Enterococcus Faecalis Infective Endocarditis: A Pilot Study on the
Relationship between Duration of Gentamicin Treatment and Outcome

Running title: Dahl et al.; Gentamicin in enterococcal endocarditis

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Abstract:

Background—Due to the nephrotoxic effects of aminoglycosides the Danish guidelines on infective endocarditis (IE) were changed in January 2007 reducing gentamicin treatment in enterococcal IE from 4-6 weeks to only 2 weeks. In this pilot study we compare the outcome in patients with enterococcus faecalis IE treated in the years before and after endorsement of these new recommendations.

Methods and Results—A total of 84 consecutive patients admitted with definite left-sided enterococcus faecalis endocarditis in the period 2002 to 2011 were enrolled. Forty-one patients were treated before, and 43 patients after January 1st, 2007, respectively. There were no significant differences in baseline characteristics. At hospitalization the two groups had similar eGFR of 66 ml/min vs. 75 ml/min (p=0.22). Patients treated before January 2007 received gentamicin for a significantly longer period (28 days vs. 14 days, p<0.001). The primary outcome, 1-year event-free survival, did not differ: 66 % vs. 69 % (p=0.75). At discharge the patients treated before 2007 had a lower eGFR of 45 ml/min vs. 66 ml/min (p=0.008), and a significantly greater decrease in eGFR: median 11ml/min vs. 1 ml/min (p=0.009).

Conclusions—Our present pilot study suggests that a recommendation of 2 weeks gentamicin treatment seem adequate and preferable in treating non HLAR enterococcus faecalis infective endocarditis. The longer duration of gentamicin treatment is associated with worse renal function and although the certainty of the clinical outcomes is limited by the sample size, outcomes appear to be no worse. Randomized controlled studies are warranted in order to substantiate these results.

Key words: enterococcus, gentamicin, endocarditis, mortality, renal function
Introduction

In more recent series enterococci are responsible for 8-17% of all infective endocarditis (IE) cases\textsuperscript{1-5}. Enterococci as a pathogen in endocarditis is becoming more prevalent as a consequence of the growing number of elderly patients with degenerative heart valve disease, prosthetic heart valves and a higher incidence of enterococcal bloodstream infections originating from the gastrointestinal or urogenital tracts\textsuperscript{4-11}. Infective endocarditis due to enterococci is a serious disease without any apparent improvement in survival during the last decades\textsuperscript{12}. No randomized clinical trials, evaluating the treatment of patients with enterococcal IE, are available and current guidelines are therefore based on empirical experience and expert consensus. The international IE guidelines from American Heart Association (AHA)\textsuperscript{13} and European Society of Cardiology (ESC)\textsuperscript{14} recommend 4-6 weeks of combined antibiotic treatment with aminoglycosides (preferable gentamicin) and an inhibitor of cell wall synthesis (beta-lactam antibiotics or vancomycin). Enterococci are highly tolerant to antibiotic-induced killing, and theoretically these IE patients therefore require prolonged administration of a combination of antibiotics with synergistic effects\textsuperscript{15-20}. However it is well-known, that aminoglycosides are nephrotoxic and prolonged duration of treatment increases the risk of renal function impairment\textsuperscript{21-24}. An important question therefore is, whether or not it is necessary to treat enterococcal IE with gentamicin for as long as 4-6 weeks in order to obtain a sufficient cure rate.

In Denmark new national guidelines on endocarditis were endorsed in January 2007, reducing gentamicin treatment in enterococcal IE from 4-6 weeks to only two weeks. The aim of the present study is to investigate the effects of these new recommendations on relapse and mortality and to evaluate the impact of the reduced duration of gentamicin treatment on renal function.
Methods

Database

Data from consecutive patients diagnosed with IE in two tertiary heart centers in Copenhagen Denmark, were prospectively collected from the 1st of October 2002. These two highly specialized university hospitals serve as the only referral centers for IE patients in the eastern part of Denmark and cover a catchment area of 2.4 million people. The diagnosis of IE was based on clinical, microbiological, and echocardiographic findings. Patients were enrolled in the database if they met the revised Duke criteria25 of definite or possible IE. Patients with possible IE were only included if they received treatment as patients with definite IE. All data were collected using a standardized case report form with more than 250 variables, including demographics, medical history, physical examination findings, results of blood tests including blood cultures, electrocardiogram (ECG), antibiotic use, surgical treatment and findings of both transthoracic (TTE) and transesophageal (TEE) echocardiography. Duration of symptoms was registered as time from appearance of the first symptoms of IE (reported by the patient or their close family) until the time of diagnosis, called diagnostic delay. Doctor’s delay was registered as the time interval from the first presentation of symptoms to a physician and until final diagnosis was established. The database was approved by the Danish Data Supervisory Committee with journal number 2011-41-6485.

