We share Nsutebu and Hobson’s concerns about the issue of selection bias and the presence of potential confounders, given the observational nature of our study, and we stated those limitations in the discussion section of our work [2]. In Nsutebu and Hobson’s view, loosening of the prosthesis and 2-stage exchange surgery are factors associated with more-severe disease. Both of these variables were more common in the combination therapy group. To our knowledge, periprosthetic loosening has not been identified as a marker of disease severity. In our study population, the presence of loosening was not a risk factor for failure ($P = .5$ and $P = .3$ in the monotherapy and combination therapy groups, respectively). A stratified analysis based on the presence of loosening did not reveal a difference in outcome between monotherapy and combination therapy groups ($P = .08$). Furthermore, when therapy was stratified by type of surgery, no difference in outcome between the combination therapy group and the monotherapy group was observed (table 1).

We do believe, on the basis of our study and clinical experience, that monotherapy may be sufficient, in combination with aggressive surgical treatment and the use of local antimicrobial therapy, for the management of the majority of penicillin-susceptible enterococcal prosthetic joint infections. Combination therapy may still be the best choice for the treatment of patients with concomitant bacteremia or metastatic infection. A randomized controlled trial will further strengthen this conclusion, but given the rarity of this disease, such a trial will be difficult to conduct.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Percentage of patients</th>
<th>Monotherapy</th>
<th>Percentage of patients</th>
<th>Survival rate, % (95% CI)</th>
<th>Combination therapy</th>
<th>Percentage of patients</th>
<th>Survival rate, % (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Stage exchange</td>
<td>17</td>
<td>53</td>
<td>100 (74–100)</td>
<td>47</td>
<td>87 (64–100)</td>
<td>3</td>
<td>36</td>
<td>74 (42–100)</td>
<td></td>
</tr>
<tr>
<td>Debridement and retention of the prosthesis</td>
<td>5</td>
<td>100</td>
<td>80 (45–100)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Resection arthroplasty</td>
<td>22</td>
<td>64</td>
<td>77 (48–100)</td>
<td>36</td>
<td>74 (42–100)</td>
<td>6</td>
<td>36</td>
<td>74 (42–100)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Survival at 2 years, stratified by type of surgery.**

**Acknowledgments**

_Potential conflicts of interest_ All authors: no conflicts.

Odette C. El Helou, Elie F. Berbari, and Douglas R. Osmon
Department of Internal Medicine, Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota

**References**


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**Tuberculosis Transmission from Patients with Smear-Negative Pulmonary Tuberculosis in Sub-Saharan Africa**

To the Editor—We read with interest the report by Tostmann et al. [1] of a national study of tuberculosis (TB) transmission in The Netherlands from 1996 through 2004. The relative TB transmission rate among patients with smear-negative, culture-positive pulmonary disease, compared with patients with smear-positive disease, was found to be 0.24. Overall, 13% of TB transmission events were attributable to source patients with sputum smear-negative, culture-positive disease. These important findings are in close agreement with similar studies from San Francisco, California, and Vancouver, British Columbia [2, 3], collectively showing that in high-income countries, 10%–20% of TB transmission at the population level is attributable to source cases with smear-negative pulmonary TB. Tostmann et al. [1] speculated on the relevance of their data for countries in which HIV infection is endemic and rates of smear-negative TB disease are high.

In sub-Saharan Africa, HIV infection has had a devastating impact on TB control [4, 5]. In a study of a community in a township in Cape Town, South Africa, for example, the antenatal HIV seroprevalence rate is ~30%, and the annual TB notification rate has increased to >1500 cases per 100,000 population [5]—almost 200-fold higher than TB rates in The Netherlands [4]. This has been associated with a major and disproportionate increase in the rate of smear-negative disease among HIV-infected individuals [5]. Moreover, the prevalence of undiagnosed TB (a key determinant of transmission) among HIV-infected patients in this community is very high, and disease duration before diagnosis is prolonged [6]. In view of these observations, transmission attribi-
utable to smear-negative pulmonary TB cases at the community level may be important.

Antiretroviral treatment services continue to expand in sub-Saharan Africa [7]. The high burden of TB in these clinical settings presents a great challenge with regard to morbidity, mortality, and risk of TB transmission [8, 9]. Nosocomial outbreaks of both drug-susceptible and drug-resistant TB virus constitute a major threat [10]. In a recent study in an antiretroviral treatment service in Gugulethu Township, Cape Town, we did routine microbiological screening for TB in all newly referred antiretroviral treatment-naïve patients who had not already received a diagnosis of TB. Using automated MGIT 960 liquid culture (Becton Dickinson) of sputum, we found that >25% of patients had culture-confirmed pulmonary TB [11]. In this highly immunocompromised patient group, however, >80% of this disease was sputum smear-negative despite use of fluorescence microscopy; culture-based diagnosis took >3 weeks, on average. Recurrent attendance of patients at these overcrowded facilities over a period of several weeks while their TB remains undiagnosed represents an unacceptable hazard. These data have important implications for screening for TB among patients entering HIV care and treatment services in Africa. Rapid and appropriate diagnostic tests that are able to detect smear-negative pulmonary TB are urgently needed to reduce risk of transmission in these clinical environments.

In summary, we suspect that TB transmission associated with smear-negative culture-positive TB in communities in Africa with high HIV prevalence may be important, especially in the context of antiretroviral treatment services, where this is the preponderant form of TB.

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Stephen D. Lawn,1,2 David Edwards,1 and Robin Wood1

1Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; and 2Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

References


Placental Malaria Increases Malaria Risk in the First 30 Months of Life: Not Causal

To the Editor—Schwarz et al. [1] have observed an association between placental malaria and increased risk of malaria in early childhood. However, this association is unlikely to be causal and may in fact be entirely the result of confounding [2].

In the study area, transmission of malaria occurred at a low rate and was focal, which is demonstrated by the facts that only 17% of the cohort ever experienced a malaria episode and that the place of residence was strongly associated with the risk of placental malaria. The estimated entomological inoculation rate of 50 infectious bites per year is likely greater than the transmission rate that the study cohort faced. These factors together lead one to the conclusion that the observation of increased risk of malaria in early childhood among the offspring of women with placental malaria is largely, if not solely, attributable to the fact that the mothers with placental malaria were the ones who lived in the foci of malaria transmission; therefore, their children are the children who experienced malaria. The authors argue against this by stating that there was a difference between multigravidae and primigravidae; however, the numbers are too small to make these judgements.

Studies of this sort need to measure the force of infection at the individual level and compare groups with equal exposure.