306 Prophylaxis and Empirical Therapy of Infection in Cancer Patients

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SHORT VIEW SUMMARY

RISK FACTORS FOR INFECTIONS IN CANCER PATIENTS

- Neutropenia is the most important, particularly if severe (<100 polymorphonuclear neutrophils) and prolonged (7–10 days).
- Other risk factors include mucositis; underlying disease and its status; intensity of chemotherapy; the use of targeted and biologic therapies, especially monoclonal antibodies, such as alemtuzumab or rituximab; surgical procedures; devices such as central venous catheters; neoplastic obstruction; and genetic factors.

EPIDEMIOLOGY AND ETIOLOGY

- Epidemiology of bloodstream infections in neutropenia is constantly changing, and after years of predominance of gram-positive cocci, gram-negative rods have been emerging in many centers as the most frequent pathogens.
- This shift has been accompanied by an increasing rate of resistant pathogens, such as extended-spectrum β-lactamase–producing Enterobacteriaceae, carbapenem-resistant gram-negative pathogens, methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, and vancomycin-resistant enterococci.
- The main challenge is the management of multidrug-resistant (MDR) gram-negative bacteria for which few therapeutic options exist.
- Invasive fungal diseases (IFDs) in hematology patients are caused mainly by *Aspergillus* species. Probably due to the widespread use of fluconazole prophylaxis, *Candida* is less frequent in hematology, but fluconazole-resistant strains are emerging; patients with solid tumors remain at risk for candidemia; and resistant or new *Candida* strains, or both, have been reported (echinocandin-resistant *Candida glabrata* or *Candida auris*).

PROPHYLAXIS (see Table 306.4)

- The role of fluoroquinolone antibacterial prophylaxis during neutropenia in an era of widespread fluoroquinolone resistance and increasing multidrug resistance among gram-negatives is controversial.
- In general, antifungal prophylaxis is indicated in patients receiving induction chemotherapy for acute myelogenous leukemia (AML), in patients with myelodysplastic syndromes undergoing high-intensity treatment, and in selected groups of cancer patients, if the incidence of IFD is approximately 8% to 10% or higher.
  - Posaconazole as mold-active prophylaxis is recommended for patients receiving induction chemotherapy for AML or myelodysplastic syndrome. Voriconazole is an alternative.
  - Fluconazole is recommended as yeast-active prophylaxis in AML patients receiving anthracycline regimens. It should be combined with an intense mold-directed diagnostic approach in centers with high baseline incidence of mold infections.
- Secondary antifungal prophylaxis should be administered to patients with previous IFD who receive high-intensity chemotherapy or a transplant.
- Prophylaxis against *Pneumocystis jirovecii* (usually with trimethoprim-sulfamethoxazole three times per week) is beneficial in patients with deficits of T-cellular immunity, particularly with chronic lymphocytic leukemia, or in those receiving high-dose corticosteroids, fludarabine, or alemtuzumab. Anti-*Pneumocystis* prophylaxis is also warranted in case of certain novel targeted therapies or novel combinations, such as idelalisib or bendamustine plus rituximab.
- Antiherpes prophylaxis with acyclovir or valacyclovir is recommended in patients with acute leukemia or receiving drugs such as alemtuzumab and bortezomib.
- Varicella postexposure prophylaxis with specific immunoglobulins and/or acyclovir is recommended for high-risk varicella-zoster virus–susceptible patients.
- Antiviral prophylaxis of hepatitis B virus (HBV) reactivation is recommended for cancer patients with chronic inactive hepatitis B (hepatitis B surface antigen [HBsAg] positive, HBV DNA <2000 IU/mL, normal aminotransferases) and for selected patients with a resolved HBV infection (HBsAg negative/hepatitis B core antibody [HBcAb] positive), particularly if receiving anti-CD20 therapies (see Chapter 145). Frequent HBV DNA testing and antiviral therapy in case HBV DNA becomes positive is the alternative for those with a resolved HBV infection.

Immunization

- Influenza and pneumococcal vaccination of patients, especially during less aggressive treatment phases, is recommended.
- Influenza and varicella vaccination of household contacts and health care workers is recommended.

