PATIENTS AND METHODS

All inpatients who were admitted with cancer to the author's unit at the Jordan University Hospital from January 1987 to the end of December 1989 were included in the study if they met the criteria for infection. Infection was diagnosed in the presence of fever above 38.5°C at any time or 38°C for 24 h, if associated with evidence of inflammatory changes on physical examination or X-ray examination, or if cultures' results supported this diagnosis. Cellulitis was diagnosed by physical examination with or without positive cultures. Urinary tract infection was diagnosed if bacteruria greater than 10^5 bacteria/ml with the same organism on two separate occasions was found in the absence of Folley's catheter. Coagulase negative staphylococci were considered the causative organism for bacteraemia only if isolated from two different peripheral sites on one occasion or from one peripheral site on two separate occasions.

Patients with neutrophil count $<0.5 \times 10^9$/l were nursed in a single side room with barrier nursing. Indwelling venous catheters were not used routinely in any of the patients. Only eight of these catheters were inserted during the period of the study. All were inserted just before the start of induction. Each was left for a mean of three weeks. All patients who were included in the study had a septic workup which included routine aerobic and anaerobic bacteriological cultures and fungal cultures from blood on at least two occasions within 24 h, nose, ear and throat swabs and midstream urine. Cultures from other sites, where applicable, were also obtained. A chest X-ray was done, and other investigations, where applicable. Routine parasitic microscopic preparation and staining procedures for examination of stools, lung tissue or sputum were performed when clinically indicated. Standard techniques for culture and drug sensitivity were used. The following definitions were used—septicaemia: a clinical illness with the growth of a non-contaminant bacteria and/or growth of fungi from blood; polymicrobial infections: more than one organism cultured concurrently or sequentially associated with a clinical illness; multisite infection: more than one site in which culture was positive in association with a clinical illness. Neutropenia was defined as neutrophil count less than 0.5×10^9/l.

No viral cultures were done. The diagnosis of viral illness was made on the clinical picture alone (typical skin or mucosal lesions).

All patients who were considered to have an infection were started on pipercillin or a penicillin derivative along with an aminoglycoside and/or a third generation cephalosporin, pending the results of culture and sensitivity. Drugs were then modified according to the sensitivity. In cases where the infection was clinically suspected to be caused by a specific organism, monotherapy or a different combination was allowed, according to the discretion of the researcher. At one stage imipenem/cilastatin was used as part of a monotherapy protocol. Similarly, aztreonam was used in substitution for aminoglycosides or as a monotherapy as part of a multicentre trial.

If fever persisted for more than 6 days despite antibiotics and if cultures were negative for bacteria, intravenous amphotericin B was added to the treatment. It was also given if blood cultures were positive for fungi or if lung infiltrates of unestablished aetiology did not respond to broad spectrum antibiotic coverage. Intravenous acyclovir was given when herpes infection was diagnosed.

Patients were classified as responders if there was a complete response clinically and negative culture on two separate occasions (if a previously positive culture was documented). In patients in whom there were no previous positive cultures, response was defined as clinical response and absence of fever for 5 consecutive days.

Hospital acquired infection was defined according to CDC definition [6]. In brief, it was diagnosed when an infection occurred while the patient is in hospital which had not been present or incubating at the time of admission. Similarly, it was diagnosed if it occurred after the patient was discharged, providing that the incubation of the organism was compatible with the diagnosis.

Mortality was defined as death attributable to infection directly or indirectly, or to the underlying disease.

For statistical analysis the χ^2 test and z score statistics were used. P value was considered significant if less than 0.05.

Table 1. Characteristics of patients and their diagnosis

Diagnosis	No. of patients	No. of infection episodes
Acute leukaemias	56	138
Hodgkin's, non-Hodgkin lymphomas and multiple myeloma	49	83
Chronic leukaemias	26	40
Soft tissue sarcomas	10	12
Lung cancer	8	11
Gastric cancer and hepatoma	6	10
Breast cancer	4	4
Renal and urinary bladder cancer	3	4
Others	12	17

Table 2. Sites of infection with positive organisms

Site	No. of positive isolates		
	PMN <500/μl	PMN >500/μl	Total
Respiratory tract and lung	29	26	55
Septicaemia	22	26	48
Urinary tract and kidney	6	27	33
Skin	9	20	29
Gastrointestinal tract	2	5	7
Other	4	4	8

