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Staphylococcal Endocarditis

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Introduction

Staphylococci are second only to streptococci as a cause of infective endocarditis. In the large series from the Medical Services Study Group reported by Bayliss *et al* in 1983, 19.3 % of 544 cases of endocarditis were caused by staphylococci compared with 63.8 % caused by streptococci. A higher incidence of staphylococcal infection (32.3 %) was found in the 260 cases of endocarditis seen at St Thomas' Hospital in the 20 year period 1968-87. *Staphylococcus aureus* is more common than *S. epidermidis:* it accounted for 60 of 105 cases (57.1 %) of staphylococcal endocarditis in the Medical Services Study Group series, but for 71 of 84 cases (84.5 %) at St Thomas'. It is still nevertheless an uncommon infection, and any individual doctor's experience is likely to be limited, whether clinician or microbiologist.

Our data from nearly 600 cases of *S. aureus* bacteraemia seen from 1970 to 1987 show that in 11 % the infection was endocarditis. It is of interest that whereas endocarditis only accounted for 6 % of hospital-acquired *S. aureus* bacteraemias, for community-acquired bacteraemias, this figure was 26 %. During the same period there were 172 *S. epidermidis* bacteraemias with an 8 % incidence of endocarditis. Endocarditis accounted for only 3 % of hospital-acquired *S. epidermidis* bacteraemias but for all 8 cases of community-acquired bacteraemias.

The diagnosis of staphylococcal endocarditis (as indeed of most bacterial endocarditis) depends on the isolation of the organism from the blood, preferably from more than one set of cultures. Staphylococci can usually be detected in blood cultures within 24 hours, and the bacteraemia is always persistent. In contrast to streptococcal infection, which is characteristically subacute, staphylococcal infection, particularly *S. aureus*, is acute. Furthermore, in staphylococcal endocarditis, heart murmurs are often absent when the bacteraemia is detected thus making the diagnosis more difficult.

Staphylococcal endocarditis is not a homogeneous entity: the pathogenicity of the two species *S. aureus* and *S. epidermidis* differs; *S. aureus* is a virulent aggressive microbe that often infects a previously normal heart valve; it has a predilection prosthetic valves. In contrast, *S. epidermidis* is a rather low grade, albeit persistent, pathogen that most commonly attacks prosthetic valves. It may also infect native valves, usually those that are abnormal or damaged. These different presentations of staphylococcal endocarditis are best considered separately.

S. aureus Endocarditis Involving a Native Valve.

Some two thirds of cases of *S. aureus* endocarditis involve native valves, quite often those that are previously normal. The infection is usually acquired in the community and the ensuing bacteraemia appears to be a "primary" infection, although it must have resulted from a minor skin lesion or from skin carriage of the staphylococcus.

Although *S. aureus* endocarditis is uncommon, it is one of the most dramatic syndromes produced by this organism. Valvular destruction with abscess formation may occur with remarkable rapidity, often within days-sometimes hours- of admission to hospital. Yet when the patient presents, specific signs of endocarditis are invariably absent. There are flu-like symptoms, sometimes with gastrointestinal disturbance, confusion and toxaemia. According to Thompson from the Mayo Clinic, about 25 % of patients present with a neurological disorder (cerebrovascular accidents, meningitis and disorders of mentation). Experience at St Thomas' Hospital in 47 cases of *S. aureus* native valve endocarditis (29 community-acquired, 18 hospital-acquired) suggests that an even greater proportion of cases present with neurological impairment, and that a diagnosis of meningitis is sometimes made on admission in patients with community-acquired disease. The CSF usually contains increased numbers of white cells but rarely grows *S. aureus* on culture. In only 25 % of our patients was a heart murmur heard on admission; one was detected later in a further 35 %.

The diagnosis of *S. aureus* endocarditis is frequently missed, particularly in patients with a previously normal valve; yet, remarkably, the salient features of the disease were accurately described by William Osler over a century ago. It thus follows that any febrile ill patient admitted from the community with neurological signs, *S. aureus* in the blood and no obvious source for the infection should be assumed to have endocarditis and treated accordingly, even in the absence of a murmur or vegetations.

Native valve *S. aureus* endocarditis may also be aquired in hospital, and in such cases there is always a predisposing cause, usually infection at an intravenous access site.