Study population

In the present study we only included patients with definite left-sided enterococcus faecalis IE, admitted from October 1st 2002 to October 1st 2011. Patients infected with enterococcus faecium or high-level aminoglycoside resistant (HLAR, MIC > 256mg/L) strains were excluded. Only patients initially treated with relevant beta-lactam antibiotics (penicillin/ampicillin) in
combination with gentamicin were included. Patients in dialysis at admission were excluded. This left us with 84 patients eligible for the study (figure 1).

**Treatment**

Patients were treated with antibiotics and surgery in close accordance with Danish and ESC guidelines. High-level disk diffusion susceptibility tests on blood cultures were performed in all participants and the choice of antibiotics was based on the results. In addition, minimal inhibitory concentration (MIC) determinations of the relevant antibiotics were performed at the discretion of the microbiologists. All patients were treated with gentamicin 3mg/kg (up to 240mg daily) administered 1-3 times daily at the discretion of the treating physician, and each patient had individualized the gentamicin dosing, guided by daily serum creatinine and trough serum gentamicin concentrations. When trough serum gentamicin was < 0.5 mg/L administration continued unchanged, when it was 0.5-1 mg/L, the dose was reduced by 50% and if serum gentamicin was >1 mg/L, gentamicin was withheld.

The Danish guidelines on enterococcal IE were changed in 2007 from recommending 4-6 weeks of gentamicin treatment to 2 weeks. This was the only significant change in the guidelines on treating enterococcal IE. Consequently we divided the patients into two groups; one in which the patients were admitted before 2007 (41 patients) and treated according to the older recommendations, and another group in which the patients were admitted after January 1st 2007 and treated according to the new guidelines (43 patients).

**Outcome**

The primary outcome was 12 months event-free survival, counting from end of treatment at the day of discharge. (i.e. 12 month cure defined as no relapse of e.faecalis IE and no death during the 12 month follow up). The secondary outcomes were in-hospital mortality and change in renal
function during treatment.

**Kidney function**

To estimate kidney function, we approximated patient glomerular filtration rate (eGFR) by calculating the Estimated Endogenous Creatinine Clearance (EECC) at the time of admission, after 14 days of treatment, and at the time of discharge, using the following equations based on the work by Siersbaek-Nielsen et al.\(^{27}\) and Kampmann et al.\(^{28}\):

\[
\text{Men; } \text{EECC} = \frac{(179.86 - (1.248 \times \text{age})) \times \text{weight (kg)}}{\text{serum creatinine (\(\mu\text{mol} / \text{L}\))}}
\]

\[
\text{Women; } \text{EECC} = \frac{(154.24 - (1.081 \times \text{age})) \times \text{weight (kg)}}{\text{serum creatinine (\(\mu\text{mol} / \text{L}\))}}
\]

EECC was measured in mL/min

**Follow-up**

Through the Danish central patient registry and central registration of death, we were able to accomplish a complete follow up on all-cause mortality and relapse of infection using each patient’s civil registration number. The follow up date was 31/7-2012.

**Statistics**

Continuous data were expressed as mean ± standard deviation (SD). When a normal distribution was uncertain the median and interquartile range (IQR) were given. Binomial data were expressed as frequencies and (%). The statistical evaluation of the 2 groups was performed with a two-sample t-test if the data were normally distributed. When the distribution was skewed, the Mann-Whitney test was used. The dichotomous variables were evaluated using chi-square test and Fischer’s exact test when appropriate. One year overall survival was compared between the
groups using Kaplan-Meier survival curves and log-rank test to estimate differences in survival.

In a retrospective power calculation a sample size of 152 patients in each group would be required to provide 80% power to detect a significant difference in primary endpoint of 15 % between the two treatment regimens (assuming 12 month cure rates of 0.60 and 0.75, respectively) with a two-sided significance level of $\alpha = 0.05$.