RESULTS

Patients

Table 1 shows the characteristics of patients, and their diagnoses. 319 episodes of infections occurred in 174 patients; 65 females and 109 males. Their mean age was 37.5 years (range 13–78). 138 episodes occurred in patients with acute leukaemia, 40 episodes in patients with chronic leukaemia, 83 episodes in patients with non-Hodgkin lymphoma and Hodgkin's disease, 58 episodes in patients with solid tumours and other tumours not included in the types mentioned. 146 episodes (46%) occurred in

Table 3. Distribution of isolated organisms

Organism	No. of times isolated			Episodes as mono-organism		Episodes as polyorganism	
	PMN+ <500/μl	PMN >500/μl	Total	PMN <500/μl	PMN >500/μl	PMN <500/μl	PMN >500/μl
Staphylococcus	41	37	78	27	26	14	11
Streptococcus	15	14	29	11	13	4	1
E. coli	14	19	33	4	10	10	9
Enterobacter	5	13	18	4	7	1	6
Candida albicans	7	8	15	6	5	1	3
Pseudomonas	3	7	10	1	3	2	4
Diphtheroids	2	5	7	0	3	2	2
Salmonella	1	4	5	0	4	1	0
Proteus	2	2	4	1	1	1	1
Klebsiella*	0	2	2	0	1	0	1

*H. influenzae, acinetobacter and providencia were isolated in equal frequency. Amoeba was isolated on two occasions and *Herpes simplex* was diagnosed in 2 patients and *Herpes zoster* in 1.

89 neutropenic patients and 173 (54%) episodes occurred in 85 non-neutropenic patients.

Sites and episodes

Only sites in which positive cultures were obtained were considered for analysis. If there was more than one site in the same patient, they were considered separately. Positive cultures were obtained from 180 sites in a total of 163 episodes, since some organisms were cultured from more than one site in the same episode. In 39 (24%) episodes more than one organism was cultured and were considered polymicrobial episodes. Table 2 describes sites with positive cultures. There were 48 episodes of septicaemia, 55 episodes of lung or upper airways infections, 33 episodes of urinary tract infections, 29 episodes of skin infections, 7 episodes of gastrointestinal tract infections and 8 episodes of other sites.

Spectrum of organisms

Positive documentation were obtained in 163 out of 319 episodes (51% of the total episodes studied). Of these, 57 episodes occurred in neutropenic patients and 106 in non-neutropenic patients. There were a total of 212 organisms isolated. 192 (90.6%) of the isolates were bacteria; of these 107 (55.7%) were gram positive and 85 (44.3%) were gram negative. 15 (7%) isolates were fungal and <1% were amoebal and viral. Table 3 shows the isolated organisms. Table 4 lists organisms causing septicaemia.

Mortality and hospital acquired infections

During the period of study, 64 patients died, accounting for 36.8% of all patients and 20% of all febrile episodes. Of these a total of 36 patients died directly or indirectly of infection. 16/36 patients (44%) of those who died of infection had a confirmed antemortem infection and death was associated directly with it. 11 of the 16 patients died because of hospital acquired infections. There was a total of 35 episodes of hospital acquired infections. Table 5 shows the effects of the depth and duration of granulocytopenia on mortality. As can be seen, mortality was significantly higher in patients with neutrophilic count of less than 1×10^8 ($P = 0.001$). Similarly mortality was significantly higher when neutropenia lasted for 6 or 11 days ($P = 0.001$ and $P = 0.0001$ respectively). Polymicrobial episodes were much more frequently seen in the patients who died than in patients who survived. 79 multiorganism episodes were found in 174 patients; of these 30 episodes occurred in 36 patients who died, while the remaining 49 episodes occurred in 138 patients who survived their infections ($P < 0.02$). 15 episodes occurred in neutropenic

Table 4. Survey of 48 septicaemia episodes and 66 isolated organisms (as mono or polyorganism episodes)

Bacterial species	Total no. of positive	Percentage
Gram positive (total)	34	51.5
Staphylococcus	21	31.8
Streptococcus	13	19.7
Gram negative (total)	29	43.9
E. coli	10	15.2
Klebsiella	3	4.5
Pseudomonas	6	9.1
Enterobacter	5	7.6
Salmonella	5	7.6
Candida (total)	3	4.5

Table 5. Influence of depth and duration of granulocytopenia on mortality

	Mortality/no. of episodes (%)	Significance
PMN count × 10^9/l		
a > 0.499	33/172 (19.2)	—
b 0.1–0.499	12/100 (12)	(a with b) NS
c < 0.1	19/47 (40)	(a with c) $P = 0.001$
Duration of neutropenia/days		
a : 4	5/94 (5.3)	—
b : 6	7/21 (33.3)	a and b: $P = 0.001$
c : 11	19/32 (59.4)	a and c: $P = 0.0001$
		b and c: $P = 0.05$

