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Infections in Cancer Patients: Differences between Developed and Less Developed Countries?

IN ORDER TO address the question of whether there are differences in infections among patients with cancer in developing compared with developed countries (see the study by A. Awidi, in this issue, pp. 423–426) it is necessary, it seems to me, to first address the key criteria that predispose to infection. I have always found it useful to divide infected patients based upon a fairly limited number of conditions that predispose to different types of infections, namely, granulocytopenia, cellular immune deficiency, humoral immune deficiency, obstructive phenomenon, and procedure related (indwelling intravascular catheter, urinary catheter, respirator, etc.). The types of infections with regard to both site and especially with regard to organism are quite different in each of these settings. The seriousness of the infection and, indeed, the mortality is also different among these settings [1–3].

GRANULOCYTOPENIA

Patients with granulocytopenia tend to have infections caused by aerobic gram-negative bacilli, especially *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*, the gram positive cocci, *Staphylococcus aureus*, *Staph. epidermidis*, and various streptococci, and, among patients further predisposed by broad spectrum antibiotics, fungal infections caused by *Candida albicans* and *C. tropicalis*, and *Aspergillus flavus* and *A. fumigatus*. Of course, other organisms do cause infection, but the ones noted cause the great majority of infections directly related to granulocytopenia. Further, more than half of these infections are caused by strains of these organisms that have been acquired in the hospital setting, thus accounting for institutional patterns of antimicrobial resistance among infections in granulocytopenic patients [4]. In that regard, it is useful to recall that not only therapeutic agents but also the use of prophylactic antibiotics, whether in an inpatient or outpatient setting, may lead to the acquisition or the emergence of resistance patterns (e.g. patients on cotrimoxazole may become colonised with *E. coli* resistant not only to cotrimoxazole but also the broad spectrum antipseudomonal penicillins and some of the cephalosporins) [5].

The patient who is profoundly granulocytopenic (defined as < 100 polymorphonuclear neutrophils per μl) is more likely to have infection proceed to bacteraemia which confers a more grave prognosis. Further, those patients with profound and persistent granulocytopenia who develop a gram negative rod bacteraemia are well recognised to have a much more adverse prognosis with regard to mortality than does the patient who has return of circulating granulocytes over the next few days [6].

What differences might one expect to find among granulocytopenic patients in a developing compared with a developed country? I would assume that the only major differences would relate principally to the acquisition of organisms. If food, water or air are more likely colonised or contaminated in one setting than the other, then acquisition rates might be higher and, hence, infection rates higher. For example it is well known that if *Ps. aeruginosa* colonises a patient who then becomes profoundly granulocytopenic, the patient almost invariably will proceed to a *Ps. aeruginosa* bacteraemia. Therefore, if the patient is in a setting where, because of water handling or food handling practices (ice machines, tap aerators, ingestion of foods commonly colonised by *Ps. aeruginosa*), then one would expect to see more acquisition and, hence, more infection by *Ps. aeruginosas* [7]. The other major factor would be the general approach to the use of antibiotics in an individual country or area. If, for example, cotrimoxazole was an over-the-counter agent available for any number of minor infectious ailments, then one might expect to find in the population at large an increased number of resistant organisms. This would then have a profound impact on the choice of antibiotics for use in empiric therapy.

INFECTIONS IN CELLULAR IMMUNE DEFICIENCY

Some cancers, such as Hodgkin's disease, have an associated cellular immune deficit. Radiation therapy and some forms of cancer chemotherapy along with corticosteroids depress the cellular immune mechanism and, of course, the acquired immunodeficiency syndrome is inherently a disease of cellular immune loss. The infections that occur in these patients are frequently those caused by obligate intracellular parasites that have the capacity to remain latent for many years [8]. Among the bacteria are *Mycobacteria*, *Nocardia*, *Salmonella* and *Listeria* spp.; among yeasts and fungi are *Cryptococcus*, *Histoplasma*, and *Coccidioides*; among the viruses are herpes simplex, varicella zoster, and cytomegalovirus; other organisms include *Strongyloides* and *Pneumocystis carinii*. Infection in these patients is then a conse-