For all analysis a 2-sided $p$-value of $< 0.05$ was considered significant. All statistical calculations were performed using IBM SPSS Inc. (Chicago, IL, US), software version 20.0 and R for Mac OS X (Version 0.94.105, http://www.R-project.org).

**Results**

**Patient characteristics**

The baseline characteristics for the two groups are presented in *Table 1*. The mean patient age was ~70 years in both groups and male gender was predominant with a 4:1 ratio. Co-morbidities were comparable between the two groups including Charlson co-morbidity score. There were no significant differences in predisposing factors between the two groups. Pre-existing valvular disease including prosthetic valve was the most predominant predisposition in both groups. At least one echocardiogram was performed in all patients, and TEE was performed in the vast majority of patients (96%). In both groups aortic location of the infection was most frequently seen, found in approximately half of the cases followed by mitral valve IE and left-sided dual valve IE. There was no difference between the two groups with regard to complications on the initial echocardiographic assessment. Pseudoaneurism or abscess formation was found in 8 patients in each group (*Table 1*).

**Diagnosis and treatment**

The diagnostic delay and doctors delay did not differ significantly between the two groups.
A total of five patients (6%) had relapse of enterococcus faecalis IE within one year from end of treatment. There was no significant difference in the number of relapses in the two groups; 3
relapses (7%) in the patients treated before 2007 and 2 relapses (5%) in the patients treated after first of January 2007, p=0.67 (table 3). The main characteristics of the five patients are shown in table 4. Native and prosthetic valve IE was evenly represented in the patients experiencing relapse. None of the patients had symptoms for more than 3 months.

In-hospital deaths

We assessed the cause of death in each of the 6 fatal cases during hospitalization. In the patients treated before 2007, two out of four patients were treated with gentamicin for a shorter period than prompted by the guidelines. Each patient course was thoroughly reviewed and the reason for discontinuing gentamicin was increasing renal function impairment in both. One out of the two patients that died, treated after 1st of January 2007 received gentamicin for less than the entire course. Again deterioration of renal function was the reason for halting gentamicin. None of the patients had persistent enterococcus faecalis bacteremia after gentamicin was removed.

Renal function in relation to gentamicin treatment

By calculating the EECC, we estimated the eGFR at admittance, after 14 days of treatment, and at discharge (Table 5). Estimated GFR at admittance was similar between the two groups with median values of 66 ml/min vs. 75 ml/min (p=0.22). After 14 days the eGFR was 57 vs. 67 ml/min – still without significant difference (p=0.65). At discharge however, there was a significant difference in eGFR (median: 45 ml/min vs. 66 ml/min, p = 0.008) and the change in eGFR also differed significantly (median: -11 ml/min vs. -1 ml/min, p = 0.009), (Table 5).

Discussion

The principal finding of our present pilot study is that antibiotic treatment of non HLAR enterococcus faecalis IE starting out with a beta-lactam combined with 2 weeks of gentamicin
appears to provide similar event-free survival as a combination with 4-6 weeks of gentamicin treatment. Furthermore, the deleterious effect on renal function induced by prolonged gentamicin administration is avoided.

It is widely acknowledged that enterococci are relatively resistant to antibiotics and therefore it can be challenging to treat enterococcal IE\textsuperscript{15–17,20}. Since the middle of the last century, in vitro studies, animal studies and many patient reports have demonstrated synergistic effect with better cure rates, when combining a beta-lactam antibiotic with an aminoglycoside\textsuperscript{29–34}. Therefore, this combination has been widely used worldwide and with 4-6 weeks of treatment, 3 month cure rates around 80 percent have been achieved\textsuperscript{1,2,7,12,35,36}. Interestingly, in 2007 Gavaldà and colleagues\textsuperscript{37} presented an alternative treatment with a 6 week combination of ampicillin and ceftriaxone in enterococcal IE. They treated 43 patients and obtained a 3 month cure rate of 67% concluding that it could be a reasonable alternative for patients infected with high-level aminoglycoside resistant enterococci or with increased risk of nephrotoxicity.

AHA\textsuperscript{13} and ESC\textsuperscript{14} guidelines on enterococcal IE, recommend a standard of 4 weeks combined antimicrobial therapy with penicillin (or ampicillin) and gentamicin. If the patient has prosthetic valve IE or the duration of symptoms has been more than 3 months the recommendations are 6 weeks of combined treatment.

