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Oral Infections and Septicemia in Immunocompromised Patients with Hematologic Malignancies

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To estimate the role of oral infections during septicemic episodes in immunocompromised patients with hematologic malignancies, 78 febrile episodes in 46 patients were monitored with daily clinical and microbiological investigations. The 19 septicemic episodes did not differ from the 59 other febrile episodes in the qualitative composition of the aerobic and facultatively anaerobic oral microflora or in the presence of teeth or acute oral infections on day 1. The oral prevalence rates of members of the family *Enterobacteriaceae* were higher on days 10, 11, and 12 in the febrile episodes with septicemia when compared with those of febrile episodes without septicemia. The prevalence of a probable oral focus in septicemia was 10.5%, and the prevalence of a probable or possible oral origin in septicemia was 31.6%. The results suggest that prevention and elimination of oral infections may reduce the morbidity and perhaps even the mortality in these patients.

In recent years, several major advances have been made in the antineoplastic treatment of patients with hematologic malignancies. Survival has improved, but one of the drawbacks has been an increased predisposition of the patients to infection. In fact, infection has remained the leading cause of morbidity and mortality among these patients. The ability to diagnose and treat infectious complications, therefore, is nowadays of even greater importance than previously, since infection is now one of the major factors limiting further intensification of treatment regimens. Rational treatment or prevention of infections, on the other hand, necessitates a knowledge of predisposing factors and infectious foci, which could be the cause of septicemia.

Septicemia is found in about 20% of the febrile episodes of patients with hematologic malignancies (4, 6). The primary focus, however, is known in only about 60% of septicemias (1, 4, 6, 7, 9, 10, 14, 16, 17). As a possible origin of septicemia in cases with unknown primary focus, the role of the oral microflora has been emphasized in one study (9).

The aim of this study was to investigate the possible relationship between oral infections and septicemia in patients with hematologic malignancies.

MATERIALS AND METHODS

All adult patients (more than 15 years of age) with hematologic malignancies (acute myeloid leukemia [AML], acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphatic leukemia, hairy cell leukemia, malignant non-Hodgkin lymphoma, Hodgkin's disease, myelomatosis, and Waldenström's disease) were consecutively and prospectively included in the study if they developed a rectal temperature of 38.5°C or more for two consecutive hours and had received treatment with antineoplastic drugs within the previous 28 days. The investigations ended when the patients had been afebrile for 2 days. Individual patients could be included with more than one febrile episode. Informed consent was obtained from the patients, and the study was approved by the local ethical committee.

Age, sex, underlying disease, administration of antineoplastic drugs, and use of antibiotics and indwelling central venous lines were recorded. A history was obtained and a physical examination was performed by the same investigator on each day to detect signs and symptoms of oral or extraoral infections. Chest and jaw X rays were performed on day 1 of inclusion in the study and were repeated on day 14, if the patients were still febrile. A blood cell count was performed on day 1 and thereafter twice a week.

Microbiology. On days 1, 2, and 3, and every second day thereafter, 24 ml of venous blood was drawn into three evacuated glass tubes (Venoject; Meda, Herlev, Denmark). On day 1, blood was drawn before antibiotic therapy was started from three separate venipunctures at intervals of 30 min. On the other days, blood was drawn from the same puncture site. Blood was never drawn through a catheter. On the same days, cultures were taken from the throat, urine samples, and if present, other clinical foci.

In the oral cavity, cultures were obtained from areas which were the most likely sources of septicemia as a result of inflammation and hence augmented permeability (5). Thus, the standard sampling method comprised a swab from the gingival margin of all teeth in dentate patients and a swab from the mucosa beneath the dentures in edentulous patients. Additional samples were obtained from acute oral infectious sites when present. All oral cultures were repeated on each day of the febrile episode.