MANAGEMENT OF FEBRILE NEUTROPENIA (see Figs. 306.2 and 306.3)

Initial Approach

- Blood cultures, including at least one set from the central venous catheter, if present
- Assessment of the risk of severe infection (e.g., Multinational Association for Supportive Care in Cancer score; see Table 306.5)
- Assessment of the risk of infection caused by resistant pathogens; risk is high in case of:
  - Colonization or previous infection caused by resistant bacteria
  - Local epidemiology with high incidence of infections caused by resistant pathogens

Choice of Appropriate Therapy: Antibacterial

- Oral versus intravenous depending on inpatient or outpatient setting and the risk of complication (e.g., Multinational Association for Supportive Care in Cancer score; see Table 306.5)
- Escalation versus deescalation strategy
  - Escalation strategy: start with anti-*Pseudomonas* β-lactam monotherapy, usually other than a carbapenem.
  - Deescalation strategy: Usually start with a carbapenem in combination with vancomycin or an aminoglycoside or both, and then deescalate to piperacillin-tazobactam or a third-generation cephalosporin depending on clinical outcome and microbiologic results. In patients colonized with MDR gram-negative organisms, start with appropriate agents targeting the colonizing pathogen (e.g., novel anti–gram-negative agents or combinations of antibiotics) and then deescalate as noted previously if no MDR pathogen is isolated.

Choice of Appropriate Therapy: Antifungal

- Empirical antifungal therapy (adding antifungal agent in patients persistently febrile despite broad-spectrum antibiotics) could be replaced by diagnostic-driven strategy based on the use of diagnostic tools, such as computed tomography scan and fungal serum markers (galactomannan and β-D-glucan).

SHORT VIEW SUMMARY—cont'd

OTHER THERAPEUTIC RECOMMENDATIONS

- In the era of increasing antibiotic resistance and shortage of agents active against MDR pathogens, antimicrobial stewardship in cancer centers is mandatory and should include:
  - Infection-control practices
  - Local surveillance of antibiotic resistance, antibiotic consumption, and patient outcomes
  - Promoting appropriate antibiotic use (e.g. timely de-escalation or discontinuation, appropriate dosing)
  - Establishing antibiotic regiments for empirical therapy according to local epidemiology

Cancer patients probably represent the best example of how both a disease and its treatment can impair the complex immunologic network aimed at maintaining the integrity of our body and defending it against infections from both the external and the internal environment. For decades we have known that a granulocyte count of less than 500 cells/mm^3 (and especially <100 cells/mm^3) is associated with an increased risk of severe bacterial and fungal infections.[1,2] There is also evidence that patients with a granulocyte count between 500 and 1000 cells/mm^3, especially if rapidly decreasing, are also at high risk of infectious complications, because neutropenia is not a static but a dynamic concept. Indeed, a survey on fever during neutropenia in children with cancer showed the presence of severe infectious complications (e.g., bacteremia or invasive mycosis) in patients with a granulocyte count that never dropped below 500 cells/mm^3, suggesting the presence of a "gray zone" that should be carefully monitored.[3] The other three main factors that impact the risk of infectious complications in these patients are the damage of anatomic barriers, such as skin or mucosal membranes; the alteration of the microbiota diversity; and the presence of indwelling devices. Indeed, mucositis itself might result in severe infections due to microbial translocation, even in the absence of neutropenia, and a central venous catheter (CVC) may facilitate the entrance of endogenous and exogenous bacteria and fungi in the bloodstream or in subcutaneous tissues. The alteration of the microbiota diversity has been recently shown to affect the risk of infection and other important outcomes in hematology, in a way that is still not properly understood. In patients with solid tumors, cancer-related obstructions and surgical procedures, together with prolonged hospital admission, are additional conditions able to increase the infection risk. Neutropenia and mucositis are usually related to the type and intensity of traditional chemotherapy, while the microbiome alteration is multifactorial in origin, although the improper and excessive use of antibiotics and other drugs (e.g., proton pump inhibitors) is pivotal in this sense. In addition to the appreciation of the role of a damaged microbiota in affecting the risk of infection, in recent years, the widespread use of the novel targeted and biological agents, which have become part of many chemotherapeutic regimens, is posing new challenges that might change substantially what we know about the pathogenesis of infections in cancer patients, as well as their type and incidence.

