


Prevention of Infection in Leukaemia

It is well recognized that infection is a major cause of morbidity and mortality in patients with acute leukaemia. Fatal infection occurs in up to 25% of patients before therapy has had a sufficient trial (Smith et al., 1977). In a recent trial of prophylactic oral nonabsorbable antibiotics in acute leukaemia, 52% of the control group died of infection (Schimpff et al., 1975). Patients with acute leukaemia are more susceptible to many types of pathogens; nevertheless, bacteria account for the great majority of serious infections (The EORTC International Antimicrobial Therapy Project Group, 1978; Gurwich, Brunton, Lank, Ronald & Harding, 1978). Although increased susceptibility to infection in acute leukaemia has many causes including decreased antibody formation, impaired cellular immunity, mucosal ulcerations, and inevitably granulocytopenia, there is little doubt that granulocytopenia is the most important defect. It is clear that the rate of infection is directly related to duration and degree of granulocytopenia (Bodey, Buckley, Sathe & Freireich, 1966; Gurwith et al., 1978).

The most frequently investigated strategy of infection prevention in acute leukaemia has been oral nonabsorbable antibiotics with or without the additional use of a protected environment, where exposure to any microorganism is limited through the use of life islands, laminar air flow isolation systems, sterilized food, etc. While the usefulness of protected environments has been investigated in at least 12 trials (Levine, 1976), only a limited number of these have been prospectively controlled (Yates & Holland, 1973; Schimpff et al., 1975). Infection was reduced but a significantly improved remission rate was found in only one (Schimpff et al., 1975).

Prophylactic oral nonabsorbable antibiotics used alone have also been widely investigated but of four recent large prospectively controlled trials (Levine et al., 1973; Yates & Holland, 1973; Schimpff, Greene, Young, Fortner, Jepsen, Cusack, Block & Wiernik, 1975; Storring, McElwain, Jameson, Wiltshaw, Spiers & Gaya, 1977), only the most recent two demonstrated a significant decrease in infection (Schimpff et al., 1975; Storring, McElwain, Jameson & Wiltshaw, 1977). In none of these studies has an improvement in long-term (>1 year) survival resulted with either method of infection prevention. There are some obvious disadvantages with both. Although not always emphasized, prophylactic oral nonabsorbable antibiotics produce a variety of unpleasant gastrointestinal side effects, and frequently patients reject their use (Bodey & Rosenbaum, 1974; Schimpff et al., 1975). Those oral nonabsorbable antibiotic regimens which include gentamicin are extremely expensive and may promote the development of gentamicin resistant organisms. Although protected environments have not been as psychologically disturbing as was expected, some patients have rejected them for this reason and/or because of the concomitant nonabsorbable antibiotics. They are also extremely expensive, and unlikely to be available to more than a small minority of patients with acute leukaemia.

Simple but prudent techniques for limiting infection include limited (single room) isolation, minimizing the use of indwelling
intravenous and urinary catheters, and restricting exposure to contagious pathogens. One group has suggested that 'less aggressive' anti-leukaemic therapy produced an increase in the 'quality and quantity of life' in their patients (Burge et al., 1975). The improvement in 'quantity of life' at least was questioned by others who felt that these patients were not necessarily comparable to those more 'aggressively' treated (Hayhoe, 1975). In addition to the 'less aggressive' chemotherapy, prophylactic trimethoprim/sulfamethoxazole (TMP/SMZ) was used by Burge et al. (1975) during granulocytopenia. A vaccine against Pseudomonas aeruginosa has been investigated in patients with acute leukaemia (Young, Meyer & Armstrong, 1973; Pennington, Reynolds, Wood, Robinson & Levine, 1975). This vaccine appeared to decrease the proportion of P. aeruginosa infections, but had less effect on the total number of infections. Furthermore, P. aeruginosa causes only a minority of severe infections in granulocytopenic patients (The EORTC International Antimicrobial Therapy Project Group, 1978; Gurwith et al., 1978). Granulocyte transfusions are effective in the treatment of infection in granulocytopenic patients (Boggs, 1977); their prophylactic use is now also being considered, although it is unlikely that prophylactic granulocyte transfusions would ever be available to more than a small fraction of such patients.

We recently investigated prophylactic oral TMP/SMZ as an alternative to oral non-absorbable antibiotics (Gurwith, Brunton, Lank, Harding & Ronald, 1977). We found that the percentage of granulocytopenic days with fever was significantly reduced in patients receiving TMP/SMZ. As a result, the TMP/SMZ group received parenteral antibiotics 35% of granulocytopenic days, compared to 65% in the control group. There were no bacteraemias in the TMP/SMZ group, while controls experienced a bacteraemic rate similar to that previously found in granulocytopenic patients in our institution (Gurwith et al., 1978). Fungal infections were relatively uncommon, and similar in frequency in the control and TMP/SMZ groups. A recently published study suggests that TMP/SMZ when used as long-term prophylaxis in leukaemia children reduces bacterial as well as Pneumocystis carinii infections (Hughes et al., 1977). There are some theoretical disadvantages to oral TMP/SMZ used prophylactically, the most compelling of which is the potential selection of TMP-resistant Enterobacteriaceae. Another disadvantage is that a small minority of patients may be allergic to TMP/SMZ.

It is not entirely clear why TMP/SMZ should be effective in this type of infection prophylaxis since its spectrum, although broad, does not include most anaerobic organisms or P. aeruginosa. It has been suggested that retention of anaerobes and other TMP/SMZ resistant organisms may be a desirable feature in a prophylactic antibiotic regimen (Guiot & van Furth, 1977). These resistant organisms may reduce colonization by pathogens, while the elimination of sensitive aerobic organisms may reduce the pathogenic potential of anaerobes.

Prophylactic use of TMP/SMZ may represent a significant advance in prevention of infection in acute leukaemia and other granulocytopenic patients. The decreased morbidity due to infection and the ease of administration and lack of unpleasant side effects are desirable in themselves, even if remission rate and long-term survival are not affected. A simple oral regimen which results in decreased infection and less intravenous antibiotic usage seems justifiable simply on the basis of improved patient comfort. Other oral systemically effective antibiotics might also be worth investigating as prophylactic regimens: for example, TMP alone may have the same advantages as TMP/SMZ in combination, with a possible decrease in numbers of allergic patients; or TMP/SMZ used in conjunction with metronidazole for anaerobic coverage and oral nystatin or 5-fluorocytosine would have broad antimicrobial coverage.

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References


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Leading articles


