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Bacteremia Due to Oral Viridans Streptococci in Neutropenic Patients with Cancer: Cytostatics Are a More Important Risk Factor than Antibacterial Prophylaxis

SIR—In their recent article Bochud et al. [1] stated that "the fluoroquinolones are frequently used as prophylaxis for patients with cancer . . . and bacteremia due to these microorganisms has been observed under this prophylactic regimen." They also stated that the problem of viridans streptococcal bacteremia ". . . is probably related to the use of quinolones as antibacterial prophylaxis." However, the references chosen to support these statements were incorrect since Cohen et al. [2] and Henslee et al. [3] reported that bacteremia developed exclusively while the patients were receiving co-trimoxazole prophylaxis, which was also the antimicrobial given to most of the patients described by Weisman et al. [4] and Elting et al. [5].

During 1986–1989, bacteremia due to oral viridans streptococci (OVS) developed in 94 (28%) of 341 neutropenic episodes that occurred in adults treated for hematologic malignancies at our center. Although both ciprofloxacin and co-trimoxazole plus colistin had been given as prophylaxis, bone marrow transplant (BMT) recipients had all been given ciprofloxacin (table 1), so the impact of each regimen on the development of OVS bacteremia could only be assessed for those treated with cytostatic chemotherapy.

Bacteremia due to OVS occurred in 23 (14%) of 168 neutropenic episodes in which co-trimoxazole plus colistin had been given as prophylaxis compared with 16 (22%) of 74 episodes in which ciprofloxacin had been given ($P = .175$; not significant). When the dose of cytarabine (cytosine arabinoside) is taken into account, the incidence of OVS bacteremia among those given >1 g/[$m^2 \cdot d$] was ~30%, whether patients had received the quinolone or co-trimoxazole. In contrast, when a lower dose of cytarabine or an altogether different regimen had been used, twice as many patients developed bacteremia after receiving prophylaxis with ciprofloxacin than did those who had received the alternative regimen, although the incidence was only one-half that observed with the higher dose of cytarabine. However, rates of bacteremia, even after administration of the higher dose of cytarabine, were still markedly lower than that (56%) for 99 allogeneic BMT recipients during the same period ($P < .001$). This remarkably high rate was attributed to the occurrence of severe oromucositis as a result of using the more-intensive conditioning regimen that included anthracyclines, particularly idarubicin [6], in conjunction with total body irradiation and cyclophosphamide [7]. Those patients who underwent conditioning for transplantation without additional anthracyclines experienced a rate of OVS bacteremia similar to that for patients treated with cytarabine (>1 g/[$m^2 \cdot d$]). Thus, the higher dose of cytarabine and, moreover, the use of idarubicin had a much greater influence on the development of OVS bacteremia than did the prophylactic regimen. Only when lower doses of cytarabine or other cytostatics were used did the negative impact of ciprofloxacin prophylaxis become clearer.

It is also of interest that the majority of strains that were isolated from BMT recipients and that could be adequately identified to the species level with use of the API Strep system (BioMérieux, Marcy l'Etoile, France) were identified as *Streptococcus oralis*, while the majority of those isolated from non-BMT patients were *Streptococcus mitis*. This finding corresponds to that of McWhinney et al. [8]. Idarubicin induces severe and

Table 1. The impact of administering cytostatic regimens plus ciprofloxacin or co-trimoxazole on the development of bacteremia due to oral viridans streptococci in BMT recipients at University Hospital Nijmegen, 1986–1989.

	No. of patients receiving indicated prophylactic agent/total no. of patients receiving cytostatic chemotherapy (%)	
Cytostatic chemotherapy	Ciprofloxacin	Co-trimoxazole/colistin
Allogeneic BMT conditioning regimen		
Idarubicin + standard*	47/77 (61)	. . .
Standard only*	8/22 (36)	. . .
Cytoreductive therapy with:		
Cytarabine > 1 g/($m^2 \cdot d$)	12/37 (32)	14/50 (28)
Cytarabine < 1 g/($m^2 \cdot d$)	2/26 (8)	4/64 (6)
No cytarabine	2/11 (18)	5/54 (9)
Total	71/173 (41)	23/168 (13)

NOTE. BMT = bone marrow transplant.
* The standard conditioning regimen is total body irradiation and cyclophosphamide.

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protracted oromucositis in BMT recipients [7, 9] that is of quite a different character than the milder form induced by cytarabine. In contrast, high doses of cytarabine can be profoundly toxic to the gut and lungs [10]. The colonization of the stomach or digestive tract might therefore provide the alternative portal of entry that Bochud and colleagues suggested. Extensive colonization of the stomach and the small intestine would also be facilitated by any H2 antagonists used to manage the dyspepsia that frequently occurs following cytostatic chemotherapy.

The use of these agents was also implicated by Elting and associates [5] as a significant risk factor for the development of the so-called alpha strep shock syndrome. Moreover, patients with oromucositis tend to swallow large volumes of slimy mucus, which may assist in protecting the oral streptococci. Therefore, the presence of gastrointestinal colonization in patients with bacteremia due to *S. mitis* might explain why only a minority of these patients go on to develop the alpha strep shock syndrome; the microbial load may well be sufficient to elicit the release of cytokines that are necessary to induce sepsis syndrome, adult respiratory distress syndrome, and, in some cases, fatal multiorgan failure.

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Reply

SIR—We agree with Donnelly et al. that bacteremia due to oral viridans streptococci (OVS) in neutropenic patients with cancer has occurred not only while the patients were receiving prophylaxis with fluoroquinolones but also while they were receiving other prophylactic antibiotic regimens. This finding was inadvertently omitted in our text but cited in the references. The interesting data of Donnelly et al. as well as data from other centers, including ours, clearly suggest that aggressive cytostatic chemotherapy is probably the key factor predisposing neutropenic patients to OVS bacteremia. However, it appears clear that several widely used prophylactic agents, including fluoroquinolones and co-trimoxazole, are not effective in preventing OVS bacteremia. Moreover, OVS bacteremia was practically unknown before the use of these prophylactic regimens, and two case-control studies have shown an association between the use of quinolones or co-trimoxazole and the occurrence of OVS bacteremia [1, 2]. Thus, certain prophylactic antibiotics may not only be ineffective in preventing OVS bacteremia, but they may also alter the endogenous bacterial flora in a way that predisposes susceptible patients to the infection.

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