

Polymicrobial Infection in Patients with Cancer: An Underappreciated and Underreported Entity

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Polymicrobial infections account for ~15% of infections in immunocompromised patients with cancer. However, limited information exists regarding the spectrum and microbiology of these infections, even in severely neutropenic patients. Most studies describe only monomicrobial bloodstream infections in detail, and information regarding polymicrobial infections and nonbacteremic infections is often incomplete or not provided at all. The current lack of well-established definitions for various infections in the immunocompromised host, including pneumonia, neutropenic enterocolitis, and polymicrobial infections, probably plays an important role in the paucity of published information. In this review, we briefly describe the limited information available regarding polymicrobial infections in patients with cancer and address the need for establishing consensus definitions for site-specific polymicrobial infections in neutropenic and nonneutropenic patients. We anticipate that, as factual information regarding such infections becomes available, a more comprehensive understanding of the true scope and impact of these infections will emerge, leading to appropriate modifications in the diagnostic work-up and in the therapeutic approaches used in treating these patients.

Neutropenic patients are susceptible to a wide variety of infections (table 1). The spectrum of infection in such patients undergoes periodic changes that have been well documented and that are influenced by the underlying immunologic deficit(s), the nature and intensity of antineoplastic therapy, the use of antimicrobial prophylaxis and empirical antibiotic therapy, the presence of catheters and other medical devices, and local epidemiological factors [1]. It is important to conduct periodic epidemiologic surveillance studies to document changing trends, because these have a significant impact on antimicrobial prophylaxis and empirical antibiotic therapy [2, 3]. Several study groups and investigators have described current trends in the epidemiology of bloodstream infection in patients with hematologic malignancies and solid tumors [4–7]. Most of these reports have documented a predominance of gram-positive organisms and a substantial decrease in gram-negative organisms as causes of bacterial infection in this patient population. Unfortunately, most of these reports have focused at-

ention only on bloodstream infections caused by a single organism (monomicrobial bloodstream infections) and have not included detailed information on polymicrobial bloodstream infections or infections at other sites. Consequently, these data provide an incomplete picture, because the overall spectrum of infection in patients with cancer may differ considerably from that associated with monomicrobial bloodstream infection alone [1, 8].

A guideline, published from a consensus report prepared for the Immunocompromised Host Society for the evaluation of new anti-infective drugs in febrile neutropenic patients, states that “it is important to prospectively define and provide standardized criteria for infectious entities that may develop during the clinical trial” [9, p. 5208]. Two broad categories of infection were defined: (1) bloodstream infection or fungemia involving ≥ 1 organism without a definable nonhematogenous site of infection and (2) infection at a specific site (e.g., pneumonia and cellulitis) with or without concomitant bloodstream infection or fungemia. Unfortunately, specific definitions for these infections were not provided, leaving it to each site institution or group to create these definitions for specific trials [10].

There are only a few reports specifically addressing polymicrobial infections, such as bloodstream infection, pneumonia, perirectal infection, neutropenic enterocolitis, and urinary

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tract infection, despite the fact that these infections are not rare [8, 11, 12]. Most information is derived from therapeutic trials in which only organisms causing bloodstream infection are reported, but even in these reports, the data on polymicrobial infection are usually sketchy and incomplete.

POLYMICROBIAL BLOODSTREAM INFECTION

Data on polymicrobial bloodstream infection from large antibiotic trials or surveillance studies involving febrile neutropenic patients are summarized in table 2. These data demonstrate that the proportion of bacteremic infections that are polymicrobial ranges from 8% to 32% [3, 13–21]. It is difficult to compare data from different institutions, because consistent definitions of what constitutes a polymicrobial bloodstream infection are lacking. For example, in one of the earliest studies of infection in patients with acute leukemia, polymicrobial bloodstream infection was defined as the isolation of >1 organism from blood culture specimens collected from a patient during a 1-week period [22]. In a subsequent study that was conducted by some of the same authors 15 years later, bloodstream infection was considered to be polymicrobial when multiple organisms were cultured during a period of 72 h [11]. These differences highlight the need for developing a standard definition of what constitutes a polymicrobial bloodstream infection.