Finally, the most important issue now challenging physicians and health care workers, as well as the scientific and nonscientific community, is the phenomenon of the growing antibiotic bacterial resistance worldwide, which has the potential to change substantially prophylactic and treatment issues. Antibiotic-resistant pathogens such as Enterobacteriaceae resistant to third-generation cephalosporins (producers of extended-spectrum β-lactamases [ESBLs]) or even carbapenems, multidrug-resistant (MDR) *Pseudomonas aeruginosa* or *Acinetobacter baumannii,* methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis,* vancomycin-intermediate *S. aureus,* and vancomycin-resistant enterococci (VRE) are spreading in cancer patients, with increasing endemicity and sporadic cases or outbreaks occurring almost everywhere in the world. For example in Italy, where carbapenemase-producing *Klebsiella pneumoniae* is currently endemic, a study of bloodstream infections (BSIs) in hematologic cancer patients found that 35% of *K. pneumoniae* strains were resistant to carbapenems and 70% of *P. aeruginosa* strains were MDR.[4] An increase in colonization and infection by carbapenem-resistant Enterobacteriaceae has been reported in the pediatric cancer population as well.[5] Although there are important geographical differences in the prevalence of carbapenem-resistant Enterobacteriaceae, no country can be considered untouched by the global spread of MDR gram-negatives.[6] National systems for surveillance, with obligation for notification and recommendations for containment and infection control measures, should be put in place.[7] This increase in MDR strains is radically changing our ability to prevent and cure infections in immunocompromised patients. The feasibility of the more aggressive medical interventions in hematologic cancer patients might be put under discussion if the actual trend toward more resistance is not reversed, since the rate of untreatable infections might become unacceptable. In addition, very few new antibiotics active against gram-negative rods have been marketed or are on the horizon, and the challenge is to ensure that an increasing antimicrobial resistance does not reverse the gains that have been made in improving survival and quality of life in patients with cancer through novel therapies or better surgical techniques.

As shown in Table 306.1, the clinical approach to a cancer patient with signs and symptoms of infection is multifactorial. Before planning a rational management strategy, physicians should answer several crucial questions about the type and stage of the underlying disease and the clinical presentation in order to provide an effective intervention. In addition, factors potentially associated with the presence of MDR bacteria, such as local epidemiology and the patient's colonization or previous infection with MDR strains, should currently be very carefully considered.

In the following sections, the epidemiology and management principles of infections in cancer patients are described. Risk factors and clinical presentations of specific infections, along with their treatment, are not discussed here but are dealt with in chapters focused on individual infectious agents. Similarly, infections in recipients of allogeneic hematopoietic stem cell transplants (HSCTs) are discussed elsewhere (see Chapter 307), and we will only briefly address these patients, particularly in regard to what concerns early infections during the preengraftment, neutropenic phase.

EPIDEMIOLOGY AND RISK FACTORS FOR INFECTIONS IN CANCER PATIENTS

The knowledge of the incidence of fever and documented infections in cancer patients according to the type of the underlying disease and related chemotherapy is mandatory for the implementation of effective management strategies, especially prophylaxis. However, the vast majority of epidemiologic data about these patients come from studies on empirical antibiotic therapy or prophylaxis, in which patients were selected according to inclusion and exclusion criteria. Thus this approach might be inadequate to describe the epidemiologic situation in real-life settings. In addition, little information is available about nonneutropenic patients.

Epidemiologic data on the incidence of infections are usually reported as percentages of events over a given number of patients or treatment courses, without adjusting for the duration of the period at risk. This is probably incorrect because the duration of exposure is crucial to understand the clinical impact of a given phenomenon. It is probably more appropriate to speak of incidence rates, that is, the number of events during a given risk period (usually 1000 days). For example, data on the rates of infectious complications that account for the number of days at risk allow for correct evaluation of the feasibility of antimicrobial prophylaxis and for comparing infectious risk among different cohorts or different treatment regimens. Unfortunately, such studies have rarely been done.