The blood was immediately transported to the laboratory and distributed into 12 tubes of culture media (4 tubes of nutrient broth, 4 tubes of semisolid nutrient broth, and 4 tubes of semisolid thioglycolate broth) and examined for aerobic and anaerobic growth during the following 7 days. Cotton swabs were immediatley placed into modified Stuarts medium (8) and seeded out within 4 h. Anaerobic bacteria are seldom reported as the cause of septicemia in hematologic patients (a fact that was confirmed in this study when none of the blood cultures yielded growth of obligately anaerobic bacteria). Accordingly, swab cultures were analyzed only for aerobic and facultatively anaerobic growth on one nonselective medium (blood agar base with 5% sheep blood) (Oxoid, Ltd., Basingstoke, Hants, England) and two selective media (MacConkey agar [Oxoid] and Sabouraud dextrose agar [Oxoid]). Urine was seeded on either MacConkey agar and PGUA-agar (12) (if rods were present) or on blood agar (if cocci were present), depending on the results of initial microscopic examination.

Septicemia was defined as the presence of at least one positive blood culture, except for *Staphylococcus aureus*, coagulase-negative staphylococci, *Corynebacterium* spp., and *Bacillus* spp., which were only considered indicative of septicemia when cultured from at least two separate specimens of blood.

All isolates from blood and oral or extraoral isolates of *Enterobacteriaceae*, *Pseudomonadaceae*, *Micrococcaceae*, *Streptococcus faecalis*, or hemolytic streptococci were stored, and whenever the same species of organism was isolated from the blood and elsewhere, the organism was characterized by (i) biotype, (ii) pattern of antibiotic resistance, (iii) serotype (for *Enterobacteriaceae*), (iv) serotype and bacteriophage type (for *Pseudomonadaceae*), (v) phage type and plasmid profile (for coagulase-negative staphylococci), and (vi) serotype (for *S. faecalis* or hemolytic streptococci).

Antibiotic therapy and oral hygiene. All febrile episodes were initially, i.e., on day 1, treated with piperacillin (12 g/day, 3 doses intravenously [i.v.]) and netilmicin (maintenance dose for patients with normal renal function: 6 mg/kg per day, 3 doses i.v.). In cases of known allergy to penicillin or allergic reactions during therapy, cefotaxim (6 g/day, 3 doses i.v.) was given instead of piperacillin. In septicemia with coagulase-negative staphylococci, the initial treatment was replaced by vancomycin (2 g/day for patients with normal renal function, 2 doses i.v.). All antibacterial therapy began at the time of inclusion in the study. If the patient remained febrile for more that 8 days, antifungal therapy with amphotericin B (maintenance dose of up to 0.65 mg/kg per day i.v.) and flucytosine (200 mg/kg per day, 4 doses i.v.) was considered. Oral candidiasis (verified by smears) was treated with local application of nystatin (suspension [100.000 U/ml] 4 ml/day, 4 doses). In all patients, a chlorhexidine gel was applied daily by a dental hygienist to the gingival margin of all teeth or to the mucosa beneath the dentures. Dentures were cleaned with a chlorhexidine soap.

Statistics. The fact that each patient could be included with more than one febrile episode implies that paired and unpaired data are mixed. Prevalence rates were calculated on the basis of number of febrile episodes. For statistical evaluation, the chi-square test was applied, and P values of less than 0.05 were considered significant.

RESULTS

The study population consisted of 46 patients, 26 women and 20 men. The median age was 62, ranging from 23 to 90 years of age. The 46 patients had a total of 78 febrile episodes. Specifically, 29 patients had one febrile episode, 7 patients had two, 7 patients had three, 2 patients had four and 1 patient had six. All patients admitted to the ward and fulfilling the inclusion criteria consented to participate in the study. Four patients died during a febrile episode. No patients were otherwise excluded in the study period. Twenty-six patients with AML had 55 febrile episodes, seven patients with acute lymphoblastic leukemia had seven, three patients with chronic myeloid leukemia had three, two patients with chronic lymphotic leukemia had four, four patients with malignant non-Hodgkin lymphoma had four, and four patients with myelomatosis had five. Central venous catheters were used in seven febrile episodes, and peripheral venous catheters were used in the remaining 71 febrile episodes.

