THE YALE JOURNAL OF BIOLOGY AND MEDICINE 50 (1977)

The "Incubation Period" of Subacute Bacterial Endocarditis

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Received July 30, 1976

In an attempt to gain information about the "incubation period" of subacute bacterial endocarditis, the literature was searched for case reports stating a specific interval between an event likely to cause bacteremia and the onset of symptoms. In 76 cases of streptococcal endocarditis for which this information was given, the median "incubation period" was one week. Symptoms began within two weeks in 64 of these cases (84%). Although there may be a bias toward reporting short incubation periods, it is concluded that the incubation period of subacute bacterial endocarditis is often shorter than is generally realized, and that procedures carried out more than two weeks before onset of symptoms are less likely to be causally related. In post-cardiotomy cases, where timing of the bacteremia causing endocarditis is less easy to define, 27% of 122 cases of staphylococcal endocarditis developed within two weeks of surgery. This information is relevant to the planning and evaluation of prophylactic chemotherapy against bacterial endocarditis.

INTRODUCTION

Considerable attention has been focused on the duration of symptoms of subacute bacterial endocarditis (SBE), but no systematic attempt has been made to determine the incubation period for this infection. By "incubation period" we refer to the time interval between the bacteremia which initiates SBE and onset of the first symptoms. If the limits of this period were better defined, clinicians could more readily identify sources of infection and evaluate the efficacy of prophylaxis.

In taking a history from patients with SBE, physicians traditionally inquire about dental work or other procedures done at any time during the preceding six months, or even during the preceding year. Cates and Christie, in their definitive report of 442 cases [1], accepted dental work done within three months of onset of symptoms as a precipitating factor. Dental extractions carried out eight or more weeks before symptoms began have been held responsible for SBE in several case reports [2–5]. Harvey suggested that the relationship between dental work and SBE was often overlooked because "the duration between dental procedures and onset of symptoms of bacterial endocarditis generally varies from weeks to months" [6]. A recently reported incubation period of three days [7] was held by another author to be "incredibly short" [8], and a subsequent editorial concurred in that opinion [9].

This widespread impression that the incubation period of SBE is prolonged has probably arisen because early symptoms are nonspecific, and diagnosis may be delayed for weeks or months. As a result, the incubation period may be confused with duration of symptoms before diagnosis, and the incubation period may appear falsely prolonged.

To determine the usual duration of the incubation period of SBE, we have surveyed the literature for case reports in which the interval between a procedure causing bacteremia and the initial symptoms is clearly stated. The major emphasis in our discussion will be on SBE, but some reference will be made also to post-cardiotomy endocarditis (PCE).

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STREPTOCOCCAL ENDOCARDITIS

Selection of Cases

In order to deal with the most representative and homogeneous group of cases possible, we have focused on streptococcal endocarditis. Although the spectrum of infecting organisms has changed over the years [10], the majority of subacute cases is still due to that group of bacteria [11,12].

An attempt was made to collect all case reports of streptococcal endocarditis which stated a definite interval between the supposed entry of bacteria and the onset of symptoms. The search was started in the bibliographies of recent papers and then expanded to older literature. Over 250 articles published between 1908 and 1975 were examined.

Most case reports did not provide useful information about the incubation period. In well over half, no portal of entry was identified. Often a procedure that could have caused bacteremia was mentioned, but no interval to onset of symptoms of SBE was given. When a relatively chronic condition such as an abscessed tooth was implicated by the authors, the starting point of the incubation period could not be determined accurately enough for our purposes. Cases were excluded if the interval was described in vague terms, or if the authors did not distinguish clearly between the time when symptoms began and the time of diagnosis. For example, cases in which symptoms "followed" a dental extraction were rejected. However, we accepted six cases in which the onset of symptoms was described as "immediate" or "within a few days." These cases were assigned an interval of one week for the purpose of inclusion in Fig. 1. To avoid bias in the direction of short incubation periods, three cases in which the interval was given as "about a week" were grouped with cases having an incubation period of one to two weeks. Cases were eliminated if any symptoms consistent with SBE were mentioned as being present before the procedure.

Results

Seventy-six cases of streptococcal endocarditis were found in which the incubation period was stated clearly enough to meet our criteria. These cases were drawn from a total of 43 articles [2,3,5–7,13–50]. The streptococci cultured from these patients were variously identified as viridans streptococci (38 cases), alpha-hemolytic (5 cases), non-hemolytic (9 cases), gamma-hemolytic (1 case), non-hemolytic anaerobic (1 case), hemolytic (1 case), "streptococci" (3 cases), *Streptococcus mitis* (1 case), and *Streptococcus mutans* (1 case). Sixteen cases were due to enterococci.

