8 New and unusual infections in neutropenic patients

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Medical practice lives with change. New advancements often bring unanticipated problems and new challenges. Thirty years ago the approach to fever in a granulocytopenic patient with acute leukemia was individualized, expectant, and based on microbiological documentation of the invading bacterial pathogen, with attribution of fever itself in large part to the underlying disease. The landmark paper of Schimpff et al. in 1971 [1] introduced the concept of empirical therapy with early administration of antibiotics directed against the most likely bacterial pathogens. This approach resulted in improved outcome from infectious episodes, and it has become the standard of therapy.

Empirical therapy was relatively simple two decades ago when the most likely infecting organisms were quite predictable: *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Staphylococcus aureus*. In fact, gram-negative rods were then responsible for over two thirds of the bacteremic infections in febrile neutropenic patients. However, over the course of these past 20 years, a dramatic and significant shift has occurred in the relative frequency of isolation of gram-negative and gram-positive pathogens (figure 1).

Using data from the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC), figure 1 plots the relative frequency of gram-negative and gram-positive organisms as single causative pathogens isolated from bacteremic episodes in febrile granulocytopenic patients with cancer. Clearly, gram-negative bacteria have declined and gram-positive organisms have increased in their pathogenetic role in this patient population.

The last decade has also witnessed the emergence of the acquired immunodeficiency syndrome (AIDS), with its ever expanding list of invading pathogens. As neutropenia is the most frequently encountered immunocompromised state in clinical medicine, this paper will review the changing array of infections in neutropenic and other immunocompromised patients with cancer and will highlight some of the more unusual infections. As will be seen, as patients are increasingly immunocompromised, and as antibiotic-susceptible organisms are facilely eradicated, then we will continue to see the increasing pathogenic significance of organisms previously thought to be commensal or 'nonpathogenic.' In this context, no organism can be safely dismissed as a contaminant, and physicians must increase their

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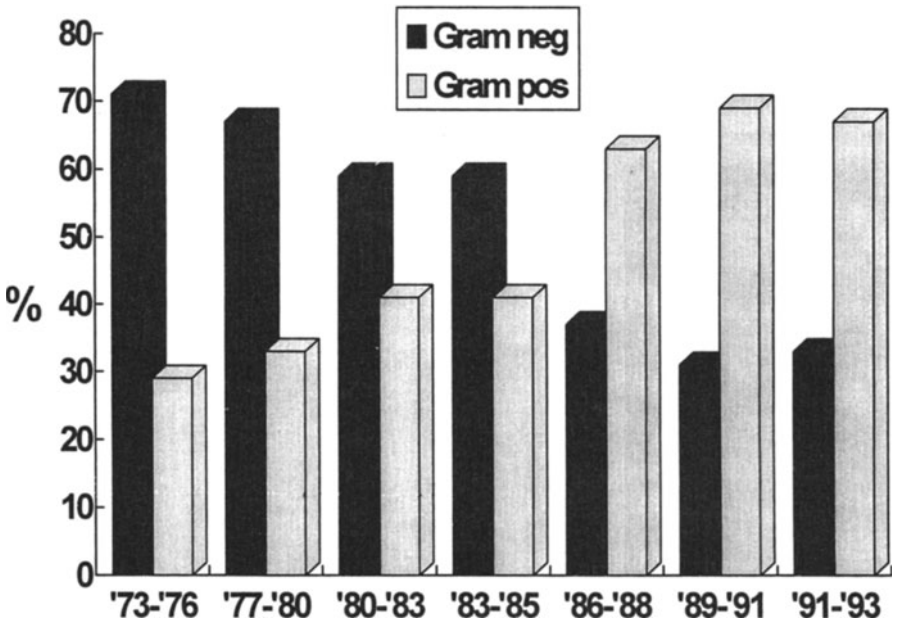

Figure 1. Relative frequency of isolation of gram-positive and gram-negative bacteria as single bloodstream isolates. (Data from the EORTC International Antimicrobial Therapy Cooperative Group.)

awareness of microbes whose names they had never encountered, even a decade earlier.

