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Comment on: Prosthetic hip joint infection with a *Streptococcus agalactiae* isolate not susceptible to penicillin G and ceftriaxone

Parham Sendi[1–3]* and Werner Zimmerli[3]

[1]*University Clinic for Infectious Diseases, University Hospital Bern, Bern, Switzerland;* [2]*Institute for Infectious Diseases, University of Bern, Bern, Switzerland;* [3]*Unit of Infectious Diseases, Basel University Medical Clinic, Liestal, Switzerland*

*Corresponding author. Tel: +41-31-632-32-99; Fax: +41-31-632-87-66; E-mail: sendi-pa@magnet.ch

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Sir,

Gaudreau *et al.*[1] reported a case of group B *Streptococcus* (GBS) periprosthetic joint infection (PJI) that was treated with oral penicillin (300 mg once daily), but without surgical intervention. After 3 years of suppressive therapy, GBS infection relapsed, and the isolate revealed reduced penicillin susceptibility. A similar case was recently reported by Longtin *et al.*[2] After 5 years of suppressive therapy, the obtained isolate revealed reduced penicillin susceptibility, although they identified different mutations from those described in the case reported by Gaudreau *et al.*[1] The mutations in the ligand-binding regions of penicillin-binding proteins probably caused the reduced susceptibility.[2]

We recently analysed treatment concepts and outcome in GBS PJI,[3] and we would like to comment on oral suppressive therapy as a treatment strategy without surgical intervention. In PJI due to GBS and other penicillin-susceptible streptococci, controlling the infection may be particularly difficult with this strategy. Penicillin MICs for GBS mostly range between 0.016 and 0.125 mg/L.[4] An oral dose of 500 mg of penicillin optimally reaches a peak serum concentration of 3 mg/L.[5] The bone/serum concentration ratios for penicillin are between 0.1 and 0.3.[6] When extrapolating these results, 300 mg of penicillin reaches a peak concentration of 0.18–0.54 mg/L at the infection site. Of note, the population at risk for GBS PJI frequently has one or more comorbidities (e.g. diabetes mellitus),[3] and enteral absorption may be reduced. For antimicrobial efficacy, a daily time above the MIC ($T>$MIC) of at least 40% should be targeted.[7] These microbiological and pharmacological variables should be taken into account when evaluating a treatment concept for PJI due to penicillin-susceptible streptococci. In our view, $T>$MIC $\geq$40% cannot be reached with 300 mg of oral penicillin once daily, in particular when considering its peak level and short half-life in serum (i.e. 30 min).[5] Moreover, GBS build biofilm and high penicillin concentrations are required for GBS eradication.[8] Thus, in PJI treated with suppressive oral penicillin without surgical intervention, a high inoculum of GBS at the infection site is exposed to subinhibitory concentrations of penicillin. This may lead to a selection pressure and result in the occurrence of mutations, causing reduced susceptibility to penicillin.

In an algorithm for PJI treatment, the recommended dose and duration of antimicrobial therapy differ for a 'curative' and a 'suppressive' approach.[9] In our clinics, the latter option is limited to very few patients who are unable to undergo surgery (e.g. they have a bad general condition or surgery is contraindicated). It is a palliative approach, since the infection is suppressed and not cured. Notably, suppressive therapy without surgery often goes along with functional impairment of the joint. However, in such cases we prefer amoxicillin because of its better bioavailability compared with penicillin. An oral dose of 500 mg of amoxicillin reaches a peak serum concentration of 8 mg/L and has a half-life in serum of up to 2 h.[5] Therefore, we often recommend 500–1000 mg 8 hourly. However, the optimal amoxicillin dosing for suppressive therapy is difficult to estimate, because the correct balance between suppressing the infection and minimizing the potential side effects of long-term antibiotic treatment can vary among patients. Following the same line of reasoning, and, hence, based on patient selection for suppressive therapy, treatment duration should be as long as necessary, but as short as possible. In PJI cases that are treated without debridement, it is plausible to stop treatment after 9–12 months and closely monitor the further clinical course.[10] If signs of relapse occur after discontinuation of antibiotic treatment, surgical and/or suppressive treatment must be reevaluated.

Given the worrisome reports on GBS and other streptococci with reduced penicillin susceptibility, PJI treatment strategies should avoid a drug selection pressure over many years.

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