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Characteristics of initial compared with subsequent bacterial infections among hospitalised haemato-oncological patients

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ABSTRACT

Surveys of bacterial infections among neutropenic cancer patients frequently report pooled antibiotic susceptibility data. Management guidelines address initial antibiotic regimens for febrile neutropenia. In this study, rates of bacterial infection and antibiotic susceptibilities among initial and subsequent or breakthrough episodes of fever were analysed. Prospective surveillance of fever of unknown origin (FUO), clinically documented infection and microbiologically documented infection (MDI) was conducted in the haemato-oncology and haematopoietic stem cell transplantation wards in a single cancer centre in Israel. Subsequent infections were defined as those developing during or after broad-spectrum antibiotic treatment. A total of 567 febrile episodes were documented among 271 patients. Bacterial MDIs were documented in 104/162 (64%) initial febrile episodes and 75/405 (19%) subsequent episodes and Gram-negative bacteria predominated (64% and 71%, respectively). *Escherichia coli* was the most common species isolated. Higher antibiotic susceptibilities were observed for initial compared with subsequent MDIs for Gram-negative bacteria [ceftazidime 80% vs. 45%, piperacillin/tazobactam (TZP) 86% vs. 40% and meropenem 95% vs.76%] and Gram-positive bacteria. TZP monotherapy was the most commonly used antibiotic and its susceptibility decreased to 22.2% following its use. Appropriate empirical antibiotic treatment was administered in 71/97 (73%) initial and 40/74 (54%) subsequent episodes ($P = 0.009$) and was significantly associated with mortality (adjusted odds ratio = 0.4, 95% confidence interval 0.18–0.87). We conclude that previous antibiotic exposure significantly impacts antibiotic susceptibility and that pooled reporting of all infections can be misleading. Treatment guidelines should address the antibiotic treatment of breakthrough fever.

1. Introduction

Infection is the most important preventable cause of death among haematological cancer patients. Bacterial infections, mainly bacteraemia, are common and increase mortality either directly or by interfering with the timeline of chemotherapy protocols. Appropriate empirical antibiotic treatment has a large and significant impact on survival following bacteraemia [1], especially among neutropenic patients [2]. Empirical antibiotic treatment is selected targeting the predicted susceptibilities of the infecting bacteria based on local and published epidemiology of these infections.

Surveys of bacterial infections among neutropenic cancer patients report a pooled pathogen/susceptibility distribution for patient risk groups [3–6]. These surveys inform policy-makers in the selection of empirical antibiotic regimens. Previous antibiotic treatment is an obvious risk factor for antibiotic resistance [6]. Thus, pooled epidemiological data might represent very different subpopulations that can be pre-defined for the selection of empirical antibiotic treatment.

In this study, pathogen distribution and antibiotic susceptibilities for infections occurring initially (at the onset of fever with neutropenia) and subsequent infections (diagnosed with persistent or recurrent fever during neutropenia, after patients have already been treated with broad-spectrum antibiotics) were compared.

2. Subjects and methods

This study was conducted in the Hemato-oncology and Bone Marrow Transplant Units at Davidoff's Cancer Center, Beilinson

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Hospital (Petah-Tikva, Israel) between March 2007 and May 2011. The centre is a university-affiliated, primary and tertiary care centre for adult patients (>18 years), including patients undergo autologous and allogeneic haematopoietic cell transplantations (HCTs). Infections were prospectively monitored according to a pre-defined protocol [7]. All consecutive hospitalised patients with fever of unknown origin (FUO), clinically documented infection (CDI) or microbiologically documented infection (MDI) after intensive chemotherapy or HCT were included. Febrile episodes related to blood products or chemotherapy or single measurements of fever without clinical or microbiological documentation of infection were excluded, although these were frequently treated with antibiotics. Patients could be included in the surveillance more than once for different episodes of infection. Different episodes were defined by a period without antibiotic treatment of ≥7 days, or a new CDI or MDI. Data were collected daily using a uniform case record form and were entered into an electronic database.

Initial, first-line episodes of infection were compared with subsequent episodes of infection. Subsequent infections were defined as those developing during or after antibiotic treatment (excluding antibiotic prophylaxis); all other infections were defined as initial infections. Consensus definitions were used for CDIs, MDIs, bacteraemia and FUO [8] and the 2008 revised definitions of invasive fungal disease (definitions were re-applied to data collected before publication of the updated guidelines) [9]. Lacking definitions of specific diagnoses (e.g. pneumonia, catheter-associated infection, etc.) in the neutropenic host, we adapted those used for healthcare-associated infections [10].

