Enterococcus faecalis Infective Endocarditis
A Pilot Study of the Relationship Between Duration of Gentamicin Treatment and Outcome

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Background—Because of the nephrotoxic effects of aminoglycosides, the Danish guidelines on infective endocarditis were changed in January 2007, reducing gentamicin treatment in enterococcal infective endocarditis from 4 to 6 weeks to only 2 weeks. In this pilot study, we compare outcomes in patients with Enterococcus faecalis infective endocarditis 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 E faecalis endocarditis in the period of 2002 to 2011 were enrolled. Forty-one patients were treated before and 43 patients were treated after January 1, 2007. There were no significant differences in baseline characteristics. At hospitalization, the 2 groups had similar estimated glomerular filtration rates of 66 and 75 mL/min (P = 0.22). Patients treated before January 2007 received gentamicin for a significantly longer period (28 versus 14 days; P < 0.001). The primary outcome, 1-year event-free survival, did not differ: 66% versus 69%, respectively (P = 0.75). At discharge, the patients treated before 2007 had a lower estimated glomerular filtration rate (45 versus 66 mL/min; P = 0.008) and a significantly greater decrease in estimated glomerular filtration rate (median, 11 versus 1 mL/min; P = 0.009) compared with those treated after 2007.

Conclusions—Our present pilot study suggests that the recommended 2-week treatment with gentamicin seems adequate and preferable in treating non–high-level aminoglycoside-resistant E faecalis infective endocarditis. The longer duration of gentamicin treatment is associated with worse renal function. Although the certainty of the clinical outcomes is limited by the sample size, outcomes appear to be no worse with the shorter treatment duration. Randomized, controlled studies are warranted to substantiate these results. (Circulation. 2013;127:1810-1817.)

Key Words: endocarditis ■ enterococcus ■ gentamicins ■ kidney ■ mortality

In recent series, enterococci were responsible for 8% to 17% of all infective endocarditis (IE) cases.1–4 Enterococci as a pathogen in endocarditis are 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.4–11 IE caused by enterococci is a serious disease with high tolerability to antibiotic-induced killing; theoretically, these IE patients therefore require prolonged administration of a combination of antibiotics with synergistic effects.15–20 However, it is well known that aminoglycosides are nephrotoxic and that prolonged treatment duration increases the risk of renal function impairment.21–24 An important question therefore is whether it is necessary to treat enterococcal IE with gentamicin for as long as 4 to 6 weeks to obtain a sufficient cure rate.

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Clinical Perspective on p 1817

In Denmark, new national guidelines on endocarditis were endorsed in January 2007, reducing gentamicin treatment in enterococcal IE from 4 to 6 weeks to only 2 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 2 tertiary heart centers in Copenhagen, Denmark, were prospectively collected beginning on October 1, 2002. These 2 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 criteria of definite or possible IE. Patients with possible IE were included only if they received treatment as patients with definite IE. All data were collected with a standardized case report form with >250 variables, including demographics; medical history; physical examination findings; results of blood tests, including blood cultures; ECG; antibiotic use; surgical treatment; and findings of both transthoracic and transesophageal echocardiography. Duration of symptoms was defined as the time from the appearance of the first symptoms of IE (reported by the patient or his or her close family) until the time of diagnosis, called the diagnostic delay. Doctor’s delay was defined as the time interval from the first presentation of symptoms to a physician until a final diagnosis was established. The database was approved by the Danish Data Supervisory Committee (journal No. 2011-41-6485).

Study Population

In the present study, we included only patients with definite left-sided Enterococcus faecalis IE who were admitted from October 1, 2002, to October 1, 2011. Patients infected with E faecium or high-level aminoglycoside-resistant (HLAR; minimal inhibitory concentration >256 mg/L) strains were excluded. Only patients initially treated with relevant β-lactam antibiotics (penicillin/ampicillin) combined with gentamicin were included. Patients in dialysis at admission were excluded. This left 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 determinations of the relevant antibiotics were performed at the discretion of the microbiologists. All patients were treated with gentamicin 3 mg/kg (up to 240 mg daily) administered 1 to 3 times daily at the discretion of the treating physician, and each patient had individualized 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 to 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 a recommendation of 4 to 6 weeks of gentamicin treatment to 2 weeks of treatment. This was the only significant change in the guidelines on treating enterococcal IE. Consequently, we divided the patients into 2 groups: 1 group in which the patients were admitted before January 1, 2007 (41 patients) and treated according to the older recommendations and another group in which the patients were admitted after January 1, 2007, and treated according to the new guidelines (43 patients).