Clinical data and septicemia. The median duration of the febrile episodes was 6 days, ranging from 3 to 53 days. The median number of days from the start of antineoplastic treatment to the time of inclusion in the study was 12 days, ranging from 1 to 28 days. Septicemia occurred in 19 (24.4%) episodes in nine (19.6%) different patients; in 18 (94.7%) cases, septicemia was diagnosed on day 1 (i.e., before start of antibiotic therapy), and only in one (5.3%) case was septicemia diagnosed on day 3 in an episode.

Septicemia occurred most often in women and in febrile episodes presenting with shivering (present in 80%), impaired consciousness (present in 25%), or a rectal temperature of more than 39.5°C (present in 75%) (Table 1). When correlated with blood cell counts, septicemia most often occurred in febrile episodes of patients presenting with leukopenia, granulocytopenia, and thrombocytopenia (Table

TABLE 1. Comparison on day 1 between febrile episodes with and without septicemia occurring in a total of 46 patients with hematologic malignancies

Parameter	No. of febrile episodes		P value
	With septicemia (n = 19)	Without septicemia (n = 59)	
Sex			
Male	5	31	$0.025 < P < 0.05$
Female	14	28	
Age			
<60 yr	12	29	NS[a]
>60 yr	7	30	
Underlying disease			
AML	15	40	NS
Not AML	4	19	
Shivering			
Yes	15	11	$P < 0.0005$
No	4	48	
Impaired consciousness			
Yes	5	5	$0.025 < P < 0.05$
No	14	54	
Central venous catheter present			
Yes	3	4	NS
No	16	55	
Teeth present			
Yes	12	31	NS
No	7	28	
Acute oral infections[b]			
Yes	8	23	NS
No	11	36	
Rectal temp			
<39.5°C	14	11	$P < 0.0005$
>39.5°C	5	48	
No. of days from start of cytostatic therapy			
<12	10	28	NS
>12	9	31	
Leukocyte count			
$<1.0 \times 10^9$/liter	14	28	$0.025 < P < 0.05$
$>1.0 \times 10^9$/liter	5	31	
Granulocyte count			
$<0.5 \times 10^9$/liter	18	37	$0.005 < P < 0.01$
$>0.5 \times 10^9$/liter	1	22	
Thrombocyte count			
$<20 \times 10^9$/liter	16	30	$0.005 < P < 0.01$
$>20 \times 10^9$/liter	3	29	

[a] NS, Not significant.

[b] Acute candidiasis, mucosal ulcers, denture stomatitis, mucosal erythema, acute gingivitis, acute necrotizing ulcerative gingivitis, herpes labialis, angular cheilitis, acute pericoronitis, and dental (pulpal and periapical) infections.

TABLE 2. Comparison of the qualitative composition of the aerobic and facultatively anaerobic oral microflora in febrile episodes with and without septicemia in patients with hematologic malignancies[a]

Microorganism	No. (%) of episodes	
	With septicemia (n = 19)	Without septicemia (n = 59)
Candida spp.	14 (74)	42 (71)
Enterobacteriaceae	4 (21)	19 (32)
P. aeruginosa	3 (16)	4 (7)
S. aureus	3 (16)	7 (12)
Coagulase-negative staphylococci	4 (21)	16 (27)
Enterococci	4 (21)	9 (15)
Members of normal oral flora[b]	16 (84)	49 (83)

[a] There were no statistically significant differences.
[b] Alpha- or nonhemolytic streptococci; nonpathogenic *Neisseria* spp. and actinomycetes.

1). On the other hand, the presence of central venous catheters, teeth, or acute oral infections (at the time of inclusion) did not occur more frequently in febrile episodes with septicemia than in febrile episodes without septicemia.

Oral microflora and septicemia. The composition of the aerobic and facultatively anaerobic oral microflora was compared in the 19 septicemic and in the remaining 59 nonsepticemic febrile episodes, respectively. No qualitative differences were present on day 1 (Table 2), but the prevalence of *Enterobacteriaceae* was significantly higher in the septicemic than in the nonsepticemic episodes on days 10, 11, and 12 (Fig. 1).