Reasons for change

Several reasons have been postulated to explain the shift in bacterial infections in neutropenic patients. First, with the increasing intensity of anticancer chemotherapy regimens, oral and upper gastrointestinal tract mucositis has become more significant, and this forms a ready site for entry of gram-positive coccal flora. Second, long dwelling intravascular catheters, such as the Hickman, Broviak, or Portacath devices, have become increasingly commonplace and routine, and these provide ready bloodstream access of gram-positive skin flora. Third, introduction of the fluoroquinolone antibiotics as prophylactic agents in neutropenic patients has impacted dramatically on the frequency of gram-negative rod bacteremia without a major effect on gram-positive infections [2]. Other pressures from widespread use of broad-spectrum antibiotics have been implicated but are more difficult to prove. Recently, data from the M.D. Anderson Cancer Center have suggested that the increasing use of H_2-antagonists in hospitalized cancer patients is related to the increase in viridans streptococcal bacteremia [3].

New gram-positive pathogens

Although not strictly 'new' organisms, recent studies have highlighted the emergence of alpha-hemolytic or 'viridans' streptococci as important pathogens in the neutropenic patient. In fact, a recent IATCG trial reported that streptococcal species were responsible for 57 of 129 (44 percent) single-organism bacteremic episodes and of these 44 (77 percent) were due to viridans group streptococci [4]. Viridans streptococci such as *Streptococcus mitis* have been associated with sepsis and the adult respiratory distress syndrome (ARDS) in leukemic patients [3,5–8]. *Leuconostoc* species had been regarded as a commensal or nonpathogen, but Handwerger and colleagues [9] reported intravenous catheter-associated bacteremias caused by this vancomycin-resistant, fastidious, slow-growing gram-positive coccus, which may be confused microbiologically with viridans streptococci, enterococci, or lactobacilli. This organism is also resistant to teichoplanin but is susceptible to aminoglycosides and clindamycin, with variable susceptibility to penicillins and first-generation cephalosporins.

Corynebacterium jeikeium are nonsporulating, small gram-positive diphtheroids that form gray-white, nonhemolytic smooth colonies in 5 percent CO_2. A characteristic metallic sheen may be useful to suspect these organisms, which also are catalase positive. J-K corynebacteria, as these organisms are also known, colonize the skin, axilla, and rectum and cause intravenous catheter-associated bacteremia in neutropenic patients, especially in those who have received third-generation cephalosporins. These organisms have caused endocarditis, peritonitis, prosthetic joint infections, etc. [10–12].

Rhodococcus equi (formerly *Corynebacterium equi*) is a pleomorphic nonmotile, nonhemolytic, gram-positive rod that is acid fast when grown on Lowenstein-Jensen media. It causes suppurative pneumonitis, abscesses, with pleural effusion and empyema in severely immunocompromised patients, including patients with AIDS [13]. Although bacteremia is relatively rare, it can occur. *Rhodococcus equi* is resistant to penicillin and first-generation cephalosporins but susceptible to macrolides, chloramphenicol, vancomycin, clindamycin, aminoglycosides, rifampin, and sulfonamides.

Stomatococcus mucilaginosus (formerly known as *Neisseria mucosa* or *Staphylococcus salivarius*) was thought to be nonpathogenic or commensal. However, this slime-producing, nonhemolytic, catalase-variable, oxidase-negative organism has been reported recently to cause catheter-associated bacteremia in severely immunocompromised patients, especially following bone marrow transplantation [14,15]. This organism is a prominent member of the oral flora and may be associated with dental caries. It forms adherent, mucoid gray colonies but does not grow on 5 percent NaCl media. *Stomatococcus mucilaginosus* is usually susceptible to vancomycin, erythromycin, penicillin (not all), rifampin, and fusidic acid. However, clinical infections in immunocompromised patients may respond slowly and might recur following therapy.

Another gram-positive organism, *Bacillus cereus*, has been reported responsible for a relatively typical scenario in severely neutropenic and immunocompromised

patients. *Bacillus cereus* may be associated with a vesicle or pustule on the digit or a limb that progresses to an eschar-coated draining wound. Although bacteremia is not common, patients may develop necrotizing fasciitis, pneumonitis, and meningitis, and may appear quite septic. This organism is resistant to penicillin, cephalosporins, and trimethoprim/sulfamethoxazole but is usually susceptible to vancomycin and also to clindamycin, erythromycin, aminoglycosides, and chloramphenicol [16].