Underlying cardiac abnormalities and initial symptoms were tabulated and analyzed. As these were typical of SBE in both respects, the information is not reported in detail here.

The incubation periods of the 76 cases are listed in Table 1, with intervals quoted exactly as stated in each reference. For 60 non-enterococcal cases, the median incubation period was one week. Symptoms began within two weeks of a dental or other procedure in 51 of these cases (85%). The incubation period of enterococcal endocarditis was equally short. Symptoms began within two weeks in 13 of 16 cases (81%), and the median time of onset was five days.

Fig. 1 displays the distribution of incubation periods by weekly intervals. It is clear that a short incubation period was not at all uncommon; indeed, it appeared to be the rule rather than the exception. An incubation period longer than one month was notably rare.

For 37 of the 60 non-enterococcal cases, two intervals were reported: from initial

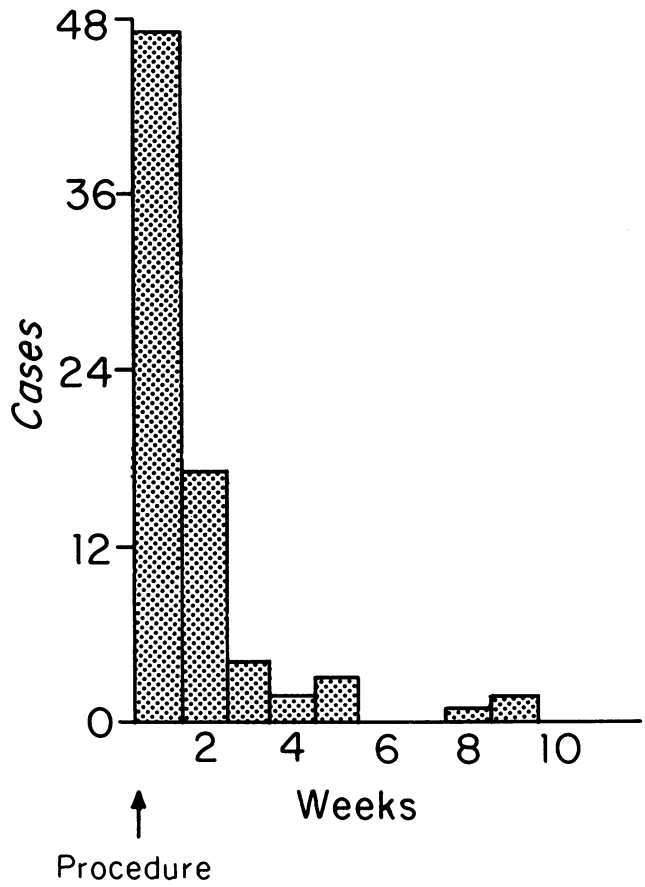

FIG. 1. Time to onset of symptoms for 76 cases of streptococcal SBE which followed procedures associated with bacteremia.

procedure to onset of symptoms (incubation period), and from initial procedure to diagnosis by positive blood culture. These intervals are compared in Fig. 2. The median incubation period was ten days, while the median time to diagnosis was six weeks. By two weeks 78% of patients had symptoms, but a correct diagnosis had been made in only 16%. Thus although symptoms began early, these cases generally followed a subacute course, and diagnosis was delayed.

Comment

In contrast to a common impression that the incubation period of SBE is usually prolonged, the data collected here show that most reported incubation periods are short. We recognize that any interpretation of data from retrospective case reports must be subject to important reservations. When a procedure known to induce bacteremia is followed promptly by symptoms of SBE, it is reasonable to infer that the procedure caused the disease, but one cannot *prove* the association in a given instance. In some cases, the infection could conceivably have been present but asymptomatic before the procedure; in others, a random bacteremia occurring afterwards may have initiated the infection. When the interval between a dental procedure and symptoms is short, the association is more likely to excite the attention of both patient and doctor. Thus there may be a bias in favor of reporting short incubation periods rather than long ones. When the interval between procedure