Outcome

The primary outcome was 12-month event-free survival, counting from the end of treatment at the day of discharge (ie, 12-month cure defined as no relapse of E faecalis IE and no death during the 12-month follow-up). 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; measured in milliliters per minute) at the time of admission, after 14 days of treatment, and at the time of discharge using the Equations 1 and 2 for men and women, respectively, based on the work by Siersbaek-Nielsen et al and Kampmann et al:

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

(1)

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

(2)

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 July 31, 2012.
Statistics
Continuous data were expressed as mean±SD. When a normal distribution was uncertain, the median and interquartile range were given. Binomial data were expressed as frequencies and percents. The statistical evaluation of the 2 groups was performed with a 2-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 with the χ² test and Fisher exact test as appropriate.

Results
Patient Characteristics
The baseline characteristics for the 2 groups are presented in Table 1. The mean patient age was 70 years in both groups, and male sex was predominant with a 4:1 ratio. Comorbidities were comparable between the 2 groups, including Charlson comorbidity score. There were no significant differences in predisposing factors between the 2 groups. Preexisting valvular disease, including prosthetic valve, was the most predominant predisposition in both groups. At least 1 echocardiogram was performed in all patients, and transeosophageal echocardiography was performed in the vast majority of patients (96%). In both groups, the infection was located most frequently in an aortic location, found in approximately half of the cases, followed by mitral valve IE and left-sided dual-valve IE. There was no difference between the 2 groups with regard to complications on the initial echocardiographic assessment. Pseudoaneurysm or abscess formation was found in 8 patients in each group (Table 1).

Diagnosis and Treatment
The diagnostic delay and doctor’s delay did not differ significantly between the 2 groups (median, 20 versus 30 days; P=0.06) and 10 versus 19 days (P=0.09; Table 2). The duration of hospital stay was also comparable in the 2 groups (42 versus 41 days; P=0.24).

As expected, patients in the group before 2007 received gentamicin for a significantly longer period of time (28 versus 14 days; P<0.001; Table 2). The majority of patients received gentamicin in a once-daily dose before (82%) and after (93%) January 1, 2007. There was no significant difference between groups in once- and twice-daily administration (P=0.18; Table 2). Only a few patients received gentamicin in a thrice-daily regimen. The number of patients undergoing cardiac surgery was similar in the 2 groups (15 versus 14; P=0.70).

Complications and Survival
The primary end point, event-free 1-year survival from discharge, occurred similarly in the 2 groups: in 66% of patients in the group before 2007 and in 69% of patients in the group after January 1, 2007 (P=0.75). The in-hospital mortality was also similar (Table 3). The cumulative 1-year-survival is shown in Figure 2 as a Kaplan-Meier plot. Patients treated after January 1, 2007, had slightly better survival rate than patients treated before January 1, 2007. However, the difference was not statistically significant (log-rank P=0.46). When stratified according to prosthetic valve endocarditis, there was still no difference in the primary end point (Table 3).

There were no significant differences in nonrenal complications between the 2 groups. In both groups, the most prevalent complication was heart failure, followed by stroke and other embolic events (Table 3).

Relapse
A total of 5 patients (6%) had relapse of E. faecalis IE within 1 year from the end of treatment. There was no significant difference in the number of relapses in the 2 groups: 3 relapses (7%) in the patients treated before 2007 and 2 relapses (5%) in the patients treated after January 1, 2007 (P=0.67; Table 3). The main characteristics of the 5 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 >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, 2 of 4 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 patients. One of the 2 patients treated after January 1, 2007, who died 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 E. 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). eGFR at admittance was similar between the 2 groups, with median values of 66 and 75 mL/min (P=0.22). After 14 days, the eGFR was 57 and 67 mL/min, still without significant difference (P=0.65). At discharge, however, there was a significant difference in eGFR (median, 45 versus 66 mL/min; P=0.008); the change in eGFR also differed significantly (median, −11 versus −1 mL/min; P=0.009; Table 5).

