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Prophylaxis and Empiric Therapy for Streptococcal Infections in Febrile Neutropenic Patients

THERE HAS been a progressive change in the microbiological nature of bacterial infections in neutropenic patients. During the past decade, sepsis caused by gram negative pathogens has been replaced by infections due to gram positive organisms, namely various streptococcal strains.

This evolution poses new questions about the management of the febrile patient with granulocytopenia; time-honoured attitudes have to be evaluated again and new approaches towards prophylaxis and therapy must be designed.

Streptococcal septicaemia is frequent in both neutropenic adults and children (respectively, 20% and 40%, at least, of all cases of bacteraemia). The morbidity and the mortality attributed to these infections have been probably underestimated in the literature. Retrospective studies indicate mortality rates of approximately 10–15%. In addition, these infections are expensive in terms of use of antibiotics, nursing care, associated treatments, days of hospitalisation and overall suffering. Consequently, prophylaxis might have a critical role in patients exposed to clinical situations known to predispose to these infections.

A large scale prophylactic study is presently being conducted by the EORTC Antimicrobial Therapy Cooperative Group and has entered 700 patients to date. This double-blind investigation includes oral administration of pefloxacin, associated with either a placebo or penicillin V. Data from this EORTC study are not available so far but they will be instrumental in designing new therapeutic attitudes and/or studies. However, it should be stressed that while pneumococci are sensitive to penicillin V, this is not the case for all streptococci, and in particular *Streptococcus anginosus*, for which the minimum inhibitory concentrations (MICs) are 10 times higher. Penicillin resistant streptococci, as well as tolerance to penicillin by these organisms have been reported as well. As far as glycopeptides are concerned, a pilot study of healthy non-neutropenic volunteers used the oral administration of teicoplanin for 3 weeks [1]. In the stools, a marked rise was noted for staphylococci (*Staph. haemolyticus* and *Staph. epidermis*) with an elevated MIC to teicoplanin; the decrease in streptococci in the stools after the start of treatment was followed by an increase due to the selection of *Escherichia faecium*, and a high level of *E. faecium* was still detectable 1 week after the cessation of treatment. These *E. faecium* are potential carriers of an autotransmissible and inductible plasmids; the gene appears identical to that coding for resistance to vancomycin in *E. faecalis*.

The rise observed recently in the frequency of streptococcal septicaemia among neutropenic patients coincides with the increased use of quinolones—to which most streptococci are resistant—for prophylactic purposes, e.g. gastrointestinal tract decontamination. However, this emergence of streptococci has also been reported in institutions that do not use quinolones for prophylaxis and infections due to streptococci have become common on paediatric services where no quinolones are prescribed. Moreover, prophylactic trials comparing quinolones with a placebo have revealed similar rates of gram positive infections [2]. Thus, the avoidance of quinolones for prophylaxis of gram negative infections in granulocytopenia patients would probably not eliminate the problem posed by streptococci. Controlled trials comparing the efficacy of quinolones for the decontamination of the gastrointestinal tract with other regimens have demonstrated that quinolones can reduce significantly the frequency of gram negative infections. Other prophylactic approaches (cotrimoxazole, vancomycin–gentamicin, etc) but not quinolones can reduce the frequency of infections caused by gram positive pathogens as well. However, these regimens are much less well tolerated than quinolones.

Since the main sanctuaries for streptococci is the mucosa of the oropharynx (*Strep. mitis*, *Strep. sanguis*, *Strep. salivarius* and *Strep. anginosus*), of the gastrointestinal tract (enterococci) and of the vagina (*Strep. anginosus*) future research should investigate

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the possibility to prevent mucosal damage, in order to reduce portals of entry for the streptococci and prevent systemic infection.

Several studies have demonstrated that sucralfate might afford protection for the oral and gastric mucosa, and preliminary studies suggest also that epidermal growth factor might be useful for the prevention and treatment of cytotoxic mucosal lesions. The use of the soft laser at the Centre Antoine-Lacassagne in Nice for both preventive and curative purposes has given encouraging results for chemotherapy-induced mucositis as have various topical ointments. However, controlled trials have yet to be performed with all these various approaches to prevent mucositis and subsequent streptococcal infection in neutropenic patients.

Herpes infections also appear to be potentially responsible for streptococcal sepsis in neutropenic patients; streptococci adhere well to herpes-infected cells, and prior incubation of these cells with an antiherpes antibody prevents bacterial adherence. Preliminary studies suggest that streptococcal septicaemias have nearly disappeared since the introduction of acyclovir for prophylactic purposes in transplant recipients [3]. These findings must, however, be confirmed by prospective studies. The avoidance of chemotherapy regimens known to alter profoundly the digestive tract mucosa might also help to reduce the frequency of streptococcal infections.

Given the low mortality rates reported for streptococcal bacteraemias, many clinicians feel that these infections are relatively trivial and that empirical prescription of a glycopeptide to a neutropenic patient presenting fever is not as mandatory as the coverage of gram negative sepsis. As already mentioned, the mortality rate for streptococcal septicaemia might actually be close to 15%; moreover, overall morbidity is considerable especially when serious complications, such as adult respiratory distress syndrome, occur.

The accepted empiric approach today, in febrile granulocytopenic patients, is the administration of a third-generation cephalosporin, with or without an aminoglycoside, with vancomycin being prescribed only for microbiologically proven gram positive infections [4]. An alternative might be a full coverage from the start; in other words, a cephalosporin (with or without an aminoglycoside) plus a glycopeptide, with prompt discontinuation of some of these components as a function of the microbiological and clinical results. So far, several studies have indicated an advantage of early empiric administration of vancomycin to febrile neutropenic patients in terms of clinical response [5–7].

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Patients Excluded from Entry to Clinical Trials

MOST PATIENTS are not entered into a clinical trial, either because the treating clinician is not participating in a trial relevant to their disease; because the patient is ineligible for entry to such a study; or, despite being eligible, the patient is not entered for a number of reasons.

Langley *et al.* [1] interviewed 52 clinical oncologists, including all available radiation and medical oncologists at two large cancer treatment centres in Toronto. During the interview, a questionnaire was completed in which the oncologists were asked to rank the factors that affected the decision to offer or not to offer trial entry to patients, and to specifically enquire about the relative importance of three variables, *viz.*, the scientific design of the study, the effect on doctor–patient rapport, and the ease of obtaining informed consent. Of 51 oncologists who completed the relevant section of the questionnaire, 47 (92%) ranked the scientific design as being the most important factor in determining their decision whether or not to participate in a trial. Only 3 (6%) put doctor–patient rapport first, and just 1 (2%) ranked difficulty in obtaining informed consent as being the most important factor. This study did not focus on a particular clinical trial, of course, and in this context the oncologists felt that the scientific quality and importance of the question being asked was the most important determinant of their decision about participation in a trial.

Taylor *et al.* [2] considered the rather different question as to why clinicians did not enter all eligible patients into a trial in which they were participating—the US National Surgical

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