Journal of Antimicrobial Chemotherapy (1999) **44**, 587–591

JAC

Leading article

The prophylaxis of bacterial infections in neutropenic patients

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Bacterial sepsis remains a major cause of morbidity and mortality in patients rendered neutropenic following cytoreductive therapy for haematological malignancy. The introduction of more aggressive anti-neoplastic chemotherapeutic regimes in individuals with solid organ malignancies has resulted in increasing numbers of these patients experiencing the profound neutropenia (i.e. granulocyte counts of $<0.1 \times 10^9$/L) that puts them at risk of infection. It is now over 30 years since Bodey *et al.*, in a landmark paper,[1] first quantified the risk of infection associated with severe neutropenia. Throughout this period much effort and considerable economic resources have been expended on developing effective approaches to prevent infection by bacteria and other microorganisms in this setting. Many of these strategies have fallen out of favour, having foundered on grounds of expense, patient unacceptability and consequent problems with compliance, and a lack of convincing scientific evidence to support their efficacy. One practice that has proved more durable than most is the use of antibacterial prophylaxis (ABP). This approach is not without its detractors and, given the problems attributed to ABP that have emerged in recent years, a re-examination of its risks and benefits is warranted.

When ABP was first introduced, Gram-negative bacteria—particularly members of the Enterobacteriaceae and *Pseudomonas aeruginosa*—were the most important bacterial pathogens encountered in neutropenic patients; infections were associated with significant case-fatality rates. Many of these bacteraemias were deemed to be autocthonous in origin, with the gut being the most likely source. The concept of 'colonization resistance', which underpinned the rationale for ABP, was developed by van der Waaij and co-workers[2] (reviewed in reference 3) following observations in laboratory animals. Mice with their own normal gut flora were able to resist colonization when challenged by exogenous Gram-negative aerobic bacteria, unless these were administered in very high doses. Conversely, in gnotobiotic mice, colonization was achieved by inocula of 10–100 organisms. Germ-free mice that had first been colonized by anaerobic flora were able to resist colonization nearly as well as normal controls. Extrapolating this concept to humans, it was argued that prevention of infection from gut-derived Gram-negative bacteria during neutropenia could be achieved by administering antimicrobials that would selectively target these bacteria and that would leave the 'beneficial' anaerobes intact. Initial regimens comprised cocktails of orally administered non-absorbable antibacterials, often in conjunction with a polyene antifungal. Frequently, these agents were used in combination with oral antiseptics. These protocols were problematic to administer and patient compliance was poor.

Experience with this approach to ABP was mixed and results derived from published studies are difficult to analyse because of differences in the combinations used, the frequency of administration of the agents involved, and in the degree and duration of neutropenia experienced by trial subjects. In addition, there were variations in the timing of commencement of ABP relative to the onset of neutropenia and also in adjunctive measures such as dietary manipulation or nursing of patients in laminar air flow environments.

Following the observations of Hughes *et al.*,[4] who reported that co-trimoxazole prophylaxis against *Pneumocystis carinii* in children with acute leukaemia was also associated with a decrease in septicaemia and bacterial infections at other sites, this combination was adopted by many centres in preference to oral non-absorbable ABP regimens. Several studies (reviewed in reference 5), in which co-trimoxazole was compared with placebo or with other prophylactic agents, yielded conflicting results, with some studies failing to demonstrate significant differences in the number of febrile episodes, use of therapeutic antibacterials and mortality. Owing to marked differences in trial design, patient mix and data analysis, results of these investigations are difficult to compare. Furthermore, the statistical validity of the data obtained was compro-

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mised because the number of patients enrolled in these studies was often very low.[6] Despite the successes in the reduction of bacterial infections that were claimed for co-trimoxazole, a number of drawbacks were associated with its use, including toxicity such as hypersensitivity and prolongation of the period of neutropenia,[7,8] breakthrough infections with resistant Gram-negative bacteria,[9] and an increased risk of Gram-positive sepsis,[10] fungal infections[8] and *Clostridium difficile* colitis.[11]

Following their introduction in the early–mid-1980s, the fluoroquinolones were embraced with some enthusiasm as agents for ABP. This was because of their increased activity against Gram-negative bacilli, particularly *P. aeruginosa*, compared with co-trimoxazole. In addition, they were not myelosuppressive and did not appear to have the problems of hypersensitivity associated with co-trimoxazole. Furthermore, the lack of anti-anaerobic activity of these compounds would preserve the anaerobic component of the gut microflora that is of crucial importance to the concept of colonization resistance. Whilst there is no shortage of clinical trials (summarized in reference 12) of quinolones versus placebo or other ABP regimes, there have been few trials in which different quinolones have been compared.[13–15] Similarly, there is a lack of data on the use of quinolone ABP in patients with solid organ malignancies.[16,17] Once again, methodological differences and very small numbers of patients[11] militate against meaningful comparisons between these studies. In addition, there are few published reports on the use of quinolone prophylaxis in the community setting.[18] Nevertheless, proponents of quinolone ABP point to data which demonstrate that many, but not all,[11,17] of these regimens are associated with fewer Gram-negative bacteraemias than controls.[12] Some investigations, however, do not show a reduction in numbers of unexplained febrile episodes in patients receiving quinolone ABP.[14,19] Whether this is because systemic absorption of quinolones from the gut is merely converting blood cultures that, otherwise, would have been positive into 'no growth' specimens or whether this is due to other reasons, such as absorption of endotoxins, remains unresolved.[14] With regard to other parameters such as the use of broad-spectrum antibacterials for suspected or documented infection, duration of hospital stay and mortality, the advantages of ABP with quinolones (and co-trimoxazole) are less clear-cut. Donnelly and co-workers,[20] for example, report that despite receiving prophylaxis, nearly 80% of patients in their trial required therapy with broad-spectrum antimicrobials. Moreover, not all studies claim to demonstrate superiority of quinolones against comparator regimes. In their study of 230 patients, Donnelly *et al.*[20] noted that patients receiving co-trimoxazole and colistin had fewer febrile days, a reduced frequency of infectious episodes and a delayed onset of fever compared with those receiving quinolones. Bacteraemia due to resistant Gram-negative bacilli, however, only occurred in the former group.[20]