Other gram-positive bacteria that might be troublesome for neutropenic patients include *Enterococcus* species (especially those resistant to vancomycin and aminoglycosides), *Lactobacillus rhamnosus, Corynebacterium striatum, Clostridium septicum*, and *Cl. tertium.*

New gram-negative pathogens

Although bacteremia due to gram-negative bacilli is decreasing in neutropenic patients, primarily attributed to increasing use of fluoroquinolone prophylaxis, these organisms are still responsible for infections in this patient population. Some of the newly recognized organisms are notable for their antimicrobial resistance and others for their epidemiology or novel clinical presentation.

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia, Pseudomonas maltophilia*) is particularly problematic because of its resistance to many antibiotics. It is resistant to imipenem, beta-lactam antibiotics, and the aminoglycosides! Some strains may be susceptible to trimethoprim-sulfamethoxazole (which is probably the first-line drug of choice) and variably to some fluoroquinolones. This organism is found with increasing prevalence in neutropenic patients as a nosocomial pathogen, especially in hospitals where imipenem use is high [17].

Alteromonas putrefaciens, an oxidase positive, non–glucose-fermenting gram-negative rod, is associated with spoiled meats and tainted butter. It has been isolated as a cause of cutaneous ulcers, cellulitis, and occasionally bacteremia in neutropenic patients. This organism is susceptible to second- and third-generation cephalosporins, ureidopenicillins, imipenem, aminoglycosides, and the fluoroquinolones [18].

A recent report showed that *Vibrio parahaemolyticus*, an organism usually associated with sea water, caused a paronychia with subsequent fever, hypotension, and hemolytic anemia in a patient with acute myelocytic leukemia who lacerated her finger while preparing fresh squid in her kitchen [19]. This organism is susceptible to trimethoprim/sulfamethoxazole, ureidopenicillins, fluoroquinolones, imipenem, ceftazidime, chloramphenicol, and tetracyclines.

Capnocytophaga species (formerly DF-1 and DF-2) are members of the normal oral, vaginal, and gastrointestinal flora. These capnophilic, facultatively anaerobic gram-negative rods grow on blood agar and are catalase, oxidase, and indole negative, but they do ferment glucose, sucrose, maltose, lactose, and mannose. They have been reported to cause bacteremia in patients with severe oral and mucosal pathology following bone marrow transplantation [20]. Although resistant to aminoglycosides and trimethoprim, these organisms are susceptible to clindamycin

and penicillins, with variable susceptibility to cephalosporins, imipenem, chloramphenicol, tetracyclines, and the fluoroquinolones. A related species, Dysgonic Fermenter-3, has been reported as a cause of bacteremia in a leukemic patient receiving broad-spectrum antibiotics [21]. This organism was susceptible to chloramphenicol and trimethoprim/sulfamethoxazole.

Other gram-negative bacteria recently associated with infections in neutropenic patients include: *Pseudomonas cepacia*, a biofilm producer susceptible to ceftazidime, piperacillin, and cotrimoxazole but resistant to imipenem, tobramycin, and ticarcillin, and associated with intravenous catheter infections [22]; *Achromobacter xylosoxidans*, a cause of bacteremia associated with mucositis, a gastrointestinal focus, and possibly intravenous catheters that respond to trimethoprim/sulfamethoxazole but not usually to aminoglycosides, cephalosporins, and quinolones [23]; *Ochrobactrum anthropi* (CDC group Vd), a non–lactose-fermenting, oxidase-positive, gram-negative rod that caused persistent bacteremia in a child with cancer despite therapy with vancomycin and ceftazidime but that responded to cotrimoxazole plus amikacin [24]; and *Agrobacterium radiobacter*, an aerobic, catalase- and oxidase-positive plant pathogen resistant to tobramycin but sensitive to ticarcillin, cefoxitin, ceftriaxone, cefotaxime, and gentamicin, and that caused catheter-related bacteremia, peritonitis, and urinary infection in three reported patients [25].