S. aureus endocarditis on a native valve has a high mortality rate (64 % in our series). The only way to reduce this is by earlier diagnosis and early effective treatment which will often mean valve replacement; this should never be delayed.

S. aureus Endocarditis in Drug Addicts

Drug addicts are at the highest risk of acquiring endocarditis of any patient group, indeed endocarditis was one of the earliest recognised medical complications of intravenous drug abuse. It is most often caused by *S. aureus*. The infection in drug addicts has several unique features that differentiate it from endocarditis in the non-addict population. It predominately affects the tricuspid valve which is previously healthy. This right-sided infection gives rise to septic pulmonary emboli and as a result the presenting symptoms and signs involve the respiratory tract and not the heart. The large series from Sklaver (1978) and Sande's group (1982) together with our own 12 cases confirm that these patients present with fever, chest pain and cough and usually have an

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abnormal chest X ray with multiple nodular infiltrates (which later cavitate); heart murmurs are seldom heard. The infection may be mistaken for pneumonia by the unsuspecting clinician. Any drug addict with fever, chest signs and *S. aureus* in the blood must be assumed to have tricuspid endocarditis and treated accordingly.

Involvement of the central nervous system is unusual in rightsided endocarditis and if present suggests combined right-sided and left-sided infection. When left-sided endocarditis does occur in addicts, there is likely to be pre-existing valvular disease; it is uncommon but carries a worse prognosis than right-sided disease. *S. aureus* tricuspid endocarditis nearly always has a favourable outcome.

S. aureus Endocarditis Involving Prosthetic Valves

S. aureus is an important but now uncommon cause of prosthetic valve endocarditis (PVE). Between 1963 and 1974 it was responsible for 44 % of early onset PVE and 10 % of late onset PVE seen at the Mayo Clinic, but more recently this ratio has been reversed and there has been a decrease in the incidence of early onset cases. At St Thomas' hospital in the period 1968-87, *S. aureus* accounted for 10 of 22 (45 %) of eary onset PVE but for only 2 of 31 (6 %) of late onset cases, figures remarkably similar to those first reported from the Mayo Clinic.

In early onset infection there is often sternal wound sepsis although initially it may appear to be trivial. Diagnosis may be difficult since sternal wound infection may result in a bacteraemia that does not necessarily equate with endocarditis. However if such infection is left untreated, involvement of the valve is likely. The appearance of new murmurs, peripheral emboli and splenomegaly, in addition to persistent fever, often with rigors, is diagnostic of endocarditis. Early onset *S. aureus* PVE has a high mortality rate, and all but one of our 10 patients died. Late onset PVE has a similar presentation to infection on a native valve.

S. epidermidis Endocarditis

S. epidermidis is generally regarded as the single most common organism causing PVE and the commonest cause of early onset infection. The organism most usually gains access at surgery, presumably from the skin of the patient or the operating team. In contrast to *S. aureus*, overt wound infection with *S. epidermidis* is unusual and the infection is more insidious. The 2 morsh latent period for early onset PVE may be inappropriate for *S. epidermidis* because strains clearly introduced at the time of surgery have been isolated from cases of PVE presenting 2-12 months after surgery. Curiously experience at St Thomas' Hospital is at variance with many reports; we have only seen 3 cases of *S. epidermidis* PVE. One patient presented at 4 weeks, one at 6 weeks (clearly both acquired at operation); the third occurred 14 years after valve replacement as a result of infection at an intravenous access site.

S. epidermidis occasionally infects a native valve; we have seen 10 cases in 20 years. The organism accounted for 5 % of the 196 cases of native valve endocarditis seen. Interestingly 5 of the cases have been seen during the last 2 years. Two infections were acquired in hospital as a result of infected intravenous access sites, but the other 8 arose de novo in the community, all but one on a previously abnormal valve. The clinical persentation of native valve *S. epidermidis* endocarditis is usually far less acute than infection with *S. aureus* and similar to endocarditis caused by the "viridans" streptococci.

Since *S. epidermidis* is the commonest organism found contaminating blood cultures, several should be done to establish the presence of the persistent bacteraemia that invariably occurs if a patient has endocarditis.