Discussion
The principal finding of our present pilot study is that antibiotic treatment of non-HLAR E. faecalis IE starting out with a β-lactam combined with 2 weeks of gentamicin appears to provide event-free survival similar to a combination with 4 to 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; therefore, it can be challenging to
treat enterococcal IE. Since the middle of the last century, in vitro studies, animal studies, and many patient reports have demonstrated a synergistic effect with better cure rates when a β-lactam antibiotic is combined with an aminoglycoside. Therefore, this combination has been widely used worldwide, and with 4 to 6 weeks of treatment, 3-month cure rates of ≈80% have been achieved. Interestingly, in 2007, Gavaldà and colleagues presented an alternative treatment with a 3-month cure rate of 67%, concluding that it could be a reasonable alternative for patients infected with HLAR enterococcal IE. They treated 43 patients and obtained a cure rate of 81% and reviewed the 15 fatal episodes during hospitalization without finding a direct connection to nephrotoxicity or with increased risk of nephrotoxicity.

AHA and ESC guidelines on enterococcal IE recommend a standard of 4 weeks of combined antimicrobial therapy with penicillin (or ampicillin) and gentamicin. If the patient has prosthetic valve IE or the duration of symptoms has been >3 months, the recommendation is 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 found no significant difference in cure rates (80% versus 69%) between 10 patients receiving combined treatment with an aminoglycoside and a cell wall inhibitor (penicillin or vancomycin) for <4 weeks (mean, 23 days) and 16 patients treated with synergistic therapy for >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 1990s, a shortened 2- to 3-week course of aminoglycoside treatment combined with 4 to 6 weeks of β-lactam treatment has often been used in clinical practice in Sweden to minimize nephrotoxic or ototoxic adverse events. A study by Olaison and Schadewitz 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 a direct connection to

### 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, 2007

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 2007 (n=41)</th>
<th>After January 1, 2007 (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, mean (SD), y</td>
<td>70 (12)</td>
<td>70 (11)</td>
<td>0.88</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>32 (78)</td>
<td>38 (88)</td>
<td>0.20</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity 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>
</tbody>
</table>

### 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>Variable</th>
<th>Before 2007 (n=41)</th>
<th>After January 1, 2007 (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic delay, median (IQR), d</td>
<td>20 (14–32)</td>
<td>30 (16–48)</td>
<td>0.06</td>
</tr>
<tr>
<td>Doctors delay, median (IQR), d</td>
<td>10 (5–24)</td>
<td>19 (7–36)</td>
<td>0.09</td>
</tr>
<tr>
<td>Symptoms for &gt;3 mo, n (%)</td>
<td>1 (2)</td>
<td>2 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gentamicin treatment, median (IQR), d</td>
<td>28 (18–42)</td>
<td>14 (7–15)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 3. Duration of Hospital Stay, Gentamicin Treatment Duration, Dosing Interval, and Frequency of Surgical Treatment in *Enterococcus faecalis* IE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 2007 (n=41)</th>
<th>After January 1, 2007 (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications for surgery, n†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure resulting from valve destruction</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Abscess, pseudoaneurysm, 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 second- or third-degree AV block</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

AV indicates atrioventricular; IE, infective endocarditis; IQR, interquartile range; and PVE, prosthetic valve endocarditis.

*When comparing once- or twice-daily administration of gentamicin between the 2 groups.
†Some patients had >1 indication for surgery; therefore, the total number of indications is larger than the number of patients operated on.
the shortened synergistic therapy. However, as the authors recognized, 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 to 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 2 large groups of consecutive patients with *E faecalis* IE treated similarly except for the different duration of gentamicin administration. Our data show a highly significant decrease in the duration of gentamicin treatment in the group of patients treated after January 1, 2007, indicating that the new recommendations were effectively implemented.