Methylobacterium extorquens used to be known by many other species names: *Pseudomonas mesophilica, Ps. methanolica, Protaminobacter rubra, Vibrio extorquens,* and *Mycoplana rubra.* It is a gram-negative, aerobic oxidase and catalase-positive motile rod that does not ferment glucose. It has caused three reported cases of catheter-associated bacteremia in leukemic patients, but these were not believed to be life threatening. Treatment with aminoglycosides and possibly with cotrimoxazole or ciprofloxacin has been recommended [26].

Anaerobic organisms in neutropenic patients

Classically, infections with anaerobic organisms such as *Bacteroides fragilis* and other species were not found frequently in granulocytopenic patients unless they had destructive gastrointestinal malignancies. Recently, infections caused by some 'new' gram-negative and gram-positive anaerobes have been reported. A beta-lactamase–producing strain of *Fusobacterium nucleatum* was isolated from a leukemic patient with ulcerative pharyngitis and nodular pulmonary infiltrates suggestive of septic emboli [27]. Clindamycin plus metronidazole was effective clinically. *Leptotrichia buccalis*, an anaerobic gram-negative rod found normally in the oral cavity, was reported to cause several cases of bacteremia in patients with leukemia and advanced stage malignancies who also had severe oral and gastrointestinal mucosal inflammation and ulceration [28]. This organism is resistant to aminoglycosides, vancomycin, fluoroquinolones, and the new macrolides, but is susceptible to penicillins, cephalosporins, clindamycin, metronidazole, and tetracycline.

Clostridium septicum is an anaerobic gram-positive rod known to cause necrotizing enterocolitis. Recently, a non–toxin-producing, presumably 'nonpathogenic'

related strain, *Clostridium tertium*, has been reported to cause bacteremia in granulocytopenic patients. This organism produces a milder illness than *Cl. septicum* and was isolated from seven patients in Finland, most with perirectal cellulitis or another presumed gastrointestinal tract source. Antibiotic therapy with a third-generation cephalosporin and an aminoglycoside was successful in most cases [29].

Fungal infections in neutropenic patients

Physicians who care for patients with cancer expect to see infections due to *Candida* spp. and *Aspergillus* spp., especially after long courses of antibiotics in profoundly neutropenic patients. Similarly, cryptococcal meningitis was not unknown in patients with lymphocytic malignancies or with lymphomas under treatment with corticosteroids. However, with increasing use of intensive chemotherapy regimens and with widespread use of new triazole and imidazole antifungal drugs, a broader spectrum of fungal infections is emerging. Many fungal infections in patients with cancer are associated with long-dwelling intravascular catheters, and these have been reviewed recently [30].

Anaissie and colleagues have recently reviewed fungal infections in patients with cancer [31] and reported that fungemia, sinus infections, and skin and soft tissue infections caused by dermatophytes and 'low-virulence' plant fungi were increasing in frequency in patients with cancer. For example, *Trichosporon beigelii*, the agent of white piedra, was isolated as a causal organism in pneumonia, nodular purpuric skin lesions, hepatitis, glomerulonephritis, endophthalmitis, and even endocarditis with fungal emboli. This organism may be resistant to amphotericin B. The therapy for fungal infections is addressed in two other chapters in this book.

Infections due to *Fusarium* spp. may be suspected clinically by the presence of painful, necrotic, and nodular skin lesions that begin as tender erythematous papules. Disseminated infections are seen and these organisms are resistant to the imidazoles and triazoles [32,33]. *Rhodotorula rubra* and other species were isolated from 23 patients with intravenous catheters at Sloan Kettering, with a good response to catheter removal and amphotericin B [34].

Dematiaceous soil fungi, such as *Exophiala jeanselmei, E. pisciphila, E. spinifera*, and *Scedosporium inflatum*, have also caused infections in neutropenic patients [35,36]. In neutropenic patients the flask-shaped *S. inflatum* has caused fungemia associated with intravascular devices, retinal lesions, esophagitis, and hepatosplenic infections. These organisms resist amphotericin and fluconazole in vitro [36].