Another significant deficiency in interpreting data on polymicrobial bloodstream infection is that reports documenting the frequency of these infections seldom describe the organisms isolated. In a large study of 507 polymicrobial bloodstream infections reported from our institution from 1972 through 1981, 385 (76%) of the infections involved at least 1 gram-negative bacillus, and 168 (33%) of the infections involved only gram-negative bacilli [11]. Polymicrobial infections caused by gram-positive, anaerobic, or fungal organisms (without the presence of a gram-negative bacillus) were infrequent. The gram-negative bacilli isolated most frequently were *Escherichia coli* (38% of infections), *Klebsiella* species (28%), *Pseudomonas aeruginosa* (20%), and *Enterobacter* species (13%). The most commonly isolated gram-positive organisms were streptococci (25% of infections), enterococci (16%), coagulase-negative staphylococci (13%), and *Staphylococcus aureus* (12%). Two organisms were isolated in 363 (72%) of the cases, 3 organisms were isolated in 109 (21%), 4 organisms were isolated in 27 (5%), and >4 organisms were isolated in 8 (2%). The overall response rate was 50%, which is substantially lower than the response rate associated with monomicrobial infection (65%–94%). The poorest responses were seen in patients with persistent neutropenia (25%), pneumonia (19%), and bloodstream infection caused by multiple gram-negative organisms (49%).

In a large study conducted by the Surveillance and Control of Pathogens of Epidemiologic Importance project, 2340 pa-

Table 1. Common infections in neutropenic patients.

Site	Infection
Bloodstream	Bloodstream infection (including catheter-related bloodstream infection), fungemia
Upper respiratory tract	Oropharyngeal infection, sinusitis, otitis
Lower respiratory tract	Pneumonia
Gastrointestinal tract	Esophagitis, enterocolitis (typhlitis)
Urinary tract	Cystitis, pyelonephritis
Skin/skin structure	Cellulites, wound infection, perirectal infection

tients with underlying malignancy and an episode of nosocomial bloodstream infection were identified [3]. Fourteen percent of these infections were polymicrobial, and only 251 patients (10.7%) were neutropenic. No details regarding the microbiological characteristics of these polymicrobial bloodstream infections were provided.

Several other studies deserve comment. Hung et al. [23] reported a study involving 76 febrile episodes in neutropenic children with cancer. Of 27 microbiologically documented infections, 4 (15%) were polymicrobial. Of interest, most of these infections involved the urinary tract. Norgaard et al. [24] reported 358 episodes of bloodstream infection in patients with hematological malignancies between 1992 and 2002. Only 110 (31%) of the patients were neutropenic, and polymicrobial infection occurred in 50 cases (14%). The only information provided regarding the infecting organisms was that *E. coli* were isolated from 30 (60%) and *S. aureus* were isolated from 7 (14%) of the patients with polymicrobial bloodstream infection.

PNEUMONIA

A total of 15%–30% of documented infections in febrile neutropenic patients are classified as pneumonia [25]. The majority of these are clinically and/or radiographically documented but do not have microbiological confirmation because of (1) the inability of patients to produce adequate sputum specimens and/or (2) the inability of many patients to tolerate diagnostic procedures, such as bronchoalveolar lavage [2]. These obstacles have severely limited our ability to identify the infecting pathogens. A recent review of 492 patients with cancer who underwent bronchoalveolar lavage at our institution demonstrated that multiple organisms were isolated from these specimens in 74 patients (15%). We excluded patients from whom coagulase-negative staphylococci were isolated (unpublished data). Among the combinations of pathogens were gram-negative bacilli (Enterobacteriaceae, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*) in ~15% of patients, a mold (predominantly *Aspergillus* species) plus a bacterium in 12%, multiple potentially pathogenic fungi in 22%, and a bacterium plus *Candida* species in the remainder of the patients. Experience at our

Table 2. Polymicrobial bloodstream infections in selected large antibiotic trials involving neutropenic patients.