Pediatric studies reported rates of any infection or fever episode ranging from 12 to 31.1 per 1000 days at risk, being higher in case of aggressive treatment for acute leukemia and in neutropenic phases of

TABLE 306.1 What Should a Clinician Wonder About and Look for When Approaching a Cancer Patient With a Suspected Infection?

QUESTIONS	RATIONALE FOR THE QUESTION
The underlying disease: 1. Acute leukemia? Solid tumor? Lymphoma? Other? 2. Active disease? In remission? Not evaluable?	The incidence of infectious complications is different according to the underlying disease and consequent intensity of chemotherapy. The stage of disease may influence type, risk, and outcome of infection.
Recent treatments: 1. Did the patient recently (within 1 month) receive chemotherapy? 2. Which drugs and which schedule? How long ago? 3. Did the patient receive autologous or allogeneic HSCT? 4. If allogeneic HSCT, what donor type? 5. Did the patient receive monoclonal antibodies (anti-CD20, anti-CD52, etc.) in the past 6 months?	Different drugs may give different type of immunosuppression and favor different infectious complications. Previous transplantation might result in long-term immunodeficiency, particularly if immunosuppressive treatment is continued. Immune reconstitution depends on the type of donor and conditioning regimens used in allogeneic HSCT.
White blood cell count: 1. Is the patient neutropenic (PMNs <500/mm^3 or <1000/mm^3 but rapidly decreasing)? 2. Was the patient neutropenic in the previous 30 days?	The presence of neutropenia increases significantly the risk of infection. The knowledge of local epidemiologic data on antimicrobial susceptibility is mandatory for a correct choice of empirical therapy.
Risk of infection caused by resistant bacteria: 1. Is the patient colonized with resistant bacteria, particularly gram-negatives? 2. Is the hospital or the country endemic for resistant organisms? 3. Any previous infections caused by resistant pathogens?	In patients colonized by resistant bacteria, particularly if neutropenic, initial empirical therapy should cover these pathogens. If not colonized, but cared for in a setting where resistance is an issue, then consider the possibility of deescalation strategy.
Central venous catheter: 1. Yes or no? 2. Has the catheter been manipulated (including infusions) within a few hours before the onset of fever?	The central venous access may be an important source of infection.
Past history of infections (both before and after the diagnosis of cancer)	It may suggest the etiology and drive the therapeutic choice (e.g., tuberculosis, toxoplasmosis, multidrug-resistant bacteria, or opportunistic fungal infections).
Country of origin	Specific endemic infections can reactivate (Chagas' disease, strongyloidiasis, tuberculosis, endemic mycoses). Epidemiology of antibacterial resistance varies worldwide; thus, patients coming from areas endemic for resistant bacteria should be treated accordingly.
The clinical picture: 1. Presence of (severe) mucositis? 2. New onset of pain (perianal, chest, everywhere)?	It may suggest the etiology and drive the therapeutic choice. The presence of mucositis is suggestive of infection with pathogens from oral flora or gastrointestinal tract. The pain may help to locate formation of abscesses or indicate presence of a locally invasive process, such as pulmonary aspergillosis.
Administration of prophylaxis (no, yes, which drugs): 1. Antibacterial? 2. Antifungal, including *Pneumocystis jirovecii*? 3. Antiviral? 4. Was the patient compliant? 5. Is there the possibility of inadequate blood levels due to lack of absorption or PK/PD problems?	Breakthrough infections are possible, and fever during prophylaxis should be considered as failure of prophylaxis, unless proven otherwise. The occurrence of a bacterial/fungal/viral infection during specific prophylaxis may influence the choice of empirical therapy, depending on the drug used for prophylaxis. A resistant pathogen should be suspected in every case, unless the patient was clearly noncompliant or there is the possibility of low drug levels caused by poor absorption, increased metabolism, or drug interaction (e.g., azoles such as itraconazole, voriconazole, or posaconazole), or both. Knowledge of local epidemiology, including susceptibility pattern, is mandatory for correct diagnostic and therapeutic management.