The Zygomycetes (*Absidia, Rhizopus*, and *Cunninghamella* spp.) also are reported with increasing frequency from neutropenic and other immunocompromised patients. *Alternaria* have been associated with minimally symptomatic sinusitis, which responded to aggressive surgical debridement plus amphotericin B [37]. *Rhizomucor pusillus* and *Cunninghamella* spp. may cause invasive pulmonary disease with hemorrhagic alveolitis [38].

Other fungi recently reported to cause infections in cancer patients include *Pseudallescheria boydii, Torulopsis pintolopesi, Geotrichum candidum, Saccharomyces cerevisiae, Drechslera* sp., *Exserohilum rostratum, Phialophora parasitica,*

Acremonium sp., *Malassezia furfur, Pichia farinosa*, and *Hansenula anomala*, among others. Most of these fungi are isolated as vascular catheter-associated fungemia in neutropenic patients.

Mycobacterial infections

As the AIDS epidemic continues its ravaging course, tuberculosis is again on the rampage and drug resistance among *Mycobacterium tuberculosis* is also increasing. In addition, neutropenic patients may be infected with so-called atypical mycobacteria, such as *Mycobacterium chelonae, M. fortuitum*, etc.

In a recent report, the *Mycobacterium fortuitum* complex (which used to include *M. chelonae*) was isolated from 15 patients at the M.D. Anderson Cancer Center [39]. Most of these infections were associated with intravenous catheters, but patients presented with cellulitis, skin nodules, and abscesses. Catheter removal or surgical excision of the catheter tunnel plus treatment with either amikacin plus cefoxitin, trimethoprim/sulfamethoxazole, doxycycline, or erythromycin was associated with clinical recovery.

Mycobacterium chelonae also is a rapidly growing species that resembles *Nocardia* on Gram stain because of its beaded-rod appearance. Three patients with prolonged neutropenia at the Royal Free Hospital in London presented with disseminated infection but responded to antibiotics as their granulocyte counts improved [40].

Viral infections

Oncologists have been familiar with disseminated infection due to Varicella-zoster and herpes simplex viruses, especially in patients with lymphomas and chronic lymphocytic leukemia. These viruses may cause meningoencephalitis or visceral involvement. The introduction of prophylactic and therapeutic acyclovir, ganciclovir, and foscarnet has had a favorable impact on these conditions, and they will not be considered further in this review.

Other emerging pathogens in neutropenic patients

Bartonella (Rochalimaea)

The application of molecular biological techniques to diagnostic microbiology is certain to enhance the identification of organisms responsible for many diseases. Among the first examples of this advance is the association of *Bartonella* (formerly, *Rochalimaea*) species with a variety of illnesses. *Bartonella quintana*, a Rickettsial-like pathogen, was initially associated with bacillary angiomatosis and peliosis hepatis in patients infected with the human immunodeficiency virus [41]. This organism

has been renamed *Bartonella henselae* [42]. This organism also has been isolated from febrile, bacteremic patients with cancer, including neutropenic patients [42,43].

Bartonella henselae can be isolated using the red blood cell lysis-centrifugation method, and it grows in 4 days on several media, including charcoal-yeast extract, and blood or chocolate agars. *Bartonella* species are susceptible to macrolides, tetracycline, and many antituberculous drugs. The organisms can be recognized in tissue biopsy specimens using the Warthin-Starry stain. A related organism, *Afipia felis*, is probably the etiologic agent of cat scratch disease. As the clinical spectrum of infections caused by *Bartonella* and related organisms is expanding, clinicians can expect to see more patients with these infections [44].

Toxoplasmosis

Infections caused by *Toxoplasma gondii* are frequent in patients with the acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection, in whom toxoplasmic encephalitis is most common. Patients with Hodgkin's disease, non-Hodgkin's lymphoma, leukemias, and a variety of solid tumors are subject to develop toxoplasmosis with more protean manifestations [45]. These patients may manifest fever, lymphadenopathy, hepatosplenomegaly, pneumonitis, retinochoroiditis, myocarditis, and rash, in addition to central nervous system signs and symptoms [45].