However, the optimal duration of combined treatment in enterococcal IE has never been properly investigated. A small retrospective study by Herzstein et al.\textsuperscript{38} found no significant difference in cure rates (80% vs. 69%) between 10 patients receiving combined treatment with an aminoglycoside and a cell wall inhibitor (penicillin or vancomycin) for less than 4 weeks (mean 23 days) compared to 16 patients treated with synergistic therapy for more than 4 weeks (mean 40 days). Although indicating that shorter synergistic therapy might be sufficient, the
study is limited by small numbers and a retrospective design.

Since the late nineties a shortened course of aminoglycoside treatment to 2-3 weeks combined with 4-6 weeks beta-lactam treatment has often been used in clinical practice in Sweden in order to minimize nephrotoxic or ototoxic adverse events. A study by Olaison et al. presented 93 patients with enterococcal IE treated for a median of 15 days with aminoglycoside. With a 3 month follow-up rate of 53%, they obtained a cure rate of 81% and reviewed the 15 fatal episodes during hospitalization without finding any of them directly connected to the shortened synergistic therapy. However, as recognized by the authors the study protocol did not allow any analysis of adverse event rates related to different choice and duration of antibiotic treatment.

The Danish guidelines on treating enterococcal IE were changed in January 2007 reducing the period of recommended gentamicin treatment from 4-6 weeks to only 2 weeks. No other major changes in the treatment of these patients were implemented. Therefore, in the present study we have the unique situation of being able to include two larger groups of consecutive patients with enterococcus faecalis IE treated similarly except for the different duration of gentamicin administration. Accordingly, our data shows a highly significant decrease in duration of gentamicin treatment in the group of patients treated after the 1st of January 2007 indicating that the new recommendations were effectively implemented.

The two groups were comparable in baseline characteristics, especially with respect to age and co-morbidities. The 12 month cure rate was similar comparing the patients treated according to the new guidelines with the patients treated before 2007. During hospitalization 6 patients died – 4 treated by the old guidelines and 2 by the new. By careful revision of these deaths we found no evidence that any of them were related to abbreviated gentamicin treatment.
In our study we found no evidence of an association between relapse and PVE, symptoms for more than 3 months or shorter duration of Gentamicin treatment.

It is well-known that gentamicin is nephrotoxic and that longer treatment duration increases the risk of renal function impairment. Based on older studies\(^7\)\(^\text{3}4\), demonstrating reversible serum creatinine increases in enterococcal IE patients treated with gentamicin, it has been suggested that the decrease in eGFR is only temporary. However Cosgrove and colleagues\(^39\) have demonstrated that even short-term gentamicin treatment may cause a sustained decrease in creatine clearance, especially among those with initially slightly reduced eGFR. Another study from our own group by Buchholtz et al.\(^22\) showed only partly reversibility in renal impairment of IE patients during hospitalization, with full restitution in 64% of the patients. The longer time the patients were treated with gentamicin the greater was the reduction in eGFR and among the patients with the greatest decline only 35% obtained restitution of renal function at follow-up\(^22\). A decrease of renal function in IE patients can also be caused by e.g. glomerulonephritis, septic embolisms and interstitial nephritis\(^40\). The two groups in the present study are very similar and have all been infected with enterococcus faecalis. Therefore we find it most unlikely that a difference in the occurrence of these renal complications play an important role for the observed difference in the change of eGFR between the two groups. In IE it is recommended to administer gentamicin in 2-3 daily doses (AHA/ESC guidelines). However, the killing effect of gentamicin is related to peak plasma concentration and in other septic diseases gentamicin is therefore given once daily\(^41\)\(^42\). In a randomized trial of IE using \(^{51}\)Cr-EDTA clearance as a measure of GFR we demonstrated that a once daily gentamicin dosing regimen had similar efficacy and similar nephrotoxic effect as a twice daily regimen\(^43\). Therefore, the more simple once daily gentamicin regimen is now recommended for IE treatment in Denmark.
Other studies\(^4^4\text{–}^4^6\) have shown that renal function at time of admission is an independent predictor of mortality in patients with IE as well as in patients with left side heart failure\(^4^7\).

Therefore, prolonged aminoglycoside treatment in patients with enterococcal IE may unnecessarily place at least some of them in a higher risk group in case of future hospital admissions.