HSCT, Hematopoietic stem cell transplantation; *PK/PD,* pharmacokinetic/pharmacodynamic; *PMNs,* polymorphonuclear neutrophils.

autologous transplantations.[3,8,9] The rate of bacteremia ranged, respectively, from 3.2 to 18.9 in adults and from 0.9 to 5.1 in children.[3,8–15] The rate of invasive fungal disease in pediatric studies ranged from 0.1 to 0.84, and was 2.4 in a study that included both children and adults.[3,9–12] Table 306.2 reports the epidemiology of febrile episodes, bacteremia, and invasive mycoses in cancer patients.[3,10–13,16–24]

These data clearly show that the incidence rate and proportion of infectious complications are mainly related to the intensity of antineoplastic chemotherapy. Additional factors are represented by the phase of chemotherapy and the status of the neoplastic disease, with higher incidence of infectious complications in patients receiving remission-induction and rescue chemotherapy, compared with maintenance or consolidation treatments.[11,18] The state of the underlying disease in terms of remission or relapse and progression is also an important factor for the occurrence and prognosis of infectious complications, as shown by studies in patients with invasive aspergillosis.[25–27] Patients with acute myeloid leukemia, both adults and children, have the highest frequency of fevers, bacteremia, and invasive fungal diseases, especially during the first induction of remission and in relapsing leukemia, when the intensity of chemotherapy is higher. Lower frequencies have been observed in lymphoblastic leukemia, chronic lymphatic disorders, multiple myeloma, and non-Hodgkin lymphomas, whereas the lowest rates are observed in solid tumors clearly depending on the lower intensity of antineoplastic treatment strategies. A new and rapidly increasing problem is represented by patients (usually with chronic leukemia or multiple myeloma) who are treated with novel targeted or biologic therapies, such as imatinib, dasatinib, ibrutinib, rituximab, ruxolitinib, and others. These new drugs have the potential to modify the infection risk profiles, with an increasing risk of infections caused by previously rare pathogens, such as *Pneumocystis jirovecii, Mycobacterium tuberculosis,* fungal pathogens, or many viruses.[28,29] On the other hand, their use instead of traditional chemotherapeutic agents might result in lower traditional toxicity, such as neutropenia.

Neutropenia

After the pivotal studies performed by Bodey and coworkers in 1966,[1] many others confirmed the strict relationship between neutropenia and infection and some of them tried to estimate an infection rate correlated with neutropenia. For example, in 1993 Carlisle and colleagues showed that the rate of infections in neutropenic cancer patients was 46.3 episodes per 1000 days of neutropenia, with rates of 12.9 for bacteremia and 2.9 for invasive mycoses.[30] More recent data from a prospective study in children with neutropenia showed a median incidence of infectious complications of 43% and a rate of 22.8 episodes per 1000 neutropenic days; bacteremia was diagnosed in 21% of the episodes and mold infections in 5%, with rates of 10.2 and 2.4 for 1000 neutropenic days,