Treatment of Staphylococcal Endocarditis

In common with any infective endocarditis, antibiotic treatment of staphylococcal endocarditis is only one aspect of its management. During the past decade it has been accepted that valve replacement should never be delayed if it is required on haemodynamic grounds or for failure to control the infection. It was previously thought to be hazardous to operate in the presence of active infection and considered essential to "finish the course of antibiotics" before operating; this is now known to be disastrous. Surgery should never be delayed, such delay may well prove fatal. A persistent fever or a persistent bacteraemia in the face of appropriate antibiotics suggests abscess formation which can only be remedied by urgent surgery.

Choice of antibiotic

Obviously the choice of antibiotic (s) will be governed by the in vitro sensitivity of the staphylococcus. It should be bactericidal or the organism and available as an intravenous preparation. In the UK most strains of *S. aureus* are resistant only to penicillin. *S. epidermidis* acquired in he community is often sensivite to penicillin, whereas strains acquired in hospital are likely to be multiresistant. No clinical trials have ever established the optimum antibiotic or antibiotic combination for the treatment of staphylococcal endocarditis nor is it known whether combinations confer therapeutic benefit over a single drug. Korzeniowski and Sande demonstrated that the bacteraemia cleared more rapidly with nafcillin and gentamicin than with nafcillin alone but the difference was marginal and those patients who received gentamicin had a higher incidence of renal dysfunction during treatment. Nevertheless, many clinicians use, and many microbiologists recommend, a combination of antibiotics for the treatment of staphylococcal endocarditis, both for *S. aureus* and *S. epidermidis*. It should be remembered that failures will occur whatever regimen is used.

The mainstay of therapy should be a penicillinase-resistant penicillin. Cephalosporins have been used sucessfully in staphylococcal endocarditis but they have a slower rate of bactericidal activity against at least some strains of *S. aureus* both in vitro and in the rabbit model of *S. aureus* endocarditis. Flucloxacillin is the preferred penicillin and is the drug recommended by the Working Party of the British Society for Antimicrobial Chemotherapy (BSAC) in their recent report. A regimen of 2g flucloxacillin intravenously every 4 hours should be used. If the *Staphylococcus* is sensitive to penicillin, intravenous benzyl penicillin can be used instead of flucloxacillin. The choice of a second agent to combine with flucloxacillin lies between gentamicin (or other aminoglycoside) and fusidic acid; neither is demonstrably superior. Gentamicin used in full therapeutic dosage, as recommended by the BSAC Working Party, carries a significant risk of toxicity especially if its use is prolonged, whereas fusidic acid may produce jaundice, although this is usually reversible. As jaundice is particularly likely to occur with the intravenous preparation, fusidic acid should be given by mouth or nasogastric tube. Most reports of staphylo-

coccal endocarditis are from the USA, where fusidic acid is not available, but in the UK, the drug has been widely used for over 20 years and is an effective anti-staphylococcal agent.

In cases where the *Staphylococcus* is multiresistant or the patient is hypersensitive to penicillin, vancomycin is usually the drug of choice. If the *Staphylococcus* is sensitive to erythromycin this can be used instead of flucloxacillin and combined with fusidic acid in patients who are hypersensitive to penicillin. Rifampicin is often combined with vancomycin, but there is no evidence that it confers additional benefit. Unfortunately staphylococci tend to develop resistance to both fusidic acid and rifampicin in vivo even if these antibiotics are used in combination with others.

The optimum length of treatment for staphylococcal endocarditis is unknown but the bacteraemia is often slow clear and defervescence correspondingly slow. We have isolated *S. aureus* from a valve excised after 9 days of appropriate antibiotic therapy despite sterile blood cultures for 8 days. At least 4 weeks treatment seems advisable but longer is often given. It may be possible to treat right-sided endocarditis in drug addicts for less than this, but such patients are often lost to follow up, making the long term assessment of any regimen difficult.

Whatever antibiotic regimen is used to treat staphylococcal endocarditis, its management should involve close liaison with a cardiologist and cardiac surgeon as soon as the infection is diagnosed. Timely surgical intervention may save the patient's life.