Whatever the perceived advantages of quinolones, the problem of superinfection with Gram-positive bacteria that are not susceptible to these compounds cannot be ignored. This was highlighted in the very first study that described the use of quinolones in neutropenia[21] and the problem remains a major disadvantage of ABP, even though some investigators have not observed this phenomenon.[22] Cruciani *et al.*,[23] in their meta-analysis of 13 trials in which quinolones were compared with co-trimoxazole, oral non-absorbable agents or placebo, concluded that quinolones were not effective in preventing Gram-positive bacteraemia.

Of particular concern has been bacteraemia with viridans group streptococci (VGS). These infections are characterized by significant morbidity including respiratory distress syndrome and endocarditis.[24] Case fatality rates may be as high as 30%.[25] It should be noted that, although several studies[20,26,27] have identified ABP as a risk factor for VGS sepsis, other predisposing factors have also been reported. These include high-dose cytosine chemotherapy,[24,28] use of antacids,[29] the presence of mucositis,[24] oral herpes simplex virus infection[30] and, indeed, co-trimoxazole prophylaxis.[31] The occurrence of VGS sepsis in quinolone ABP is, perhaps, not altogether surprising given the relative insusceptibility of the bacteria to earlier antimicrobials of this class. For example, McWhinney *et al.*[32] reported that of 47 blood culture isolates of VGS from neutropenic patients, only 4.3% were susceptible to ciprofloxacin and ofloxacin at breakpoints of 1 and 2 mg/L, respectively. It has been suggested that ofloxacin use is less likely to be associated with VGS sepsis than other quinolones.[33] Although most attention has focused on VGS infection in quinolone ABP, infections with other Gram-positive bacteria, such as *Stomatococcus mucilaginosus*[34,35] and coagulase-negative staphylococci,[36,37] have also been documented.

Strategies to counter the problem of VGS have centred around the addition of other agents with increased anti-Gram-positive activity to ABP regimens. The rationale for this practice is supported by animal work, in which survival rates in irradiated mice were higher in those animals receiving a combination of penicillin and ofloxacin compared with a group receiving only ofloxacin.[38] Given that some neutropenic populations may have a high prevalence of penicillin-resistant VGS[39] and that blood culture isolates of these bacteria from neutropenic patients are frequently penicillin resistant,[32] it is not altogether surprising that studies have reported an increase in infections with strains of VGS intermediately susceptible, or resistant, to penicillin.[40,42] Subsequent approaches have included the addition of macrolides,[33,42] rifampicin[14] and vancomycin[41] to quinolone ABP, with varying degrees of success. However, the potential for the selection of resistant bacteria, especially vancomycin-resistant enterococci must be acknowledged.[43] Although much attention has been focused on Gram-positive infections in patients receiving

quinolone ABP, there is increasing awareness of superinfection with resistant Gram-negative pathogens including *Escherichia coli*,[44,45] *P. aeruginosa*[46,47] and *Stenotrophomonas maltophilia*[47] as well as more unusual bacterial species such as *Leptotrichia buccalis*.[48]

With the introduction of newer agents of the quinolone class which have increased activity against Gram-positive bacteria in general,[49] and VGS in particular,[50] whilst retaining good activity against the Enterobacteriaceae and *P. aeruginosa*, is there further hope for quinolone ABP? Clearly, it is too early to predict the role of these newer compounds in this setting but it should be noted that many, although not all, of these newer drugs have significant in-vitro activity against anaerobes and would thus undermine the concept of colonization resistance. Well designed trials that avoid some of the pitfalls encountered by early investigations, particularly small numbers of subjects and the inclusion of patients with marked variations in the degree and duration of neutropenia, are awaited.

Although ABP will continue to be championed by many, perhaps it is a practice that has outstayed its welcome. As has been noted,[5] the response rate with timely administered empirical therapy is, currently, gratifyingly high, thus calling into question whether the putative benefits of ABP outweigh the risks of antimicrobial resistance and adverse effects.[51] Although this may be regarded by some as an overly pessimistic view, there are alternative strategies for preventing bacterial infections in the neutropenic patient that do not rely on administration of prophylactic antimicrobials. These include use of recombinant colony stimulating factors,[52] bone marrow protective agents such as amifostine,[53] which also has general cytoprotective properties and thus may reduce mucositis[54] (itself a risk factor for bacteraemia in neutropenia) and negative bone marrow regulators, including MIP1α.[55] Technical developments have also led to a reawakening of interest in the use of prophylactic granulocyte transfusions which may also play a role in preventing infection.[56] Whilst the benefit of these new approaches remains to be assessed in full, the role of simple, if technologically unexciting measures such as good hand hygiene, care of vascular access devices and appropriate dietary advice, should also not be forgotten.

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