TABLE 306.2 Incidence of Main Infectious Complications in Cancer Patients

		PERCENTAGES OF PATIENTS OR PERIODS WITH INFECTIOUS COMPLICATIONS[a]					
				INVASIVE FUNGAL DISEASE			
PATIENT POPULATION	TYPE OF DISEASE	ANY TYPE OF INFECTIOUS OR FEBRILE EPISODE	BACTEREMIA	Any (Proven, Probable, and Possible)	Proven and Probable		REFERENCE
					Yeasts	*Molds*	
Adults and children	Malignancies, not analyzed in detail	62	35	—	—	—	Gafter-Gvili et al., 2005[16]
Adults	Malignancy or autologous HSCT, not analyzed in detail	—	18	0	—	—	Dettenkofer et al., 2005[13]
Adults	High-risk acute leukemia	78	30	—	—	—	Bucaneve et al., 2005[17]
	High-risk NHL or HSCT in solid tumors	73	23	—	—	—	
Adults	Acute promyelocytic leukemia	59	22	7.3	3	0.3	Girmenia et al., 2003[18]
	Other AnLL	—	37	4.2	4	0.2	
Children	AnLL	94	25	4.2	0.6	1.6	Lehrnbecher et al., 2004[19]
Children	ALL, aggressive treatment	—	30	10	—	—	Castagnola et al., 2005[10]
	ALL, less aggressive treatment	—	17	3	—	—	
	AnLL, aggressive treatment	—	34	9	—	—	
Adults	Low-risk solid tumors, not analyzed in detail, including lymphomas	12	0.4	—	—	—	Cullen et al., 2005[20]
Adults	AnLL	—	—	—	6	11	Caira et al., 2008[21]
Adults	New-onset hematologic malignancies	27	10	4	0.5	1.3	Pagano et al., 2012[22]
Adults and children	Hematologic malignancies	—	21	5	—	—	Orasch et al., 2010[12]
Children	AnLL:	—	51	16	—	—	Castagnola et al., 2010[11]
	Incidence per patient						
	Incidence per treatment course		32	10			
Children	Aggressive treatment for solid tumor, including autologous HSCT	—	24	1.6	1	0.5	Haupt et al., 2001[23]
	Less aggressive treatment for solid tumors, not analyzed in detail		3	0			
Children	Neutropenic AL/NHL, aggressive treatment	48	25	10	1.6	1.2	Castagnola et al., 2007[3]
	Neutropenic AL/NHL, not aggressive treatment	21	8	1	0.8	0	
	Neutropenic ST, aggressive treatment	32	6	0.4	0.1	0.1	
	Neutropenic ST, not aggressive treatment	22	7	4	0.5	0.5	
	Neutropenic postautologous HSCT	58	14	2	0.6	0.6	
Children	Neutropenic with AML, receiving G-CSF	61	14	2	1.8	0.6	Lehrnbecher et al., 2007[24]
	Neutropenic with AML, not receiving G-CSF	56	11	0	—	—	

[a]Numbers are percentages of event over enrolled patients.
—, Data not reported; *AL,* acute leukemia; *ALL,* acute lymphocytic leukemia; *AML,* acute myelocytic leukemia; *AnLL,* acute nonlymphocytic leukemia; *G-CSF,* granulocyte colony-stimulating factor; *NHL,* non-Hodgkin lymphoma; *HSCT,* hematopoietic stem cell transplant; *ST,* solid tumor.

respectively.[12] The rate of infections is higher after high-intensity chemotherapies and lower after maintenance treatment. The majority of primary febrile episodes usually occur soon (a few days) after the onset of neutropenia.

Mucositis and Microbiota Alterations

As already mentioned, in addition to neutropenia, the severity of mucosal barrier injury may have an impact on infection rates (for major details, see Chapter 305). Mucositis is one of the most important factors predisposing to fever and BSIs, caused both by bacteria and by *Candida*.[31] The ulcerative phase induced by antineoplastic drugs with increased permeability and damage to the intestinal mucosal barrier promotes bacterial translocation, but the potential role of alterations in diversity of the intestinal microbiome in the development of mucositis and subsequent BSIs is increasingly recognized.[32] Quantitative and qualitative alterations of the normal oral and intestinal microflora have been described in cancer patients and depend on many factors, such as underlying disease, chemotherapy (drugs and dosages) and radiotherapy, mucosal disruption, bowel motility disturbance, enteral/parenteral nutrition, and broad-spectrum antibiotic administration.[33–35]

Microbiologic analyses of fecal samples of children aggressively treated for acute leukemia showed a decreased amount of microbial flora, and in particular of bifidobacteria, *Lactobacillus,* and *Escherichia coli,* and a 100-fold reduction of the total number of bacteria, mainly for anaerobes, with a concomitant increase of potentially pathogenic enterococci.[33,36] Moreover, in patients receiving HSCT, occupation of at least 30% of the microbiota by a single predominating bacterial taxon (intestinal domination) was associated with an increased risk for bacteremia due to specific pathogens.[37,38] Finally, *non-albicans Candida* strains, mainly *C. glabrata* and *C. krusei*, also seem to be increased in stool from children receiving chemotherapy or HSCT, especially in the case of prolonged hospitalization.[39,40]

