Antimicrobial treatment of infective endocarditis caused by viridans streptococci highly susceptible to penicillin: historic overview and future considerations

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In this article we present the path that led to current concepts regarding antimicrobial treatment of endocarditis caused by viridans streptococci highly susceptible to penicillin. Early treatment trials indicate that some patients with subacute endocarditis can be cured with shorter treatment duration than currently advised by international guidelines. Also, high-dose antibiotics, as recommended today, have a predominantly pharmacokinetic and pharmacodynamic rationale that is based mostly on experimental animal studies. Shortening antimicrobial treatment in select patients with endocarditis would be of great benefit. As yet there are no predictors of cure that can be used to individualize treatment duration in patients with bacterial endocarditis.

Keywords: antimicrobial therapy, Streptococcus spp., subacute endocarditis

Introduction

‘It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future’. These are the first words of William Osler’s famous lecture on endocarditis1 and they summarize the intention of this article, be it not to take stock of our knowledge of the disease itself but of its treatment, or, more specifically, of the duration of antimicrobial treatment of endocarditis caused by viridans streptococci.

The viridans streptococci are a heterogeneous group of microorganisms that form part of the normal flora of the oropharyngeal cavity. The most important clinical representatives are: Streptococcus oralis (mitis), Streptococcus sanguis, Streptococcus mutans, Streptococcus milleri and Streptococcus salivarius. Viridans streptococci are the causative micro-organisms in 40–60% of the cases of community-acquired endocarditis of the native valve.2,3 Because the viridans streptococci are relatively avirulent, the course of endocarditis caused by these micro-organisms is slow and metastatic abscesses are rare. It is for this reason that endocarditis caused by these micro-organisms is also known as subacute endocarditis or endocarditis lenta. In this article, we want to provide a historic review of the path that led to the current concepts of treatment of subacute endocarditis and to discuss possible future recommendations.

Pre-antibiotic era

Endocarditis was almost universally fatal before the introduction of antimicrobial agents.4–11 The disastrous outcome of the disease at the time led to rather bizarre and highly imaginative forms of therapy such as injections with mercury, arsenic and formalin, as also radiation of the heart, body hyperthermia and inoculation with living malaria parasites. Even inoculation with viridans streptococci isolated from the blood of the endocarditis patient himself was attempted. Not surprisingly none of these therapies was curative; in fact they most probably only increased discomfort in the patient and may even have hastened death.

Sulphonamides

The first clinical report on the chemotherapeutic agent sulfanilamide or streptozon/prontosil appeared in 1933.12 Subsequently many new chemotherapeutic compounds were introduced and used against a wide variety of infectious diseases including bacterial endocarditis. Sulphonamides caused prolonged suppression of fever and clinical symptoms in some patients; however, actual cure of the disease was seldom achieved.6,7,9,10,13–24 In 1942, Lichtman published a review of the literature indicating that only 21 (4%) of 489 patients with infective endocarditis caused by viridans streptococci recovered under sulphonamide chemotherapy.5 The explanation for the observed lack of effect is probably the bacteriostatic action of

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sulphonamides. Also, experimental studies have shown that sulphonamides do not penetrate the fibrin-platelet protectorate around the bacteria in vegetations.

**Antibiotic era**

**Penicillin**

The antibacterial action of penicillin was first described by Fleming in 1929, and small amounts of penicillin became available for clinical use in 1942. The first articles describing the use of very low dosages in patients with endocarditis were largely disappointing. In 1944, however, Loewe published a report describing successful treatment, with a combination penicillin and heparin, of seven patients with subacute endocarditis. Now, a nearly always fatal disease had suddenly been transformed into a disease that could have a cure. In the years following, many other authors presented their experience with penicillin in the treatment of endocarditis. Durack published an elaborate overview of these early treatment years of endocarditis. In the early reports the diagnostic criteria for endocarditis varied; some studies included both patients with acute and subacute endocarditis, and in some even patients with negative blood cultures were included. Treatment with penicillin was empirical and there was a wide variation in routes of administration, dosage, dosage interval and duration of treatment. Intravenous (iv) administration was then still considered dangerous and technically cumbersome; therefore, most authors advised intramuscular (im) administration of penicillin. Daily dosages varied from 50 000 to 2 000 000 IU and the duration of treatment varied from 10 to 60 days.

