, similar to that of *S. aureus*. It has only been recently identified as a cause of human IE (77,78). However, this figure may be a significant underestimation. A recent study, both a prospective and retrospective review of the world's literature, profiled 69 cases of *S. lugdunensis* IE. This organism is capable of producing infection of native (77%) and prosthetic valves (13%) along with pacemaker IE (10%). The mitral valve is the most commonly infected native valve. Prosthetic valve endocarditis primarily involves the aortic valve. Both types are associated with a high rate of abscess formation, embolization, and heart failure. Pacemaker IE has a better prognosis with a death rate of 25%. Mortality was 42% in the former type and 78% in PVE. Surgery was performed in >2% of cases. Because they are coagulase negative, they may be erroneously identified as a species of CoNS in a clinical laboratory using routine commercial identification approaches (79). Many cases of CoNS NVE might have been caused by this organism. Their yellow pigmentation and alpha hemolysis may cause the isolates to be classified as *S. aureus*. As compared with other CoNS, they usually are sensitive to all of the beta-lactam antibiotics. No definitive virulence factors have been yet identified.

THE STREPTOCOCCI

Streptococci are gram-positive cocci that arrange themselves in pairs or in chains. They are frequent colonies of the respiratory, gastrointestinal (GI), and genitourinary tracts. Most are facultative anaerobes and all are catalase negative. The genus Streptococcus is composed of streptococci and enterococci. Members of this genus can be identified by the type of hemolysis that they produce; by their antigenic and serologic properties; by biochemical tests; and by molecular testing (80). The nomenclature of the subdivisions of streptococci has become extremely confusing as the classic well-known classification systems do not necessarily correspond to those that are based on genetic taxonomic techniques. Because the older terminology is a well-established one, it will be used when appropriate, and the newer term placed in parentheses.

Streptococcus viridans

Currently, the members of the viridans group of the streptococci group are responsible for less than 25% of cases of IE as compared with >75% before the availability

TABLE 4 Clinically Important Viridans Streptococci Groups

Streptococcus mitis group
S. mitis
Streptococcus sanguis (biotypes 1, 2, 3)
Streptococcus mutans group
S. mutans
Streptococcus salivarius group
S. salvarius
Streptococcus bovis group
Streptococcus anginosus group (also known as *Streptococcus milleri* group)
S. anginosus
Streptococcus intermedius
Streptococcus constellatus

of antibiotics (81,82). *Streptococcus viridans* remains the most common cause of mitral valve prolapse associated IE (83). The term viridans (Latin, for green) was applied to the original recognized members of this group because of their characteristic alpha hemolysis (green hemolysis) on blood agar. Many, however, are gamma hemolytic (nonhemolytic). Their cell walls are composed of peptidoglycans, teichoic acids, and lipoteichoic acids. As compared with the pyogenic streptococci (groups A, B, C, and G), there is no relationship between their particular Lancefield serogroup and the pattern of biochemical reactions used to classify them. Currently, we focus not on an in-depth discussion of the biochemical and enzymatic assays used to identify the various types of *S. viridans*, but present their most clinically relevant properties (Table 4).

In the current classification of viridans streptococci, *Streptococcus mitior* has been classified as a subtype of *Streptococcus mitis* (84). Streptococcus morbillorum is now classified as Gemella morbillorium. Long considered as part of the *S. mitis* group, nutritionally variant streptococci have been reclassified as Abiotrophia (85). The species of viridans streptococci most commonly involved in IE are *Streptococcus sanguis*, *Streptococcus mutans*, and *Streptococcus mitior/mitis* (86). There has been an increasing involvement of microaerophilic streptococci in IE. Most prominent of these is *S. mutans*. It is quite fastidious and difficult to grow from the blood. Sixty-six percent of *S. mutans* hydrolyze bile-esculin XL, which could be confused with enterococci.