Study	Year	No. of bloodstream infections	No. (%) of bloodstream infections that were polymicrobial
Peacock et al. [13]	1995	109	15 (14)
Cometta et al. [14]	1996	227	28 (12)
Gonzalez-Barca et al. [15]	1996	438	48 (11)
Giamarellou et al. [16]	2000	60	5 (8)
Del Favero et al. [17]	2001	277	26 (9)
Sanz et al. [18]	2002	236	38 (16)
Wisplinghoff et al. [4] ^a	2003	2340	329 (14)
Rossini et al. [19]	2005	75	8 (11)
Sigurdardottir et al. [20]	2005	95	18 (19)
Harter et al. [21]	2006	81	26 (32)

^a In this study, all patients had cancer. Only 798 patients were neutropenic. Information was not provided on polymicrobial bloodstream infections in this subgroup.

institution indicates that *Candida* species are rarely a cause of pneumonia, even in severely immunosuppressed patients [26]; therefore, in most culture samples from which *Candida* species were isolated, their presence probably did not represent a cause of the infection.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis (typhlitis) occurs predominantly in children with acute leukemia but can occur in others who experience prolonged neutropenia [27, 28]. The reported incidence among patients with acute leukemia varies from 0.8% to 26%, and the mortality rate approaches 50% [29–31]. Neutropenic enterocolitis is believed to be attributable to chemotherapy-induced mucosal injury that facilitates infection by aerobic and anaerobic enteric organisms [27, 32, 33]. The usual symptoms include fever, abdominal pain, tenderness, and diarrhea [29]. Although it is likely that these infections are polymicrobial, the offending pathogens are seldom identified antemortem except when isolated from blood culture specimens. Aerobic gram-negative bacilli are isolated most often, although *Clostridium septicum* has been associated with this disease, and polymicrobial bloodstream infection is not uncommon in patients with neutropenic enterocolitis [27, 32, 34].

PERIRECTAL INFECTION

Perirectal infection occurs in ~10% of patients with acute leukemia and is increasing in frequency among patients with solid tumors [35]. These infections are predominantly polymicrobial, and frequent pathogens include *E. coli*, *P. aeruginosa*, *Bacteroides* species, *Clostridium* species, *Prevotella* species, *Peptostreptococcus* species, *S. aureus*, and *Enterococcus* species. [36, 37]. It is

often difficult to identify the true pathogens from fecal contaminants, because few patients form abscesses that can be aspirated. Concomitant bloodstream infections, however, are usually polymicrobial.

OTHER POLYMICROBIAL INFECTIONS

The increasing use of hepatobiliary procedures, such as hepatic artery catheterization for embolization and chemotherapy, and various biliary drainage procedures has been associated with infectious complications [38, 39]. The infections most often encountered include cholangitis, bloodstream infections, liver abscess, gallbladder abscess, and subphrenic abscess. The majority of these infections are polymicrobial, with enteric gram-negative bacilli, *Enterococcus* species (including vancomycin-resistant enterococci), and *Candida* species being isolated frequently from abscesses, as well as from blood culture specimens.

Similarly, there has been a substantial increase in the frequency of recurrent, complicated urinary tract infection with the increasing use of stents and nephrostomies, as well as other urinary diversion procedures, and the creation of orthopic neobladders following extensive pelvic surgery [40–44]. The frequency of urinary tract infection in such patients is high (12%–39%), and the infections are often polymicrobial. These infections are frequently recurrent, difficult to treat, and may require administration of prolonged suppressive antibiotic regimens.

DISCUSSION AND RECOMMENDATIONS

A review of the current literature and our own extensive experience confirm that polymicrobial infections occur frequently in patients with cancer, both in the presence of neutropenia and in patients who are not neutropenic. These infections are given minimal attention in the large clinical trials of therapeutic regimens for neutropenic patients. For example, many laboratories do not process culture specimens from respiratory secretions, voided or catheterized urine, drainage from intra-abdominal or pelvic collections, or infected surgical sites when multiple organisms are recovered. Most of these culture results are simply reported as “normal site flora” or “contaminated specimens,” without identification of the organisms to the species level or the performance of drug-susceptibility testing. Laboratories may also not process specimens or may reject specimens as inadequate if they do not contain an adequate number of inflammatory cells (neutrophils), an issue which is of great importance in neutropenic patients, because these specimens will invariably not contain the requisite number of neutrophils.