It soon became clear that clinical studies were necessary to determine the optimum dosage and treatment duration. The first trials regarding the dosage and duration of treatment were the Penicillin Clinical Trials performed from 1945 to 1949 in Great Britain. The Medical Research Council appointed 14 centres that participated in the trials, and by the end of the study 442 patients had been included. Methodologically the studies were not optimal, in the sense that both patients infected by viridans streptococci, Staphylococcus aureus and patients with negative blood cultures were included. Nevertheless, these were the first trials in which the dosage and duration of the treatment with penicillin were systematically and prospectively studied in patients with infective endocarditis. The first 52 patients received a total of 5 million units of penicillin each, but the daily dosage and, therefore, the length of therapy was varied between 5, 10 and 20 days. In the second study the length of treatment was established at 28 days, but the daily dose was varied between 100 000, 250 000 and 500 000 IU. The most remarkable outcome from this study is that 4 of the 12 surviving patients were cured with a treatment duration of 10 days (Table 1).

**Repository types of penicillin and oral administration**

Although endocarditis could now be cured, the length of therapy and consequent hospital admission constituted an economic burden on the medical system, and lengthy hospital admissions and frequent intramuscular injections were traumatic experiences for the patients involved. To avoid frequent injections, attempts were made to treat with repository types of penicillin and, after the development of penicillin V, with oral penicillin.

Examples of repository types of penicillin were preparations in which penicillin was dissolved in beeswax and peanut oil, and procaine penicillin. The use of beeswax and peanut oil preparations were abandoned after they caused large gluteal abscesses. Treatment with procaine penicillin was successful in some patients; however, bacteriological failure after lengthy admission of procaine penicillin has also been described previously.

The major drawbacks of oral penicillin administration were the required ingestion of excessive amounts, often causing severe intolerance and the uneven absorption of the drug, which required frequent blood level monitoring during treatment. It is for these reasons that the oral form of penicillin has generally been discarded as inadequate for the treatment of endocarditis. It became clear that the only possible solution to facilitate treatment was shortening its duration.

**Shorter treatment schedules with penicillin alone or penicillin combined with aminoglycosides**

In 1949 King et al. described the first trial in which patients with endocarditis were deliberately treated with a short treatment schedule. They treated eight patients with a regimen of 10 rapid intravenous injections of 1 million units of penicillin at hourly intervals and four intramuscular injections of 1 million units of penicillin at equal time periods for the remaining 14 h, for a period of 10 days. Caronamide was used as an adjuvant to inhibit tubular secretion of the antibiotic. The results were disappointing; only one patient was cured while seven suffered a relapse. Three years later, Hamburger published much more favourable results.

**Table 1. Medical Research Council penicillin trials, 1945 and 1946**

<table>
<thead>
<tr>
<th>Penicillin (million units)</th>
<th>Duration of treatment (days)</th>
<th>Total number treated</th>
<th>Died with infection apparently controlled (no.)</th>
<th>Died with infection uncontrolled (no.)</th>
<th>Relapsed (no.)</th>
<th>Cure (no.)</th>
<th>Relapsed or died of infection [no. (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>18</td>
<td>3</td>
<td>2</td>
<td>13</td>
<td>0</td>
<td>15 (83)</td>
</tr>
<tr>
<td>0.5</td>
<td>10</td>
<td>16</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>8 (50)</td>
</tr>
<tr>
<td>0.25</td>
<td>20</td>
<td>18</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Second trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>28</td>
<td>17</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>7 (41)</td>
</tr>
<tr>
<td>0.25</td>
<td>28</td>
<td>83</td>
<td>30</td>
<td>2</td>
<td>11</td>
<td>40</td>
<td>13 (16)</td>
</tr>
<tr>
<td>0.5</td>
<td>28</td>
<td>58</td>
<td>22</td>
<td>3</td>
<td>1</td>
<td>32</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>
Table 2. Shorter treatment schedules for subacute endocarditis