Viridans streptococci are part of the normal microflora of the mouth, upper respiratory tract, and upper intestinal tract. *Streptococcus mitior/mitis*, *S. sanguis*, *Streptococcus milleri*, *Streptococcus salivarius*, and *S. mutans* constitute up to 60% of the microflora of the mouth. *S. mutans*, *S. mitis*, and *S. sanguis* (formerly known as Streptococcus SBE) reside most commonly on the surface of the teeth. *S. mitis* is also found in the oropharynx. *Streptococcus salivarius* resides on the tongue, pharynx, and hard palate (87). This propensity to adhere to dental enamel provides insight into how these bacteria produce IE.

Most viridans streptococci lack classical virulence factors. They, as a rule, do not produce toxins, hemolysins, or cytotoxins. As we shall discuss, it is their ability to adhere, to infect, and to promote the growth of the fibrin/platelet thrombus, which makes the viridans streptococci the classic organism of subacute IE. Unlike the situation with *S. aureus*, this group requires a preformed fibrin/platelet thrombus that is the result of previously damaged endothelial cell production of extracellular matrix proteins that trigger its formation. From this point on, the process is very

similar to that of vegetation formation by *S. aureus* (15,88). The production of extracellular dextran (glucan) is positively associated with both attachment of the bacteria to the dental enamel and to the fibrin platelet thrombus. Those strains that adhere best to dental enamel have the highest rate of IE complicating bacteremia. *Streptococcus sanguis* I and II produce 16.4% of streptococcal IE. In an experimental model, dextran production has been shown to shield viridans streptococci from the effects of penicillin (89). The production of dextran is not an absolute requirement for the development of endocarditis. However, nondextran-producing *S. mitior* (*mitis*) also are involved significantly in subacute IE, whereas 7.3% of all cases of IE was produced by dextran-producing *S. mitior* (*mitis*). These figures represent data collected in the 1970s. Clearly because of the decrease in subacute IE and the rise in acute disease, the percentage of all cases of IE caused by *S. mitior* would be less (86). More recent data indicates that dextran production is found in equal frequency in the isolates of *S. viridans* that were obtained from the oral cavities of individuals with and without IE (90).

Fibronectin is produced by the endothelium, fibroblasts, and platelets in response to vascular injuries. Although fibronectin constitutes a small percentage of the platelet/fibrin thrombus, the IE-associated strains of *S. viridans* bind more avidly to this substance than do those not so involved in valvular infections (91,92).

Fim A and homologous adhesions enable viridans streptococci to adhere to fibrin and the extracellular matrix. Platelet adhesions of *S. sanguis* appear to promote the growth of the infected vegetation (93). The binding of these streptococci to fibronectin and other extracellular matrix components is probably quite heterogeneous involving multiple adhesion components (94).

Table 5 presents the MSCRAMMs of the viridans streptococci for which there is significant experimental evidence supporting their role in the pathogenesis of IE. In short, there are strains of viridans streptococci that are associated with IE and others that are not. This division of pathogenic potential occurs for a variety of reasons, many probably not yet defined.

There is evidence that certain types of *S. viridans* can invade and kill endothelial cells. *Streptococcus gordonii* were demonstrated to be cytotoxic to monolayers of human umbilical vein endothelial cells. Several surface proteins were vital for cellular invasion. Death of the endothelial cells was felt to be to the result of peroxidogenesis by the streptococcus (95). The relevance of this endotheliosis to clinical IE is yet to be determined.

The *Streptococcus anginosus* group, formerly known as the *S. milleri* group, is composed of three species—*S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus* (96). They have varying abilities to produce IE. *Streptococcus anginosus* isolates do so frequently; *S. intermedius* the least (97). They are microaerophilic with

TABLE 5 Streptococcal MSCRAMMs–Ligand Systems Relative to the Pathogenesis of Infective Endocarditis

MSCRAMM	Ligand
Dextrans of *Streptococcus sanguis* and *Streptococcus mutans*	Fibrin/platelet thrombus
Tn917 of *S. sanguis*	Fibronectin
Extracellular matrix molecules	Fim A proteins
Phase I, II of *S. sanguis*	Platelets

Abbreviation: MSCRAMM, microbial surface components recognizing adhesive matrix molecule.