In the present study patients with HLAR enterococcus faecalis IE were omitted, but HLAR is a serious and increasing problem in enterococcal endocarditis with reports comprising up to 28-48\(^%\)\(^\text{37,48}\) of the patients. Decreasing aminoglycoside treatment duration is one important way to limit further development of HLAR.

**Implications**

Since the length of aminoglycoside treatment has never been accordingly evaluated, and because there is clear evidence of progressive decline in renal function with the length of this treatment, our present data imply that recommendations on duration of aminoglycoside treatment in enterococcus faecalis IE should be revisited.

**Limitations**

While our study is not a randomized clinical trial, it is a prospectively collected consecutive cohort with a historical control group. The study period was approximately 4 years before and after 1\(^\text{st}\) of January 2007. The relatively short time period favors standardized treatment regimens with only few changes over time. Our results are limited by the size of the cohorts, and due to the lack of sufficient power, our results need to be interpreted with caution. Nevertheless, we do present the so far largest investigation on the relationship between gentamicin treatment and one year outcome in enterococcus faecalis IE.

According to the power calculation a randomized clinical trial of e. faecalis IE treatment
would require several hundred patients and since it is a quite rare disease such a trial would be difficult to complete.

Additionally, our study only included 3 patients with symptoms for more than 3 months and therefore no firm conclusions can be drawn for this group of patients. Finally, referral bias may influence our results, as only patients from tertiary centers were included.

**Conclusion**

Our present pilot study suggests that a recommendation of 2 weeks gentamicin treatment seem adequate and preferable in treating non HLAR enterococcus faecalis infective endocarditis. The longer duration of gentamicin treatment is associated with worse renal function and although the certainty of the clinical outcomes is limited by the sample size, outcomes appear to be no worse. Randomized controlled studies are warranted in order to substantiate these results.

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**Conflict of Interest Disclosures:** None.

**References:**


26. [Infective Endocarditis. Diagnosis and treatment. Danish Society of Cardiology Guidelines 2007] [Internet]. [cited 2012 Apr 12];Available from:


38. Herzstein J, Ryan JL, Mangi RJ, Greco TP, Andriole VT. Optimal therapy for enterococcal


Table 1. Patient characteristics (n=84) of patients treated according to guidelines before 2007 and patients treated according to the new guidelines after January 1\textsuperscript{st} 2007.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 2007 (n=41)</th>
<th>After 1/1 2007 (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years); mean (SD)</td>
<td>70 (12)</td>
<td>70 (11)</td>
<td>0.88</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>32 (78)</td>
<td>38 (88)</td>
<td>0.20</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson co-morbidity score, mean(SD)</td>
<td>1.8 (1.9)</td>
<td>2.1 (1.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Chronic renal impairment, n (%)</td>
<td>7 (17)</td>
<td>8 (19)</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (15)</td>
<td>6 (14)</td>
<td>0.93</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>9 (22)</td>
<td>7 (16)</td>
<td>0.51</td>
</tr>
<tr>
<td>Neurological disease, n (%)</td>
<td>5 (12)</td>
<td>5 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Predisposing conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing valvular disease, n (%)</td>
<td>22 (54)</td>
<td>26 (61)</td>
<td>0.53</td>
</tr>
<tr>
<td>Prosthetic valve IE, n (%)</td>
<td>14 (34)</td>
<td>16 (37)</td>
<td>0.77</td>
</tr>
<tr>
<td>Late prosthetic valve IE, n (%)*</td>
<td>10 (24)</td>
<td>13 (30)</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous endocarditis, n (%)</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Intravenous drug abuse, n (%)</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Immunosuppressant therapy, n (%)</td>
<td>3 (7)</td>
<td>4 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Echocardiography performed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTE, n (%)</td>
<td>41 (100)</td>
<td>43 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>TEE, n (%)</td>
<td>39 (95)</td>
<td>42 (98)</td>
<td>0.61</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic, n (%)</td>
<td>21 (51)</td>
<td>23 (54)</td>
<td>0.84</td>
</tr>
<tr>
<td>Mitral, n (%)</td>
<td>13 (32)</td>
<td>12 (28)</td>
<td>0.70</td>
</tr>
<tr>
<td>Aortic and mitral, n (%)</td>
<td>7 (17)</td>
<td>8 (19)</td>
<td>0.86</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudo-aneurism or abscess, n (%)</td>
<td>8 (20)</td>
<td>8 (19)</td>
<td>0.92</td>
</tr>
<tr>
<td>Valve cusp damage, n (%)</td>
<td>11 (27)</td>
<td>12 (28)</td>
<td>0.91</td>
</tr>
<tr>
<td>Paravalvular leak, n (%)</td>
<td>8 (20)</td>
<td>8 (19)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Prosthetic valve IE occurring later than one year from implantation of valve.
Table 2. Diagnostic delays, duration of hospital stay, gentamicin treatment duration, dosing interval and frequency of surgical treatment in enterococcus faecalis IE.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Before 2007 (n=41)</th>
<th>After 1/1 2007 (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic delay (days), median (IQR)</td>
<td>20 (14-32)</td>
<td>30 (16-48)</td>
<td>0.06</td>
</tr>
<tr>
<td>Doctors delay (days), median (IQR)</td>
<td>10 (5-24)</td>
<td>19 (7-36)</td>
<td>0.09</td>
</tr>
<tr>
<td>Symptoms for more than 3 months, n (%)</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gentamicin treatment days, median (IQR)</td>
<td>28 (18-42)</td>
<td>14 (7-15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of hospital stay (days), median (IQR)</td>
<td>42 (35-51)</td>
<td>41 (36-44)</td>
<td>0.24</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>15 (37)</td>
<td>14 (33)</td>
<td>0.70</td>
</tr>
<tr>
<td>Indications for surgery†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure due to valve destruction</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Abscess, pseudo aneurism or fistula</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism and residual vegetation</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Large vegetations</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Persistent uncontrolled infection</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PVE with significant paravalvular leak</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Newly developed 2. or 3. degree AV-block</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* When comparing once or twice daily administration of gentamicin between the two groups.
† Some patients had more than one indication for surgery and therefore the total number of indications is larger than the number of patients operated.
Table 3. Complications and outcomes of patients with enterococcus faecalis IE treated according to guidelines before 2007 and patients treated according to the new guidelines after January 1st 2007.