Central Venous Catheters

The presence of a CVC is another well-known factor facilitating infections in cancer patients and influencing their etiology. A detailed description of problems related to infections associated with CVCs is beyond the scope of this chapter and can be found elsewhere in this text (see Chapter 300). Long-term vascular access devices adopted during antineoplastic chemotherapy or HSCT are represented by partially implanted silicone devices (Hickman or Broviac catheter), with or without valves, single or double lumen; peripherally or centrally totally implanted catheters (Port-A-Caths); and peripherally inserted central catheters.[41] Patients with less frequent need of venous access are usually fitted with totally implanted catheters, while more intensive supportive care generally requires partially implanted single- or double-lumen devices, which allow rapid infusion of large amounts of liquids. Risk factors generally associated with the development of CVC-related infections are represented by the type of CVC, the number of lumens, and the number and characteristics of CVC manipulations, all mainly related to the intensity, duration, and schedule of antineoplastic chemotherapy, the type of supportive care, and the severity of clinical conditions. Bacteremia represents the most frequent infectious complication, whereas exit site, tunnel, and pocket CVC-related infections are less frequently reported. Partially implanted catheters have been associated with a three- to fourfold increase in the risk of infectious complications compared with totally implanted devices, and in a study in patients with a totally implanted device, younger age was the only identified risk factor.[42,43] The risk of infection is generally higher in adults compared with children, and lower in the outpatient setting.[42,44,45]

A recent review reported infection rates varying from a mean of 22.5 (95% confidence interval [CI], 21.2–23.7) per 100 devices for Hickman and Broviac catheters, 3.5 to 4 (95% CI, 2.4–5.6) for Port-A-Caths, and 3.1 (95% CI, 2.6–3.7) for peripherally inserted central catheters, with mean rates per 1000 catheter-days of 1.6 (95% CI, 1.5–1.7), 0.1 (95% CI, 0.01–0.2), and 1.1 (95% CI, 0.9–1.3), respectively.[41] Patients with hematologic malignancies, and especially those with acute leukemia, have a higher incidence of catheter-related infections compared with patients with lymphoma, myeloma, or solid tumors, probably due to different type of catheters and frequency of catheter use.[41] It is important to be very balanced when discussing the role of central catheters in predisposing to infection. Indeed, the role might be overestimated, because the catheter might just be the site of a secondary localization of pathogens actually coming from the intestinal flora.[46] New definitions now suggest that 40% to 50% of BSIs in oncologic settings are actually endogenous and associated with mucosal barrier injury.[41,47–49] This has an impact on the expectations regarding strategies that should prevent infections by improving catheter management.[47–49]

Gram-positive bacteria represent the pathogens most frequently associated with CVC-related infections, but gram-negatives are reported with increasing frequency, especially in nonbacteremic episodes.[41] Finally, some age-related differences in the proportions of pathogens causing CVC-related bacteremia have been reported, with gram-negatives being observed more frequently in adults and gram-positives and fungi in children.[47–50]

Genetic Factors

The existence of genetic factors able to increase or decrease the susceptibility to infection in immunocompromised patients underlines an apparently trivial but important aspect: cancer patients are not the same, and every single patient might deserve an individualized approach. For example, in nonleukemic patients receiving less intensive chemotherapy, decreased levels of mannose-binding protein were associated with an increased risk of infection (49.9 vs. 29.6 per 1000 days at risk, $P = .01$).[15] In a recent study of 269 children with cancer, mannose-binding lectin deficiency influenced both the incidence and the severity of febrile neutropenia.[51] In breast cancer patients, genetic factors also were found to influence the risk of febrile neutropenia.[52] Polymorphisms of Toll-like receptors and other components of innate immunity have been associated with an increased risk of invasive aspergillosis, both in cancer patients (including recipients of HSCT) and in other immunocompromised patients.[53] The future will tell us whether genetic polymorphisms, alone or in combination, have a clinically significant impact on infection risk and might dictate prophylactic or therapeutic approaches.