The diagnosis of toxoplasmosis in the patient with cancer depends on serological evidence, biopsy to identify organisms in tissue, and/or cell culture or mouse inoculation to isolate the organism. New antibody detection methods and polymerase chain reaction techniques are being developed. Treatment modalities include pyrimethamine and sulfonamides, or clindamycin with pyrimethamine; experimental studies with the new macrolide/azalide drugs and atovaquone are in progress.

Pneumocystis carinii

Like toxoplasmosis, pneumonia due to *Pneumocystis carinii* is very common in patients with AIDS (although prophylactic therapy has reduced its incidence). However, prior to the AIDS epidemic infectious disease clinicians were familiar with this infection in unprophylaxed patients with lymphocytic malignancies, Hodgkin's disease, rhabdomyosarcoma, severe combined immunodeficiency syndrome, and in those undergoing bone marrow or organ transplantation [46]. Patients with cancer have a similar illness to those with AIDS, except that cancer patients have a shorter prodrome of a brief illness, with fever, dry cough, and dyspnea, which may rapidly progress to respiratory distress. Today, *Pneumocystis carinii* pneumonia presents less commonly in patients with malignancies than in those with HIV infection in the absence of prophylaxis. Corticosteroid use is a major risk factor in cancer patients [47]. Extrapulmonary manifestations are not common in either patient group.

As the organism load appears to be much greater in patients with HIV infection than in those with malignancies, biopsy or direct sampling of bronchial secretions

was often necessary in patients with cancer. However, recent series have suggested that induced sputum as well as bronchoalveolar lavage are useful in identifying pneumocysts [48]. Polymerase chain reaction amplification techniques are under development to increase the diagnostic yield. Physicians have been familiar for a long time with other parasitic diseases, such as strongyloidiasis, in the immunocompromised host. These will not be further reviewed here.

Treatment for 2 weeks with trimethoprim/sulfamethoxazole and pentamidine is effective. Experience with other regimens used in patients with AIDS has not been adequate to recommend them in patients with malignant underlying diseases.

Microsporidia

Microsporidia are pathogens relatively recently associated with cancer and immunosuppressing conditions or treatments. The AIDS epidemic has brought to the forefront infections caused by *Encephalitozoon, Nosema*, and enterocytozoon species and cryptosporidial diarrhea as well. In one report of 20 patients with hematologic malignancies, *Cryptosporidium parvum* was associated with severe intestinal disease, moderate diarrhea, acalculous cholecystitis (similar to patients with HIV infection), and even pneumonia. Resolution occurred spontaneously but relapse was common [49]. Although no effective therapy is available for cryptosporidiosis, the new azalide/macrolide drugs reduce coccidial load in experimental animal infections.

Algae

As a prime example of infection with organisms previously thought to be noninfectious for humans, recent reports have indicated that the unicellular algae *Prototheca wickerhamii* and other *Prototheca* species may cause algemia and localized granulomatous infections in immunocompromised as well as some immunocompetent patients. Ulcerative skin lesions have been described in a patient with systemic lupus erythematosus [50] and an ulcerating soft tissue pharyngeal mass in a chronically endotracheally intubated patient [51]. *Prototheca wickerhamii* also has been isolated from a case of peritonitis associated with chronic ambulatory peritoneal dialysis [52] and from the blood of an immunocompromised child with Hodgkin's disease and a Hickman catheter [53]. Treatment with amphotericin B or imidazole or triazole antifungal agents has met with some success.

Summary

Infections in immunocompromised patients with cancer are common and the primary risk factor is neutropenia, usually induced by chemotherapeutic agents. The spectrum of bacterial infection is shifting from gram-negative to gram-positive. The array of fungal infections in cancer patients is expanding to include organisms previously unknown as invasive human pathogens. New species are being defined

to explain extant pathologies, and free living algae are now emerging as pathogens in immunocompromised patients. Physicians must remain alert to these emerging pathogens and to the need to evaluate optimal treatments for the usual and unusual infections in neutropenic and other compromised patients with cancer and allied diseases.

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