<table>
<thead>
<tr>
<th>Year</th>
<th>Author (reference no.)</th>
<th>Treatment length (days)</th>
<th>Penicillin (million units)</th>
<th>Streptomycin (im g)</th>
<th>Patients (no.)</th>
<th>Relapse [no. (%)]</th>
<th>Cure [no. (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1949</td>
<td>King\textsuperscript{56}</td>
<td>10</td>
<td>14</td>
<td>–</td>
<td>8</td>
<td>7 (87)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>1952</td>
<td>Hamburger\textsuperscript{57}</td>
<td>11–14</td>
<td>15–16</td>
<td>–</td>
<td>12</td>
<td>2 (17)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>1955</td>
<td>Hall\textsuperscript{66}</td>
<td>10–17</td>
<td>2.4</td>
<td>1–2</td>
<td>15</td>
<td>1 (7)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>1958</td>
<td>Geraci\textsuperscript{65}</td>
<td>14</td>
<td>1.2–2.4</td>
<td>1.2–2.4</td>
<td>82</td>
<td>3 (4)</td>
<td>63 (77)</td>
</tr>
<tr>
<td>1958</td>
<td>Tomsett\textsuperscript{67}</td>
<td>10–18</td>
<td>0.6–6</td>
<td>2</td>
<td>35</td>
<td>3 (9)</td>
<td>24 (69)</td>
</tr>
<tr>
<td>1961</td>
<td>Hamburger\textsuperscript{68}</td>
<td>14–15</td>
<td>oral 3000–4500 mg</td>
<td>1–2</td>
<td>17</td>
<td>0 (0)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>1971</td>
<td>Tan\textsuperscript{69}</td>
<td>14</td>
<td>2</td>
<td>–</td>
<td>13</td>
<td>2 (15)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>1981</td>
<td>Wilson\textsuperscript{72}</td>
<td>14</td>
<td>4.8</td>
<td>1</td>
<td>91</td>
<td>0 (0)</td>
<td>89 (98)</td>
</tr>
</tbody>
</table>

The results of a systematic study in which 10 of 12 patients with subacute bacterial endocarditis were successfully treated with a 2 week penicillin schedule, consisting of a daily administration of 15–16 million units given intravenously.\textsuperscript{57}

The major breakthrough towards shorter treatment schedules, however, originated from the synergistic activity of streptomycin plus penicillin in the treatment of endocarditis. Until that time the opinion prevailed that aminoglycosides should be reserved for culture-negative endocarditis or endocarditis caused by Gram-negative or highly resistant Gram-positive micro-organisms. Hunter, acknowledging the importance of the synergistic bactericidal effects of combined penicillin and streptomycin, was the first author to suggest the combination in patients with penicillin-sensitive streptococci thereby shortening the treatment duration of subacute endocarditis.\textsuperscript{58–60} He used the combination successfully in a treatment regimen of 10 days in three patients. Synergism between the two antibiotics had already been proven \textit{in vitro} and in animal experiments.\textsuperscript{61–63}

In 1953 Geraci and Martin published a larger study,\textsuperscript{64} in which they treated 23 patients with subacute endocarditis for 2 weeks with a combination of penicillin, 1.2–2.4 million IU per day, and streptomycin, 1.2–2.4 g per day. There were no treatment failures or relapses, although five patients died during or after treatment from complications of the infection. After this success, Geraci described an equally successful short-term combined therapy in an additional 23 and 36 patients with subacute endocarditis caused by viridans streptococci.\textsuperscript{65} Later reports by other authors were slightly less favourable: in one study 1 of 15 patients treated with short-term combined therapy was retreated because of persistent fever,\textsuperscript{66} in another study 3 of 35 suffered a definite relapse.\textsuperscript{67} In 1961 Hamburger treated 17 patients with subacute endocarditis with a 2 week schedule of oral penicillin V and intramuscular streptomycin, and none of the patients suffered from relapses.\textsuperscript{68}

Hunter and Paterson pooled the results of 23 investigators who treated 146 patients with endocarditis caused by streptococci highly susceptible to penicillin, using a combination of penicillin and streptomycin for ~2 weeks.\textsuperscript{69} The relapse rate was 6%. In 1971 Tan published an article in which patients were treated with either penicillin alone or with a combination of penicillin and streptomycin.\textsuperscript{70} Penicillin was administered orally, intramuscularly or parenterally in daily dosages varying from 2 to 12 million U. With penicillin alone two of the 13 patients relapsed. Of the 36 patients treated with penicillin plus streptomycin for 2 weeks, none relapsed whether the penicillin was given by mouth or parenterally.

In 1978 Wilson \textit{et al.} performed a study in which 33 patients with subacute endocarditis caused by viridans streptococci were treated with a 2 week schedule consisting of intramuscular procaine penicillin 1.2 million IU every 6 h and intramuscular streptomycin 500 mg twice daily.\textsuperscript{71} Although nine patients (27%) had infections with relatively penicillin-resistant micro-organisms (MIC > 0.1 mg/L) all 33 patients were cured and there were no relapses. In 1981 Wilson expanded the study to a total of 91 patients and again there were no relapses.\textsuperscript{72} The results of 2 week treatment trials for subacute endocarditis are summarized in Table 2.

The success of combination therapy above monotherapy in shorter treatment schedules for subacute endocarditis is reflected in current treatment guidelines in which the 14 day treatment is only advised when penicillin and gentamicin are administered together.