Table 6. Antimicrobial usage in 319 episodes of infections

Group	Total episodes*	Episodes with documented infection (%)	Total no. of antibiotics 1	2	3	4	>4
Patients receiving antibiotics	311	50.5	69	151	69	19	3
Patients receiving amphotericin B	38	39.5					
Patients receiving acyclovir	3	100					

*The patient may have received antibiotics alone, amphotericin B alone, acyclovir alone or a combination of these three (see text).

patients and 20 episodes in non-neutropenic patients. The most commonly isolated organisms were: staphylococcus in 9 episodes, *E. coli* and pseudomonas in 4 episodes each, streptococcus in 3 episodes and klebsiella and acinetobacter each in 2 episodes.

Antimicrobial usage

Table 6 summarises the antimicrobial usage in a total of 319 episodes of infection. None of the patients received prophylactic co-trimoxazole or acyclovir. There was a total of 710 various antimicrobial, antifungal and antiviral drugs given in 319 episodes. An average of 2.3 different antimicrobials was given to each patient per episode of infection.

DISCUSSION

The aim of this work was to study prospectively infections in hospitalised patients with cancer in a developing country. Infections in cancer patients are important cause of death and morbidity [7]. They contribute significantly to the total hospital cost in these patients.

In this study a total of 319 episodes of infection occurred in 174 patients with neoplastic diseases. The patients were nursed in a single side room if their neutrophilic count fell below 0.5×10^9/l. No prophylactic oral antimicrobial or antiviral drugs were given.

In 51% of the episodes, an organism was documented to be the cause of infection. Bacterial infections accounted for 90% of these culture positive episodes. Gram positive bacteria accounted for 60% of these isolates and gram negative for 40%. Staphylococcus is an important organism in the culture positive episodes. In the absence of long-term intravenous catheters, it is unclear why there was a high incidence of staphylococcal infection. The finding that gram positive bacteria are the most commonly isolated bacteria in this study is very similar to that reported recently by many authors [8, 9] from developed countries.

Infection episodes occurred in equal frequency in neutropenic and non-neutropenic patients. In 89 neutropenic patients 146 episodes of infection occurred with a mean of 1.64 episodes/patient; in the 122 non-neutropenic patients a total of 173 episodes occurred with a mean of 1.41 episodes/patient. There was no significant difference between these two figures.

Neutropenia, however, contributed significantly to mortality. Mortality was higher when neutrophilic count fell to 1×10^8 or less ($P = 0.001$). The duration of neutropenia was an important contributing factor to mortality. Mortality was higher in those episodes where the duration of neutropenia was 6 or 11 days ($P = 0.001$ and $P = 0.0001$, respectively) as compared to episodes where neutropenia lasted for 4 days only.

The organisms mostly isolated were staphylococci, *E. coli* and streptococci. This confirms the need for proper coverage of staphylococcus and other gram positive organisms in these patients. The seriousness of polymicrobial episodes in this study and the high mortality associated with it is consistent with that reported [7]. There were no isolates of anaerobic bacteria in this study. This is in contrast with that reported in the literature in which 10% of bacteraemia are due to anaerobes, especially *B. fragilis* [10]. The reason for this observation is not currently understood. All of these patients were on the medical floor and very few had documented gastrointestinal tract infection. This may account partly for this low incidence of anaerobes. Technical difficulties in isolating these organisms may also play a role.

Among patients receiving antibiotics only 50% had positive cultures. The rest received empiric antibiotic therapy. The patients received a mean of 2.3 antibiotics per episode of infection. This reflects the practice of not using a single antibiotic for the treatment of infection in immunocompromised patients. This number is less than that reported in leukaemic patients [8]. This is because only one, or at most two, experienced physicians decide the antimicrobial combinations or modifications needed. Another reason is the inhibitory cost of some antibiotics which frequently puts them out of reach in developing countries.

In conclusion, this study shows that gram positive bacteria are frequently isolated from cancer patients with infections in developing countries. Mortality compares well with that in advanced centres but there is less use of antibiotics than in developed countries. Hospital acquired infections are associated with high mortality in this group of patients. Similarly multiorganism episodes are associated with higher mortality. Neutropenia both in depth and duration is associated with high mortality.

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