The 2 groups were comparable in baseline characteristics, especially with respect to age and comorbidities. The 12-month cure rate was similar between patients treated according to the new guidelines and patients treated before 2007. Six patients died during hospitalization: 4 treated by the old guidelines and 2 treated by the new guidelines. A careful review of these

### 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 1, 2007

<table>
<thead>
<tr>
<th>Complications</th>
<th>Before 2007 (n=41), n (%)</th>
<th>After January 1, 2007 (n=43), n (%)</th>
<th>P Value</th>
<th>Absolute Difference in Proportions, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>7 (17)</td>
<td>10 (23)</td>
<td>0.48</td>
<td>6 (−11 to 23)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (15)</td>
<td>2 (5)</td>
<td>0.15</td>
<td>10 (−3 to 23)</td>
</tr>
<tr>
<td>Other embolisms</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td>0.71</td>
<td>3 (−9 to 15)</td>
</tr>
<tr>
<td>Ostitis</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>0.35</td>
<td>5 (−4 to 14)</td>
</tr>
<tr>
<td>1-y event-free survival*</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†</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‡</td>
<td>18 (67)</td>
<td>16 (70)</td>
<td>0.83</td>
<td>3 (−22 to 28)</td>
</tr>
<tr>
<td>Relapse*</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</td>
<td>4 (10)</td>
<td>2 (5)</td>
<td>0.43</td>
<td>5 (−6 to 16)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; IE, infective endocarditis; NVE, native valve endocarditis; and PVE, prosthetic valve endocarditis.

*Number of patients treated after January 1, 2007, with 1-year follow-up: n=39.
†Number of patients with PVE and 1-year follow-up in the 2 groups: 14 and 16.
‡Number of patients with NVE and 1-year follow-up in the 2 groups: 27 and 23.

![Figure 2. Comparison of survival rates between patients treated for Enterococcus faecalis infective endocarditis according to guidelines before 2007 and patients treated according to the new guidelines after January 1, 2007.](http://circ.ahajournals.org/)

No. at Risk
Before 2007: 41
After 1/1-07: 43
After 1/1-07: 34 33 31 30 29 29

Log-Rank p-value = 0.46

Time since end of treatment (days)
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 1, 2007

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treated Before 2007</th>
<th>Age, y</th>
<th>Sex</th>
<th>PVE, Late vs Early</th>
<th>Symptoms, d</th>
<th>Complications</th>
<th>Surgery</th>
<th>Time From Discharge to Relapse, mo</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</td>
<td>PNC and Genta, MVR</td>
<td>Died 9 d 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</td>
<td>4 wk 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</td>
<td>3 d PNC and Genta</td>
<td>Died in shock after 3-d 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</td>
<td>6 wk PNC, 2 wk Genta</td>
<td>Survivor, lifelong antibiotic</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</td>
<td>6 wk Amp and Moxiflox</td>
<td>Survivor, lifelong antibiotic</td>
</tr>
</tbody>
</table>

Amp indicates ampicillin; Genta, gentamicin; IE, infective endocarditis; Moxiflox, moxifloxacin; MVR, mitral valve replacement; and PNC, penicillin.

despite the lack of evidence that any of them were related to abbreviated gentamicin treatment. In our study, we found no evidence of an association between relapse and prosthetic valve endocarditis symptoms for >3 months and 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. On the basis of older studies, 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 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 showed only partial reversibility in renal impairment of IE patients during hospitalization, with full restitution in 64% of the patients. The longer the patients were treated with gentamicin, the greater the reduction in eGFR was; among the patients with the greatest decline, only 35% obtained restitution of renal function at follow-up. A decrease in renal function in IE patients can also be caused, for example, by glomerulonephritis, septic embolisms, and interstitial nephritis. The 2 groups in the present study were very similar and were all infected with E. faecalis. Therefore, we find it most unlikely that a difference in the occurrence of these renal complications plays an important role in the observed difference in the change of eGFR between the 2 groups. In IE, it is recommended that gentamicin be administered in 2 to 3 daily doses (AHA/ESC guidelines). However, the killing effect of gentamicin is related to peak plasma concentration; therefore, in other septic diseases, gentamicin is given once daily. In a randomized trial of IE with 53Cr-EDTA clearance used as a measure of GFR, we demonstrated that a once-daily gentamicin dosing regimen had an efficacy and a nephrotoxic effect similar to those of a twice-daily regimen. Therefore, the simpler once-daily gentamicin regimen is now recommended for IE treatment in Denmark.