<table>
<thead>
<tr>
<th></th>
<th>Before 2007 (n = 41)</th>
<th>After 1/1 2007 (n = 43)</th>
<th>P</th>
<th>Absolute difference in proportions % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>7 (17)</td>
<td>10 (23)</td>
<td>0.48</td>
<td>6 (-11 to 23)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>6 (15)</td>
<td>2 (5)</td>
<td>0.15</td>
<td>10 (-3 to 23)</td>
</tr>
<tr>
<td>Other embolisms, n (%)</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td>0.71</td>
<td>3 (-9 to 15)</td>
</tr>
<tr>
<td>Ostitis, n (%)</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>0.35</td>
<td>5 (-4 to 14)</td>
</tr>
<tr>
<td>1 year event-free survival, n (%)*</td>
<td>27 (66)</td>
<td>27 (69)</td>
<td>0.75</td>
<td>3 (-17 to 23)</td>
</tr>
<tr>
<td>PVE, 1-y-event-free survival, n(%)†</td>
<td>9 (64)</td>
<td>11 (69)</td>
<td>1.00</td>
<td>5 (-29 to 39)</td>
</tr>
<tr>
<td>NVE, 1-y-event-free survival, n(%)‡</td>
<td>18 (67)</td>
<td>16 (70)</td>
<td>0.83</td>
<td>3 (-22 to 28)</td>
</tr>
<tr>
<td>Relapse, n (%)</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>0.67</td>
<td>2 (-8 to 12)</td>
</tr>
<tr>
<td>In hospital mortality, n (%)</td>
<td>4 (10)</td>
<td>2 (5)</td>
<td>0.43</td>
<td>5 (-6 to 16)</td>
</tr>
</tbody>
</table>