TABLE 1
Incubation Periods in 76 Case Reports of Streptococcal SBE

Non-enterococcal streptococcal SBE			Enterococcal SBE		
No. of Cases	Interval to symptoms	Reference	No. of Cases	Interval to symptoms	Reference
1	2 hours	13	1	less than a day	41
1	3 hours	14	1	1 day	38
1	on return home	15	4	2 days	41–44
	(from dentist)		1	3 days	44
1	followed directly	16	2	5 days	45, 46
3	immediately	2, 15, 17	1	7 days	41
1	12 hours	18	2	one week	44, 47
1	same day	19	1	2 weeks	48
1	following afternoon	2	1	3–4 weeks	49
1	the day after	20	1	less than a month	50
1	the following day	17	1	2 months	3
1	2 days	21			
3	3 days	7, 22, 23	16		
1	4 days	24			
2	5 days	25, 26			
1	6 days	27			
6	within 7 days	28			
2	a few days	15, 16			
1	less than a week	29			
6	one week	2, 6, 16, 30, 31			
3	about a week	32–34			
2	10 days	17, 21			
1	11 days	35			
3	less than 2 weeks	36–38			
7	2 weeks	2, 16, 17, 21, 26, 30, 39			
1	20 days	40			
3	3 weeks	2, 21			
1	4 weeks	2			
1	1 month	6			
1	4–5 weeks	24			
1	8 weeks	2			
1	2 months	5			
60					

and symptoms is long, coincidence becomes more likely, because dental treatment is so common. If diagnosis is long delayed, patients may not recall when the first symptoms began, or may have forgotten them entirely. Although the validity of any retrospective study may be questioned, these data provide the only means presently available of defining the incubation period. We believe that sufficient evidence has been gathered here to demonstrate that for SBE a short incubation period is common.

Information on the pathogenesis of SBE provides little basis for postulating a long interval between the initial bacteremia and onset of symptoms. Bacteremia following dental extraction is short-lived. Circulating organisms are cleared rapidly from the bloodstream by the reticuloendothelial system; in most cases this process is complete within one hour [51], so that there is no likelihood of delayed infection of the endocardium. Bacteria entering the circulation via any portal pass through the heart within seconds, allowing the possibility of immediate endocardial infection. This has been demonstrated experimentally: when streptococci are injected intravenously into

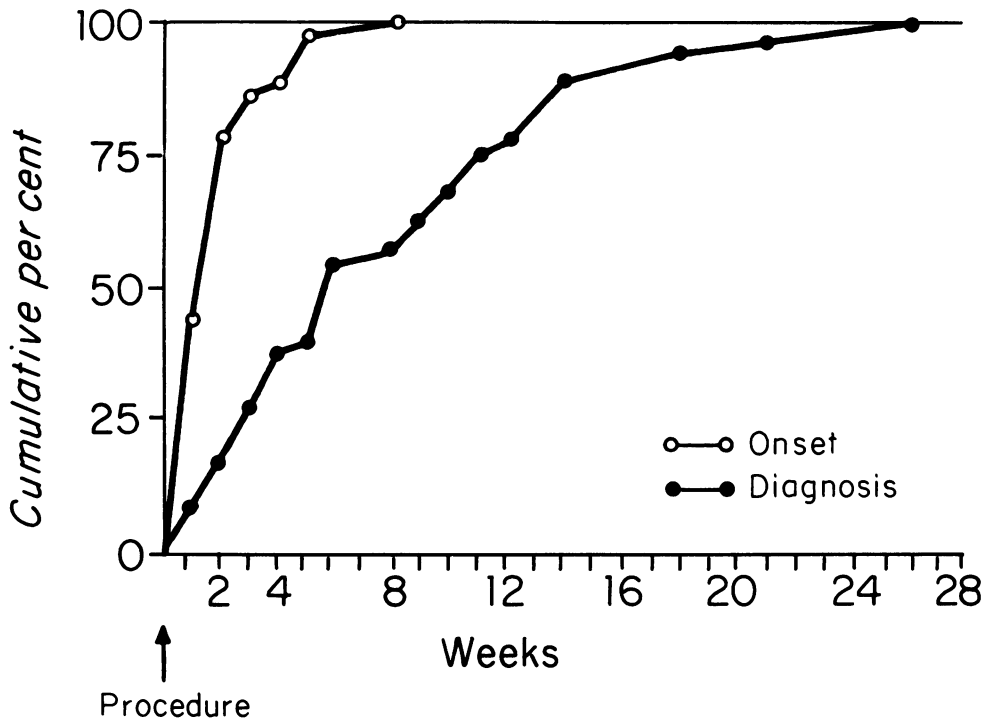

FIG. 2. Comparison between time to onset of symptoms and time to diagnosis in 37 cases of streptococcal SBE which followed procedures associated with bacteremia.

rabbits with valvular damage due to intra-cardiac catheters, organisms can be recovered from the site of valvular damage within minutes. These organisms enter a phase of exponential growth after a latent period of only one to two hours, and the population reaches about 10^9 per gram of vegetation within 24 hours [52]. It seems reasonable that the same sequence of events occurs in persons with pre-existing valvular disease.