Fever was defined as a single temperature measurement ≥38.3 °C or ≥38 °C on two measurements taken at least 1 h apart. Neutropenia was defined as <500 cells/mm^3 or as functional neutropenia [11]. Empirical treatment was defined as that given in the first 48 h prior to receipt of susceptibility test results. Appropriate antibiotic treatment was defined as that matching the in vitro susceptibility of subsequently isolated bacteria. Antibiotic prophylaxis using ciprofloxacin was administered from the onset of neutropenia until its resolution or the need for broad-spectrum antibiotic treatment, to patients with acute leukaemia during induction and consolidations, and autologous and allogeneic HCT. Antifungal prophylaxis using fluconazole was administered to patients with acute leukaemia and allogeneic HCT. The empirical antibiotic regimen for febrile neutropenia was piperacillin/tazobactam (TZP) monotherapy, with or without vancomycin, according to the established indications [11]. Empirical antifungal therapy with voriconazole was administered following 5–7 days of fever persistence or breakthrough during broad-spectrum antibiotic treatment when neutropenia was not expected to resolve within the next 2–3 days. There were no specific guidelines for the antibiotic management of subsequent or breakthrough fever, and antibiotic modifications were considered on an individual basis. During induction or salvage treatment for leukaemia and allogeneic HCT, patients were hospitalised in single, high-efficiency particulate air (HEPA)-filtered, positive air-pressure rooms. Antibiotic susceptibilities were tested by disk diffusion and were defined by Clinical and Laboratory Standards (CLSI) criteria [12]. Intermediately susceptible bacteria were considered as resistant.

Categorical variables were compared using χ^2 or Fisher Exact test, as appropriate. Two-sided *P*-values are presented. Multivariate logistic regression analysis was conducted for 30-day mortality entering all included variables. The study was approved by the Ethics Committee of Rabin Medical Center (Petah-Tikva, Israel). Informed consent was not required since the study was non-interventional and data were analysed anonymously.

3. Results

During the study period there were 1326 admissions (527 individual patients) to the haemato-oncology and bone marrow transplant inpatient units and 15 658 hospital days. A total of 567 febrile episodes fulfilling inclusion criteria were documented among 271 patients (mean of 2.1 episodes per patient). Baseline diagnoses were acute leukaemia (n = 130), lymphoma (n = 87), multiple myeloma (n = 32) and other haematological disorders (n = 22). Of the 271 patients, 116 (43%) underwent HCT. Most patients (173/271; 64%) had an active disease prior to onset of the infectious episode.

Of all episodes, 162 were classified as initial, first-line episodes and 405 were classified as subsequent episodes; 243 breakthrough episodes were preceded by antibiotics given for a single measurement of fever or other reasons that did not fulfil criteria for FUO, CDI or MDI. Nearly all subsequent episodes occurred whilst the patient was receiving antibiotic treatment for the initial episode ('breakthrough' fever). The median time interval between the first episode of infection and the subsequent episode was 14 days (range 2–27 days). Death within 30 days from episode onset occurred in 16% of the initial episodes and 7% of the subsequent episodes.

Bacterial MDIs were present in 104/162 (64%) initial febrile episodes (bacteraemias, n = 76 and MDI, n = 28) and 75/405 (19%) subsequent episodes (bacteraemias, n = 58 and MDI, n = 17) (P < 0.001). Invasive fungal infections (IFIs) (proven or probable) were present in 7/162 (4%) initial and 13/405 (3%) subsequent episodes. Neutropenia was present in 106/179 MDIs (59%), although most patients had functional neutropenia at the time of episode onset. Seventy-eight MDIs (44%) were preceded by antibiotic prophylaxis with ciprofloxacin.

No statistically significant differences with regard to bacterial distribution between initial and subsequent episodes were observed (Table 1). In both groups Gram-negative bacteria predominated (64% and 71%, respectively) and *Escherichia coli* was the most common (29% and 25% of all episodes, respectively). *Staphylococcus aureus* was the most common Gram-positive bacteria in patients with initial MDIs, whilst *Enterococcus* spp. was most common in subsequent episodes. In subsequent episodes, *S. aureus* was isolated only in 3% of all patients. Results were similar when only episodes of bacteraemia were analysed.

Higher antibiotic susceptibilities were observed with initial MDIs compared with subsequent MDIs in patients with Gram-negative MDIs (ceftriaxone 71% vs. 28%, ceftazidime 80% vs. 45%, TZP 86% vs. 40% and gentamicin 78% vs. 52%, respectively) (P < 0.001 for all) (Table 2). Most importantly, this was also true regarding carbapenem susceptibility (meropenem 95% vs. 76%, respectively; P = 0.004). Carbapenem-resistant infections included

Table 1
Distribution of bacteria among initial and subsequent episodes [n (%)].

	Initial (N = 104)	Subsequent (N = 75)
Gram-negative bacteria		
Escherichia coli	30 (28.8)	19 (25.3)
Klebsiella pneumoniae	9 (8.7)	9 (12.0)
Pseudomonas aeruginosa	10 (9.6)	9 (12.0)
Acinetobacter baumannii	0	3 (4.0)
Enterobacter sp.	3 (2.9)	4 (5.3)
Campylobacter sp.	3 (2.9)	2 (2.7)
Stenotrophomonas maltophilia	3 (2.9)	4 (5.3)
Others	9 (8.7)	3 (4.0)
Gram-positive bacteria		
Staphylococcus aureus	14 (13.5)	2 (2.7)
Enterococcus sp.	6 (5.8)	12 (16.0)
Streptococcus viridans	4 (3.8)	1 (1.3)
Others	5 (4.8)	3 (4.0)
Other		
Clostridium difficile	8 (7.7)	4 (5.3)