Clinical data, surveillance cultures, and septicemia. The blood isolates from the 19 cases of septicemia were *Escherichia coli* in seven cases, *Klebsiella pneumoniae* in four, coagulase-negative staphylococci in three, *Pseudomonas aeruginosa* in two, *Streptococcus pneumoniae* in one, *S. faecalis* in one, and hemolytic streptococci (group C) in one. No obligately anaerobic bacteria or fungi were found.

In 10 (52.6%) of the 19 septicemic episodes, bacteria identical with the blood isolate were found in the surveillance cultures (i.e., mouth, throat, urine samples, and if present, other clinical foci) (Table 3). In two patients (A and B), the bacteria were found only in the oral cavity and simultaneous clinical infection could be demonstrated only in the mouth. In a third patient (C), the blood isolate (*Staphylococcus epidermidis*) was only found orally, while clinical signs of infection were present in the oral cavity and in the skin as well. From the skin site, a *S. epidermidis* was also cultured. Its biotype and plasmid profile were identical to, but the pattern of antibiotic resistance was different from, that of the blood isolate (with respect to cephalothin and cefotaxim). In patients D and E, the blood isolate and clinical infection could be demonstrated orally and extraorally as well. In the remaining patients with septicemia (F to J), the blood isolates and the clinical infections were present only outside the oral cavity, i.e., oropharynx in two instances, the urine in two, and the perianal region in one instance (Table 3).

Among the nine (47.4%) remaining septicemic episodes, when the blood isolate was not found in the surveillance cultures, there were seven concurrent skin or mucosal infections. In all seven cases, only one infectious site was present. In one of these (the blood isolate being *S. epidermidis*), only oral infections (mucosal ulcer and acute gingivitis) were present. The remaining six were comprised of three acute gastrointestinal infections, two pneumonias, and one acute tonsillitis.

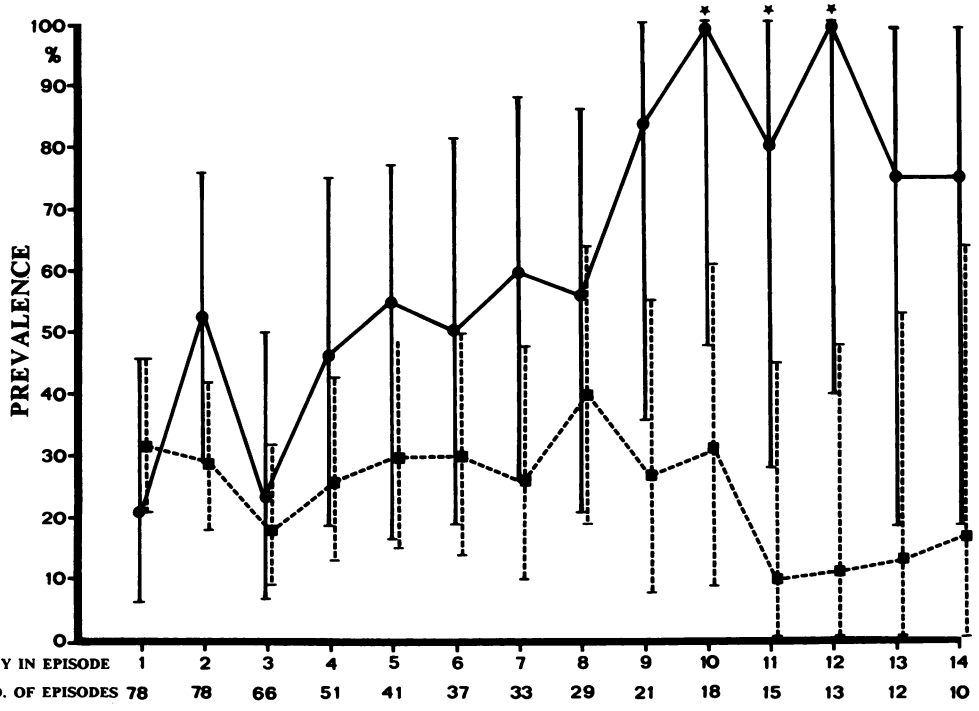

FIG. 1. Occurrence of *Enterobacteriaceae* in febrile episodes with (——) or without (---) septicemia. The prevalence rates were calculated on the basis of 78 febrile episodes in 46 patients. Statistically significant differences (★) are indicated.