Delay in Diagnosis

The median time to diagnosis lagged behind onset of symptoms by about five weeks in these cases (Fig. 2), as is usual in cases of subacute disease [11]. Contributing factors presumably include the mild and non-specific nature of early manifestations, which are often attributed to viral illness. Patients may be slow to seek medical advice for such minor symptoms, and physicians in turn may not consider the correct diagnosis until symptoms have persisted for weeks or months. In addition, indiscriminate use of antibiotics for "upper respiratory infections" can temporarily alleviate symptoms of SBE and render blood cultures negative, thus further delaying diagnosis.

Sources of Infection

This study indicates that reported incubation periods are generally less than two weeks. If it is realized that procedures associated with bacteremias carried out more than two or three weeks before onset of symptoms are unlikely to be causally related to SBE, it may be possible to identify sources of infection more accurately. The presumed sources of bacteremia for the 76 cases in the present series are listed in Table 2. Fifty-five (92%) of the 60 non-enterococcal cases and four of the 16 enterococcal cases followed dental work. Eleven enterococcal cases (69%) were

TABLE 2
Portals of Entry in the Present Series of 76 Cases of Streptococcal SBE

	Non-enterococcal streptococcal SBE	Enterococcal SBE
Dental extraction	43	2
Dental cleaning and/or filling; unspecified dental procedures	12	2
Tonsillectomy	3	—
Septic abortion; curettage; delivery	1	3
Prostatectomy or other urologic procedure	—	8
Hemorrhoidectomy	—	1
Cardiac catheteriaation	1	—
TOTAL	60	16

attributed to genito-urinary procedures. Although these cases confirm that SBE can result from dental operations, it should be emphasized that this is actually a rare complication [16,53]. Dental operations account for nearly all the 60 non-enterococcal cases in this series only because such procedures provide a precise starting point for the incubation period. However, in a combined series of 1,164 cases [1,17,20,21,33,54–57;Table 3] extractions were considered responsible for only 144 (12.4%). In many of these cases, a causal relation is doubtful because no sensible limit was set on the incubation period. Thus, only a small proportion of all cases of SBE is caused by dental operations.

In the combined series of 1,164 cases, an oral source other than dental extraction was listed for 172 (14.7%, Table 3). Abscesses, "dental sepsis," and pyorrhea were thought to provide an on-going source of infection in some instances, while tonsillectomy was implicated in others. In an additional 130 cases (11.2%) such procedures as prostatic and rectal surgery, abortion, delivery, and catheterizations provided a portal of entry for bacteria. Bronchitis and upper respiratory infections were considered responsible for many cases of SBE in the older literature [20,58], but these authors and others also noted that symptoms of "respiratory infection" may be the first manifestations of SBE [16,59,60]. It now seems unlikely that upper respiratory infections, which are usually caused by viruses, are related to SBE.

In the majority of cases (61.7%) no source of bacteremia was identified (Table 3). Therefore, many cases must arise when bacteria enter the blood through insignificant breaches in mucosa, or penetrate an apparently intact mucosal barrier. Everyday activities such as chewing hard candy or brushing the teeth can cause bacteremia [61]. Consequently, the source of bacteremia will often remain unknown, even after a diligent search.

Prophylaxis

Since dental, urologic or gynecologic procedures can lead to SBE, such procedures are often "covered" by antibiotics when performed on patients thought to be at risk, even though there is still no clinical evidence that prophylaxis is actually effective [62]. The present study leads us to suggest that if endocarditis is causally related to a procedure, the first manifestations will usually occur within two weeks. Therefore patients should be closely observed during this period, and should also be alerted to

TABLE 3
Portals of Entry in Combined Series of 1,164 Cases of SBE
(References 1, 17, 20, 21, 33, 54–57)

	No.	%
Dental extraction	144	12.4
Other dental or oral source	172	14.7
All other sources	130	11.2
Unknown	718	61.7
TOTAL	1,164	100.0

report any symptoms compatible with SBE. Those cases in which symptoms begin more than two weeks after cessation of prophylactic antibiotics are more likely to originate from unrelated bacteremias occurring at some time after the procedure, and probably do not represent failed prophylaxis. In 8 of the cases listed in Table 1, endocarditis occurred despite attempted antibiotic prophylaxis [7,23,27–30,35,37]. These may represent true failures of prophylaxis, because the first symptoms began within two weeks in all 8 cases.