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Staphylococcus aureus Toksinleriyle Oluşan Klinik Tablolar

Halûk Eraksoy

Giriş

Stafilokokların belirli bir konakta kolonize olma ve konuk durumunda oldukları bu konağı hastalandırma yeteneklerini, çok karmaşık ve dinamik ilişkiler belirlemektedir. "Virülans" denen bu yeteneği, konak ve çevre koşullarından başka, birtakım stafilokok komponentleri ve ürünleri de etkiler. Stafilokok lezyonlarının başlamasında ve ilerlemesinde rol oynadığı düşünülen ve virülans faktörü adı verilen bu komponent ve ürünlerin çoğunun konak dokularına nasıl zarar verdiği açıkça anlaşılmış değildir. Öte yandan birtakım stafilokok toksinlerinin spesifik klinik tablolardan sorumlu olduğu kesin olarak ortaya konmuştur. Bu tablolar üç ana başlık altında toplanabilir: (I) stafilokoksik besin zehirlenmesi; (II) stafilokoksik haşlanmış deri sendromu; (III) toksik şok sendromu. İlk ikisinin iyi bilinmesine karşılık üçüncüsü yani toksik şok sendromu nispeten yeni tanınan bir antitedir. Bu nedenle bu yazıda ele alınan stafilokok toksinozları arasında toksik şok sendromuna daha geniş yer verilmiştir. Stafilokoksik enterokolit ise varlığı bugün pek kabul edilmeyen ve *Clostridium difficile* koliti ile özdeş olduğu düşünülen bir antitedir (1).

Stafilokoksik Besin Zehirlenmesi

Bu tablo stafilokokların kontamine besin yenmeden önce çoğalarak oluşturdukları enterotoksinlere bağlıdır. Enterotoksin oluşturan suşların hemen hepsi *Staphylococcus aureus*'tur. Ancak bazı koagülaz-negatif stafilokok suşları da sorumlu tutulmuştur. İki önemli kontaminasyon kaynağından biri, salgınların % 90'ına neden olan burun ve deri taşıyıcısı insanlar, diğeri ise mastitli ineklerdir. Stafilokoksik besin zehirlenmesinde mikroorganizmalar, yiyeceklerin oda sıcaklığında bekletilmeleri veya pişirildikten sonra soğutulmaları sırasında çoğalabilirler. Daha sonraki yeniden ısıtma bakteriyi tahrip etse bile, ısıya oldukça dayanıklı olan toksin bir besin zehirlenmesine neden olabilir.

Enterotoksinlerin etki mekanizması iyi anlaşılamamıştır. Enterotoksin, deney hayvanlarında gastrointestinal mukoza hücrelerinde destrüksiyona yol açar ve iltihabi bir yanıt oluşturur. Beyindeki kusma merkezi gibi başka organ sistemlerinin de etkilendiği ileri sürülmektedir. Belirtiler besin alındıktan 2-4 saat gibi kısa bir süre sonra ortaya çıkar. Bir hipersalivasyonun hemen ardından bulantı, kusma, karın ağrısı ve ishal görülür. Hastalık çoğunlukla kısa sürer; 24 saatten uzun sürmesi nadirdir ve çoğu kez hekime başvuruncaya dek hafifler. Ancak yaşlılarda veya başka bir ciddi hastalığı olanlarda yaşamı tehdit edebilir. Kuşkulu besinde enterotoksinin gösterilmesi tanıyı kesinleştirir (2).

Stafilokoksik Haşlanmış Deri Sendromu

Stafilokoksik haşlanmış deri sendromu (SHDS), genellikle 5 yaşın altındaki çocuklarda görülür; erişkinlerde nadirdir. Daha çok II. faj grubunda yer alan 71. tip *S. aureus* ile oluşmaktadır. Önceden lokalize bir deri infeksiyonu bulunur. Hastalık viral üst solunum yolu infeksiyonunu andıran prodrom belirtileriyle başlar. Çok yüksek olmayan bir ateş ve hafif bir lökositoz vardır. Çoğunlukla birdenbire ortaya çıkan perioral eritem görülür. 2-3 günde tüm vücuda yayılır. Görünüşte sağlam olan deriye parmakla basılırsa epidermis buruşur ve soyulur (Nikolsky bulgusu). Bundan sonra steril berrak sıvıyla dolu büyük büller belirir. Gevşek büllerin soyulmasıyla ortaya çıkan alanlar kurur. Geniş ve kalın seboreik pullar belirerek 3-5 gün süren bir deskuamasyon olur.

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