TABLE 3. Clinical and microbiological findings in 10 septicemias in which a bacterium identical with the blood isolate was found in the surveillance cultures

Patient	Extraoral infection	Oral infection	Blood isolate	Blood isolate found extraorally and location	Blood isolate found orally
A	No	Acute gingivitis (day 1) and mucosal ulcer (day 1)	*K. pneumoniae* (K28)[a] (day 1)	No	Yes (day 1)
B	No	Acute gingivitis (day 1)	*S. faecalis* (day 1)	No	Yes (day 1)
C	Acute skin infection (day 1)	Denture stomatitis (day 1)	*S. epidermidis* (phage type: NT[b], 2 plasmid bands) (days 1, 4, 5, 6, 7, and 10)	Skin[c] (day 7)	Yes (day 6)
D	Acute urinary infection (day 1)	Acute gingivitis (day 1) and acute candidiasis (day 1)	*P. aeruginosa* (O118)[a] (phage type: 21/44/119x/Col 18/Col 21 u) (day 1)	Yes, urine (day 1), oropharynx (day 2)	Yes (day 2)
E	Acute tonsillitis (day 1)	Mucosal erythema (day 1)	*E. coli* (O2K1:H−)[a] (day 1)	Yes, oropharynx (day 1)	Yes (day 5 and 6 days before septicemia)
F	Acute tonsillitis (day 1)	No	*K. pneumoniae* (K19)[a] (day 1)	Yes, oropharynx (day 3 and 51 days before septicemia)	No (49 days before septicemia)
G	Acute tonsillitis (day 1)	No	Hemolytic streptococci (group C) (day 1)	Yes, oropharynx (day 1)	No
H	Acute urinary infection (day 1)	Acute candidiasis (day 3)	*E. coli* (O75:K5:H5)[a] (day 1)	Yes, urine (day 1)	No
I	Acute urinary infection (day 1)	Mucosal erythema (day 1)	*E. coli* (O13:K92:H4)[a] (day 1)	Yes, urine (day 1)	No
J	Acute perianal infection (day 1)	Mucosal ulcer (day 1) and acute gingivitis (day 1)	*E. coli* (O75:K100:H5)[a] (day 1)	Yes, perianal region (day 1)	No

[a] Serotype
[b] NT, Not typeable.
[c] Same biotype and plasmid profile but different antibiotic resistance compared with those of the blood isolate.

DISCUSSION

The observed septicemia rate (24.4%), the fact that *Enterobacteriaceae*, *P. aeruginosa*, and *Micrococcaceae* altogether were present in 84.2% of the septicemias, and that *E. coli* was the single most frequent blood isolate (36.8%) are in accordance with earlier investigations (4, 6). In no instance were obligately anaerobic bacteria or fungi detected in the blood cultures. Although this is in agreement with previously published prevalence rates of anaerobic bacteria and fungi in septicemia in patients with hematologic malignancies (4, 6, 7, 9, 10, 14, 16, 17), it could theoretically be due to a failure of the method used to detect these groups of microorganisms. However, comparisons between the standard method applied and other blood culture methods (2, 3) have not revealed significant differences with respect to the detection of obligately anaerobic bacteria or fungi.

A comparison between the composition of the aerobic and facultatively anaerobic oral microflora in the 19 septicemic episodes and the 59 other febrile nonsepticemic episodes revealed no qualitative differences on day 1, but the prevalence rates of *Enterobacteriaceae* on days 10, 11, and 12 were between 80 and 100% in the septicemic episodes and between 10 and 30% in the nonsepticemic episodes. A possible explanation of this difference is a more profound morbidity in the septicemic than in the nonsepticemic patients, in agreement with the fact that the septicemic patients were more leukopenic, granulocytopenic, and thrombocytopenic at the time of inclusion into the study. An association between morbidity and increased prevalence of *Enterobacteriaceae* has also been found in previous studies (11, 18). It was not possible to point to the presence of teeth or acute oral infections as possible factors disposing to septicemia.