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quence of both the presence of the latent organism and the degree of immune suppression or deficiency. One would assume that differences between developed and undeveloped countries would relate principally to the organisms to which the population is exposed over a lifetime. Within the USA, for example, coccidioides infection develops in people who live in or have travelled through certain areas of the Southwest United States whereas those who develop histoplasma infection have lived in distinctly different areas of the country. In the USA, *S. stercoralis* infection occurs among those who have immigrated from or travelled to endemic areas of Latin America. Of course, this is a more common infection in those countries where the parasite is endemic. It is well known that *M. tuberculosis* is spread by person to person transmission most readily in crowded conditions most typical of those in lower socioeconomic strata. To the extent that those in underdeveloped countries live under crowded conditions, then one might expect to see a higher frequency of reactivation of tuberculosis among the immunosuppressed.

In some areas of the world, a specific organism may be present due to environmental or other conditions which, if acquired during a state of granulocytopenia or other form of immune deficiency, would predispose an individual to that organism causing infection. For example, in southeast Asia, particularly Thailand, Laos and Cambodia and areas of Vietnam, there is a high frequency of melioidosis. *Ps. pseudomalei* tends to cause infection, especially bacteraemia, among rice paddy farmers during the rainy season. It is presumed that the organism gains access to the blood stream via small abrasions in the feet, and it has been noted that infections are more common in patients who are diabetic or who have other immune deficiencies [9]. Thus, a person living and working in that area who also has cancer and cellular immune deficiency would be at risk of developing melioidosis while someone living in a developed country where *Ps. pseudomalei* is not indigenous would be at no risk unless the organism was acquired and remained latent during travel to southeast Asia.

HUMORAL IMMUNE DEFICIENCY

The absence of normal circulating immune globulin renders individuals predisposed to infection with the encapsulated pyogenic bacteria, especially *Streptococcus pneumoniae*, and to a lesser degree, *Haemophilus influenzae* and *Neisseria meningitidis* [10]. These are ubiquitous organisms which can be transmitted from person to person under crowded circumstances, as is seen with meningococcus among military recruits. One would assume that the patient with a disease such as multiple myeloma with absent or reduced normal circulating immunglobulins would be at risk for the same organisms irrespective of the country, although the state of development of the country might have an impact on transmission and, hence, risk.

INFECTIONS RELATED TO OBSTRUCTION AND INSTRUMENTATION

Partial obstruction of a natural passage, such as bronchus, ureter or bile duct, leads to infection with organisms colonising at or near that site. Thus, postobstructive pneumonias are caused by oral flora and postobstructive urinary tract infections are caused by fecal flora, especially *E. coli*. Infections related to vascular catheters are usually those associated with skin commensals, such as *Staph. epidermidis* and those related to indwelling urinary catheters are usually caused by fecal flora, again, usually *E. coli* [11]. The infection patterns themselves between developed and underdeveloped countries would be expected to be essentially the same. Differences might be related to organisms present in the environment which can colonise and then cause infection, or differences could be due to the use of antimicrobials both in and out of hospital leading to different patterns of resistance or colonisation and, hence, infection.

CONCLUSIONS

To summarise, to the extent that there are differences in infections among patients with cancer in developed compared with less developed countries, they will be affected in large measure by the individual factors that predispose a specific person to infection. Among granulocytopenic patients, the only major differences in infection would probably be related to either patterns of acquisition or patterns of antimicrobial usage. The latter, in turn, might predispose a person to acquisition, colonisation and, ultimately, infection with more resistant organisms. Among individuals with cellular immune deficiency, differences in infection patterns would be related primarily to what organisms are acquired and become latent throughout an individual's lifetime prior to the onset of the immune suppression. It is unlikely there would be significant differences among patients who have humoral immune deficits except that close quarters might increase transmission rates of pneumococci, haemophilus or meningococcus. Finally, it is unlikely that there would be significant differences among patients with obstructive phenomenon or instrumentation except to the extent that there are differing patterns of antimicrobial usage in a particular area.

Stephen C. Schimpff
University of Maryland Medical System
Baltimore
Maryland 21201, U.S.A.

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