* Number of patients treated after 1/1-2007 with 1-year follow-up: n = 39.
† Number of patients with PVE and 1-year follow-up in the two groups is 14 and 16, respectively.
‡ Number of patients with NVE and 1-year follow-up in the two groups is 27 and 23 respectively.
Table 4. Main characteristics of patients with relapse of enterococcus faecalis IE treated according to guidelines before 2007 and patients treated according to guidelines after January 1st 2007.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Treated before 2007</th>
<th>Age (years)</th>
<th>Gender (M/F)</th>
<th>PVE late vs. early</th>
<th>Symptoms (days)</th>
<th>Complications</th>
<th>Surgery</th>
<th>Time from discharge to relapse</th>
<th>Relapse treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>76</td>
<td>M</td>
<td>Yes Late</td>
<td>30</td>
<td>None</td>
<td>No</td>
<td>4 months</td>
<td>PNC* and Genta†</td>
<td>Died 9 days after surgery</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>55</td>
<td>M</td>
<td>No</td>
<td>44</td>
<td>Renal impairment</td>
<td>No</td>
<td>10 months</td>
<td>MVR‡ 4 w Amp§</td>
<td>Survivor</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>51</td>
<td>F</td>
<td>No</td>
<td>33</td>
<td>None</td>
<td>Yes</td>
<td>4 months</td>
<td>3 days PNC* and Genta†</td>
<td>Died in shock after 3 days admittance</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>86</td>
<td>M</td>
<td>Yes Late</td>
<td>56</td>
<td>None</td>
<td>No</td>
<td>1 month</td>
<td>6 w PNC* 2 w Gen†</td>
<td>Survivor</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>76</td>
<td>M</td>
<td>No</td>
<td>30</td>
<td>None</td>
<td>No</td>
<td>4 months</td>
<td>6 w Amp§ Moxiflvox™</td>
<td>Survivor</td>
</tr>
</tbody>
</table>

* PNC = Penicillin † = Gentamicin ‡ MVR=Mitral valve replacement § Amp = Ampicillin ‖ Moxiflvox = Moxiflvoxacin
Table 5. Renal function in relation to duration of gentamicin treatment in patients with enterococcus faecalis IE treated according to guidelines before 2007 and patients treated according to guidelines after January 1st 2007.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 2007 (n = 41)</th>
<th>After 1/1 2007 (n = 43)</th>
<th>P</th>
<th>Difference between medians (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin treatment days, median (IQR)</td>
<td>28 (18-42)</td>
<td>14 (7-15)</td>
<td>&lt;0.001</td>
<td>15 (11 to 22)</td>
</tr>
<tr>
<td>eGFR* admittance, median (IQR)</td>
<td>66 (41-95)</td>
<td>75 (52-99)</td>
<td>0.22</td>
<td>-10 (-25 to5)</td>
</tr>
<tr>
<td>eGFR* at 14 days, median (IQR)</td>
<td>57 (40-90)</td>
<td>67 (38-95)</td>
<td>0.65</td>
<td>-10 (-31 to 11)</td>
</tr>
<tr>
<td>eGFR* discharge, median (IQR)</td>
<td>45 (32-75)</td>
<td>66 (50-93)</td>
<td>0.008</td>
<td>-19 (-32 to 5)</td>
</tr>
<tr>
<td>eGFR* change, median (IQR)</td>
<td>-11 (-25 to-3)</td>
<td>-1(-13 to 4)</td>
<td>0.009</td>
<td>9 (2 to 15)</td>
</tr>
</tbody>
</table>

* Measured in ml/min

Figure Legends:

Figure 1. Flowchart showing inclusion of patients with definite left sided enterococcal IE and exclusion of HLAR, E. faecium and patients in dialysis or not treated with gentamicin and penicillin/ampicillin.

Figure 2. Comparison of survival rates between patients treated for enterococcus faecalis IE according to guidelines before 2007 and patients treated according to the new guidelines after January 1st 2007.
124 patients with enterococcal endocarditis

3 Were excluded
1 Possible IE
2 Right sided IE

121 patients with definite left sided enterococcal endocarditis

37 Were excluded
13 HLAR
13 No initial gen + Pc/amp
6 E. faecium
5 Dialysis

84 patients with enterococcus faecalis IE without HLAR

41 patients treated before 1/1 2007

43 patients treated after 1/1 2007

Figure 1
Figure 2

No. at Risk
Bef 1/1-07:  41          32           30         28           28 28 28 28 28
Aft 1/1-07:  43          38           37           35         34        33         31           29   29

Log-Rank p-value = 0.46
Enterococcus Faecalis Infective Endocarditis: A Pilot Study on the Relationship between
Duration of Gentamicin Treatment and Outcome
Anders Dahl, Rasmus V. Rasmussen, Henning Bundgaard, Christian Hassager, Louise E. Bruun,
Trine K. Lauridsen, Claus Moser, Peter Sogaard, Magnus Arpi and Niels E. Bruun

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