POST-CARDIOTOMY ENDOCARDITIS

Infective endocarditis occurs at some time after surgery in some four percent of cases [63]. The organisms may establish themselves in the heart at the time of surgery, or during later bacteremias. By analogy with SBE, it seemed possible that the incubation period of PCE might also be short.

To provide evidence on this question, we reviewed reports of PCE from the literature. In order to make the series as homogenous as possible, the analysis was limited to staphylococcal PCE, but cases due to both *Staphylococcus aureus* and *Staphylococcus epidermidis* were included. Mixed infections due to staphylococci with other organisms were excluded. In all, 230 cases of PCE reported between 1955 and 1975 by 25 authors were examined [64–88]. Among these were 122 cases of staphylococcal PCE for which the interval between surgery and time of onset was given (Fig. 3).

The first evidence of endocarditis was taken as "time of onset." In some cases, this was fever or other manifestation not obviously due to infection at another site. In many instances, it was the time of the first positive blood culture. Cases were also accepted for which the author gave only the date of "onset of PCE" without further details. Therefore for these cases, the distinction between onset of symptoms and time of diagnosis was blurred, and the interval from surgery to onset of PCE cannot be compared directly with the incubation period of SBE as described in the preceding section.

Five cases of coagulase-positive and seven cases of coagulase-negative staphylococcal PCE began within three days after surgery. Twenty-one of the 122 patients (17%) had manifestations of PCE by one week, and 33 (27%) by two weeks. The onset of coagulase-positive staphylococcal PCE was not significantly earlier than onset of coagulase-negative infections (Fig. 3). It is clear that the incubation period for staphylococcal PCE is often short.

Unfortunately, the incubation period remains in doubt in those cases where the first manifestations occurred more than two weeks after surgery. Although most cases (70%) occurred within two months (Fig. 3), the operation itself was not necessarily the source of infection. Procedures carried out during the post-operative

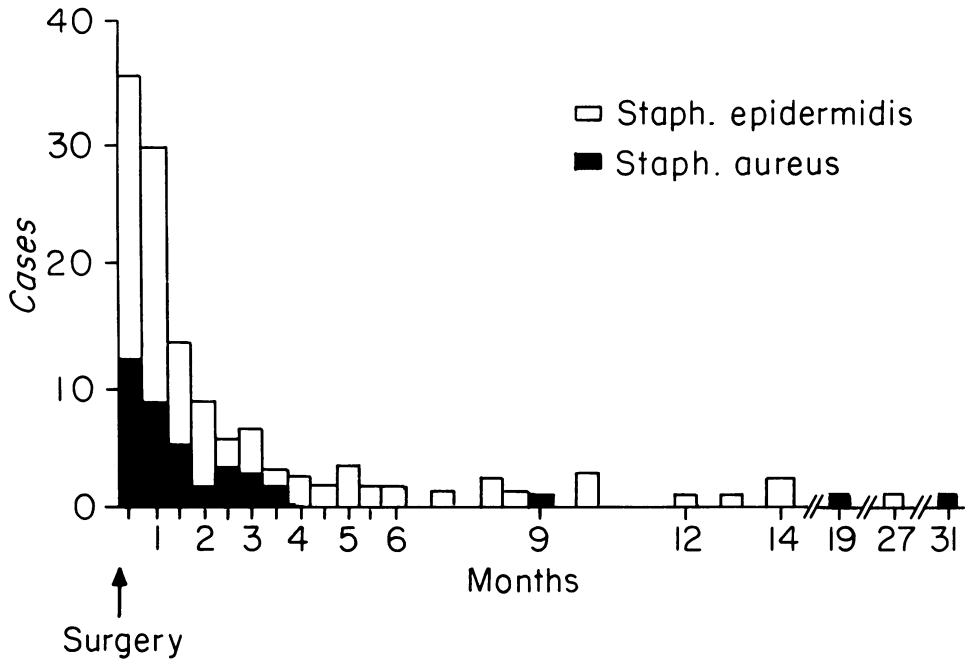

FIG. 3. Interval between surgery and onset of post-cardiotomy endocarditis in 122 cases due to staphylococci.

period may be associated with bacteremia, and the heart may become secondarily infected from the surgical wound, an intravascular catheter, pneumonia, or some other septic focus. Moreover, onset of symptoms may be be delayed by antibiotics, which are employed for prophylaxis or therapy close to the time of surgery in most of these patients. Although no conclusion can be drawn as to the incubation periods of those cases with late onset, the findings are consistent with the hypothesis that the incubation period of PCE, like that of SBE, is often short.

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