A major obstacle to our understanding of these infections is a lack of definitions of what constitutes a polymicrobial infection. Table 3 presents some definitions to help resolve this problem. They are, admittedly, preliminary and will require

Table 3. Suggested definitions for patients with cancer with polymicrobial infections.

Infection site, diagnosis	Suggested diagnostic criteria
Bloodstream ^a	
Definite	>1 Organism isolated from blood culture specimens obtained within 24 h
Probable	>1 Organism isolated from blood culture specimens obtained within 48–72 h
Lung	
Definite	>1 Pathogenic organism isolated from sterile BAL fluid
Probable	>1 Pathogenic organism isolated from nonsterile bronchial wash or adequate sputum samples, excluding the organism associated with endogenous oropharyngeal flora; OR ≥1 microorganism isolated from sterile BAL fluid that is considered to be of low pathogenicity occurring in severely immunosuppressed patients, such as CoNS, diptheroids, <i>Bacillus</i> species, <i>Candida</i> species, and saprophytic molds
Biopsy specimens	
Definite	>1 Organism isolated from a sterile tissue sample; organisms such as CoNS, enterococci, and <i>Candida</i> species would be considered, provided that the other organism(s) are known pathogens
Probable	>1 Organism isolated from nonsterile tissue samples, excluding the local microflora, unless heavy growth of an otherwise-normal commensal organism is noted
Neutropenic enterocolitis	Because tissue cultures are generally not accessible, it is reasonable to presume that most infections are probably polymicrobial
Perianal infection	Because of the difficulties of obtaining uncontaminated specimens from this area, all of these infections should be considered to be polymicrobial
Skin and soft-tissue infection	Skin cultures and cultures of samples obtained from draining lesions are difficult to interpret, and unless heavy growth of a normal colonizing organism is isolated, only noncutaneous flora may be considered to be disease-associated pathogens, such as <i>Pseudomonas</i> species, <i>Stenotrophomonas</i> species, <i>Staphylococcus aureus</i> (including multidrug-resistant strains), <i>Aspergillus</i> species, <i>Fusarium</i> species, <i>Scedosporium</i> species, and other opportunistic molds in severely immunosuppressed neutropenic patients with cancer

NOTE. BAL, bronchoalveolar lavage; CoNS, coagulase-negative staphylococci.

^a Concurrent infections due to saprophytic molds, such as dematiaceous fungi, may also occasionally cause serious pulmonary infection, although the usual pathogenic molds in patients with hematologic malignancy and hematopoietic stem cell transplantation include *Aspergillus* species, *Fusarium* species, *Scedosporium* species, and organisms that are associated with zygomycosis. The saprophytic organisms are especially more important in patients with refractory or relapsed hematologic malignancy, severe and prolonged neutropenia, and extended therapy with systemic corticosteroids.

modifications, but they represent a starting point for further deliberations.

Even with the acceptance of uniform definitions, other problems exist. It is important to understand the pathogenic potential of certain organisms that are part of normal skin, orointestinal, or lower urinary tract flora, such as coagulase-negative staphylococci and *Candida* species, when they are isolated from sites other than the bloodstream. For example, coagulase-negative staphylococci are often contaminants but have been identified as the cause of pneumonia in neutropenic patients [45]. Despite these difficulties, we believe that it is important to accurately describe the spectrum, frequency, and microbiological characteristics of polymicrobial infections in both neutropenic and nonneutropenic patients, especially because such infections, compared with monomicrobial infections, are associated with greater morbidity and mortality [11]. This will result in a more complete understanding of the nature of infection in patients with cancer and may lead to changes in empirical antibiotic therapy when such infections are suspected, as well as to the more judicious use of targeted gram-positive agents, such as vancomycin, linezolid, and daptomycin. Consequently, we recommend that societies such as the Infectious Diseases Society of America and the International Immunocompromised Host

Society develop and publish standardized definitions for the various infections that occur in immunocompromised patients and/or patients with cancer. We also recommend that laboratories—at least those in institutions that deal with substantial numbers of patients with cancer—develop separate guidelines and/or protocols for handling, processing, and reporting microbiological specimens and data from patients with cancer, particularly those with neutropenia. Finally, we encourage clinicians caring for such patients to focus on and report the entire spectrum of infections that they encounter.

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