### Cephalosporins

The first publication describing the successful use of cephalosporins in the treatment of subacute bacterial endocarditis dates from 1969.\textsuperscript{73} After this, not much was heard of the use of cephalosporins in the treatment of endocarditis until the early 1990s when two clinical trials were published nearly simultaneously in Switzerland and Argentina. In both studies patients with subacute endocarditis were successfully treated with ceftriaxone monotherapy for 4 weeks. In 1995 the Swiss and Argentine groups combined their efforts and performed a prospective multicentre study.\textsuperscript{76} In this trial 50 patients with streptococcal endocarditis were treated with a single daily dose of intravenous ceftriaxone and netilmicin for 14 days. In this group there were no relapses. In 1998 a randomized, multicentre trial compared the efficacy and safety of ceftriaxone monotherapy for 4 weeks with a 2 week combination therapy of ceftriaxone and gentamicin.\textsuperscript{77}

Clinical cure was observed in 25 (96.2%) of the 26 monotherapy recipients and 24 (96%) of the 25 combination therapy recipients. There were no relapses. The great advantage of the use of ceftriaxone was that it was administered once daily and therefore allowed partial or complete outpatient treatment in select patients.
Discussion

In endocarditis caused by viridans streptococci highly susceptible to penicillin current international guidelines advocate three parenteral treatment schedules,78–82 (i) 4 weeks of monotherapy with penicillin G; (ii) 2 weeks of combination therapy of penicillin G with gentamicin followed by 2 weeks of penicillin G; and (iii) 2 weeks of combination therapy with penicillin G and gentamicin (in select cases). The total daily dosage of penicillin varies from 12 to 18 million U. High-dose antibiotics, as recommended today, have a predominantly pharmacokinetic and pharmacodynamic rationale that is based mostly on experimental animal studies.83–86 In these studies it was shown that tissue penetration in vegetations is faster when serum concentration of the antibiotic is higher and that time over the MIC is critical for β-lactam activity. Another argument in favour of high dosage schedules is the existence of penicillin-tolerant streptococcal strains. Tolerance was first described by Sabath in 1977 and was defined as the bactericidal dose of penicillin being much higher than the inhibitory dose for certain strains of micro-organisms.87 The therapeutic significance of penicillin-tolerance was later demonstrated in experimental streptococcal endocarditis.88,89

There are no clinical trials in human endocarditis patients, however, that have proven the advantage of these high dosages in regard to bacterial cure and clinical outcome. The early MRC treatment trials46–49 show that most patients with endocarditis are cured with much lower daily dosages than currently advised. An objection against gaining evidence for lower dosages from early trials may be the lack of diagnostic criteria for endocarditis at that time so that one cannot be sure that all the patients truly suffered from the disease. Also, most studies did not precisely define the patients’ demography and co-morbidities, e.g. renal insufficiency that could increase drug serum level.

Regarding the duration of therapy, monotherapy has been administered for as short as 5 days, but there have been no trials in which combination therapy was administered for <2 weeks. Yet, early reports about treatment with monotherapy showed that some patients are cured within 14 days. Also, the choice between the above-mentioned (i), (ii) and (iii) schedules remains controversial. Even today many physicians prefer the 4 week treatment schedules above the 2 week schedule. In 1966 Lerner and Weinstein stated that only with longer treatment schedules can one be assured of curing all patients, so as long as there are no prognostic indicators to recognize patients who will respond to short-term therapy one should abandon this form of treatment.90 Moreover, although in the past viridans streptococci were uniformly susceptible to β-lactam agents, a recent study with viridans streptococci isolated from patients with infective endocarditis demonstrated a level of penicillin non-susceptibility of 13%.91 New, effective drugs with rapid bactericidal activity should be sought to ensure the possibility of shortening treatment in this patient group.

Unfortunately, in the 40 years that have passed since the paper of Lerner and Weinstein, no specific predictors of cure have been detected for endocarditis. With such a predictor the duration of therapy could be individualized in each patient. Some studies have shown that C-reactive protein values remain elevated in complicated cases of infective endocarditis whereas they rapidly seem to normalize in uncomplicated cases.92–94 The value of serial C-reactive protein measurements and of other inflammatory parameters, e.g. cytokines, as predictors of cure should be further explored in an observational study in patients with endocarditis. In such a study an inflammatory parameter, or combination of parameters, should be sought that closely correlates with the clinical course of the disease. When found, the next step is a randomized controlled trial in which the treatment duration is individualized based on inflammatory parameters in the experimental group and of standard duration according to current guidelines in the control group.

Transparency declarations

None to declare.

References


Review