In the present study, all oral and extraoral infections were diagnosed and surveillance cultures were carried out. The aim was to demonstrate a possible association between infectious foci in the oral cavity and septicemia and at the same time to estimate the strength of the association by searching for concomitant extraoral foci. In two (10.5%) of the 19 septicemias, an isolate identical to the blood isolate was found only in the mouth and at the same time acute infection was present only in the oral cavity. Because the bacteria were found on the same day, the oral cavity was the most probable origin in these two cases. In one additional case, a strain identical to the blood isolate (*S. epidermidis*) was detected only in the oral cavity. During the same episode, *S. epidermidis* was also isolated from skin infection. The skin isolate was identical to the blood and oral isolate with respect to biotype and plasmid profile but differed in antibiotic susceptibility pattern. Because the latter characteristic seems less valid than plasmid profile as an indicator of identity (13, 15), it cannot be excluded that the skin lesion was a possible focus in this case. In another two cases, the blood isolate was isolated from infections in both the oral cavity and an extraoral site. Thus, from the combined microbiological and clinical investigations, the prevalence of a possible oral focus was five (26.3%) of 19 cases (95% confidence limits, 9.2 to 51.2%) and the prevalence of a probable oral focus was two (10.5%) of 19 cases (95% confidence limits, 1.3 to 33.1%).

In nine (47.4%) cases, it was not possible to isolate a bacterium phenotypically identical to the blood isolate from the surveillance cultures. However, it is possible that examination of stool cultures would have identified more. Among these nine septicemic episodes, a clinical acute infection was diagnosed in seven cases, and in one of these, only oral

infections were diagnosed. Thus, on the basis of combined microbiological and clinical investigations or on clinical observations alone, a probable or possible oral focus of septicemia occurred in 6 (31.6%) of the 19 septicemias (95% confidence limits, 12.5 to 56.6%).

In the majority of previous studies, the aim was not primarily to describe oral findings during septicemias in hematologic patients, and the reported prevalence rates of an oral origin in the septicemias investigated were presented as secondary findings, the values being between 0 and 13.8% (3, 4, 6, 7, 10, 14, 16, 17). In the studies mentioned, the sampling methods used and the frequency of oral cultures in most cases were not described. Only Greenberg et al. (9) focused primarily on possible associations between oral infections and septicemia. Their study included 70 febrile episodes in 33 patients with AML. The patients were monitored with daily routine cultures from the oral cavity, throat, sputum, urine, stool, and blood samples, and in seven (53.8%) of 13 septicemias, the agent causing the septicemia was also isolated from clinical oral infections, while other body sites were negative for the bacteria isolated from the blood. Thus, the strong association found between oral infections and septicemia in the present study is in accordance with that observed by Greenberg et al. (9) and demonstrates that the role of oral infections has been previously underestimated.

The most frequent type of oral infection found in the present study, in cases of possible or probable oral origin of a septicemic episode, was acute gingivitis, which was present in four (67%) of six cases. This result is in agreement with the results of Greenberg et al. (9), in which correspondingly, three (43%) of seven septicemias had a possible periodontal origin. The present study did not include direct sampling of deep periodontal pockets. However, in view of the species of bacteria that were recovered from the blood samples and the previous finding (9) that in this patient group, the flora of the periodontal pockets reflects that of other oral sites, it is unlikely that sampling of these sites would have added anything to the results.

In conclusion, the present study suggests that prevention of bacteremias in patients with malignant blood diseases should include prevention and elimination of oral infections. This may reduce the morbidity and perhaps even the mortality in these patients. Future studies concerning the possible effect of preventive measures on the frequency of septicemia are needed.

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