Other studies have shown that renal function at the time of admission is an independent predictor of mortality in patients with IE and in patients with left-sided heart failure. 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 excluded, but HLAR is a serious and increasing problem in enterococcal endocarditis, with reports indicating that up to 28% to 48% of patients are affected. Decreasing aminoglycoside treatment duration is one important way to limit further the development of HLAR.

**Implications**

Because the length of aminoglycoside treatment has never been 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 the duration of aminoglycoside treatment in E. faecalis IE should be revisited.

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 1, 2007

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 2007 (n=41)</th>
<th>After January 1, 2007 (n=43)</th>
<th>PValue</th>
<th>Difference Between Medians (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin treatment, median (IQR), d</td>
<td>28 (18 to 42)</td>
<td>14 (7 to 15)</td>
<td>&lt;0.001</td>
<td>15 (11 to 22)</td>
</tr>
<tr>
<td>eGFR admittance, median (IQR), mL/min</td>
<td>66 (41 to 95)</td>
<td>75 (52 to 99)</td>
<td>0.22</td>
<td>−10 (−25 to 5)</td>
</tr>
<tr>
<td>eGFR at 14 days, median (IQR), mL/min</td>
<td>57 (40 to 90)</td>
<td>67 (38 to 95)</td>
<td>0.65</td>
<td>−10 (−31 to 11)</td>
</tr>
<tr>
<td>eGFR discharge, median (IQR), mL/min</td>
<td>45 (32 to 75)</td>
<td>66 (50 to 93)</td>
<td>0.008</td>
<td>−19 (−32 to 5)</td>
</tr>
<tr>
<td>eGFR change, median (IQR), mL/min</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>

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; IE, infective endocarditis; and IQR, interquartile range.
Limitations
Although our study is not a randomized, clinical trial, it is a prospectively collected consecutive cohort with a historical control group. The study period was 4 years before and after January 1, 2007. The relatively short time period favors standardized treatment regimens, with only a few changes over time. Our results are limited by the size of the cohorts, and because of the lack of sufficient power, our results need to be interpreted with caution. Nevertheless, we present the largest investigation so far of the relationship between gentamicin treatment and 1-year outcome in E. faecalis IE.

According to the power calculation, a randomized clinical trial of E. faecalis IE treatment would require several hundred patients. Because it is quite rare, such a trial would be difficult to complete.

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

Conclusions
Our present pilot study suggests that the recommended 2-week treatment with gentamicin seems adequate and preferable in treating non–high-level aminoglycoside-resistant E. faecalis infective endocarditis. The longer duration of gentamicin treatment is associated with worse renal function. Although the certainty of the clinical outcomes is limited by the sample size, outcomes appear to be no worse with the shorter treatment duration. Randomized, controlled studies are warranted to substantiate these results.

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Disclosures
None.

References
Reduced renal function is in general an indicator of an ominous outcome. Therefore, reducing the duration of gentamicin treatment should be considered in these patients. Reduced renal function is in general an indicator of an ominous outcome. Therefore, reducing the duration of gentamicin treatment should be considered in these patients.

Our study indicates that 2 weeks of gentamicin treatment might be adequate and preferable for treating patients with Enterococcus faecalis infective endocarditis. The data apply to patients with symptom duration of <3 months. Our results show equal cure rates and survival between patients treated with gentamicin for a median of 14 days and those treated for a median of 28 days. However, a progressive decline in renal function was revealed only during the prolonged gentamicin treatment. Reduced renal function is in general an indicator of an ominous outcome. Therefore, reducing the duration of gentamicin treatment should be considered in these patients.
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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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