New Therapies

Biologic Agents and Other New Drugs

As already mentioned, in recent years, monoclonal antibodies and other pharmaceutical compounds that are specifically engineered for targeting enzymes, cytokines, or receptors involved in the pathogenesis of specific types of cancer have been introduced into the armamentarium of antineoplastic chemotherapy. Main infectious complications associated with their use are reported in Table 306.3.[54–59]

Several issues impair our ability to understand the exact role of these new compounds on the risk of infection in cancer patients. First, even in randomized, placebo-controlled trials and in large open-label studies, it is difficult to establish the rate of infectious complications, because these trials were powered to measure efficacy in relation to their primary objective, but not safety. If the risk of infection is low, it might go undetected. Second, there are many confounding factors because new drugs are usually used together or in sequence with old therapies, making it difficult, if not impossible, to evaluate their respective role. Third, very often, because of the lack of infectious disease expertise, registration studies did not use the same definitions of infectious complications or simply did not pay enough attention to them. Sadly, in some cases there was a tendency toward minimization and covering. There is at least one example showing that the infection risk might have been forecast. This is the case of eculizumab used for paroxysmal nocturnal hemoglobinuria, which targets the C5 complement component. As should be widely known, the inherited deficiency of the C5 complement component is associated with repeated episodes of invasive meningococcal disease. Thus this risk might have been forecast before starting large trials or before marketing this new drug, so appropriate preventive strategies could have been put in place.

There is hope that multicenter projects concentrating on infectious complications might help in determining their true risk and possible early preventive or diagnostic measures. For example, the Southern Network on Adverse Reactions (SONAR) project conducts safety initiatives focusing on monoclonal antibody–associated progressive multifocal leukoencephalopathy (PML).[60] The field of biologic agents and anticancer molecules is rapidly changing, with a constant influx of new drugs and with new indications for the older ones. Therefore the data on their safety profile is also in constant evolution. As already mentioned, novel drugs are frequently administered in combination with "classic" antineoplastic agents and therefore it is not easy to disentangle their role in the development of infectious diseases. For example, a recent meta-analysis that investigated the impact of immunomodulatory drugs (e.g., thalidomide and derivatives) and proteasome inhibitors (e.g., bortezomib), variously associated with "classic" antineoplastic drugs in different phases of treatment for multiple myeloma, showed that the rate of severe infections in protocols including immunomodulatory drugs seemed generally lower than that observed with conventional therapy.[61] Unfortunately, despite the great number of patients and clinical trials analyzed, the authors repeatedly commented on insufficient detail about methods for detecting and diagnosing infections and limited generalizability to broader nontrial populations.[61]

For the compounds that have been in use for many years, we obviously have more information. For example, the monoclonal antibody anti-CD52 has been associated with a wide spectrum of infectious complications (mainly viral and fungal), and a low $CD4^+$ T-lymphocyte count (with

TABLE 306.3 Selected Biologic Drugs for Treatment of Solid Tumors and Hematologic Malignancies and Possible Infectious Complications

CLASS/SITE AND MECHANISM OF ACTION	DRUG	POSSIBLE INFECTIOUS COMPLICATIONS
Monoclonal Antibodies (mAbs) Targeting Surface Antigens on Lymphoid Cells		
Bispecific T-Cell Engager (BiTE): anti-CD19 mAb conjugated to anti-CD3 mAb leading to T-mediated lysis of CD19+ cells	Blinatumomab	CVC-associated infections due to continuous prolonged intravenous infusion. Severe and prolonged hypogammaglobulinemia and possible neutropenia, with consequent infectious risk. VZV and HSV infections, pneumocystosis, and HBV reactivation.
Anti-CD20 mAbs	Rituximab	Possible hypogammaglobulinemia of variable duration, not associated with an increased risk of bacterial infections. HBV reactivation (both of chronic inactive and resolved infection); exacerbation of HCV infection. Possible neutropenia; severe viral respiratory tract infection. Cases of severe enteroviral infections, PML, VZV, CMV parvovirus infections. Vaccine response is almost absent in the first 6 months after rituximab administration.
	Obinutuzumab	Similar to rituximab. Neutropenia and severe enteroviral infections have been reported.
	Ofatumumab	Probably similar to rituximab. Reported neutropenia, HSV, viral respiratory infection, fatal case of HBV reactivation.
	Ocrelizumab	Risk of infections associated with increasing doses, PML. Potentially increased risk of neutropenia and HBV reactivation.
	Veltuzumab Ublituximab	No data available for evaluation of the risk of severe infectious complications. Probably similar to rituximab.
Anti-CD20 mAbs conjugated with a radioactive isotope	^{90}Y-Ibritumomab tiuxetan ^{131}I-tositumomab	Higher rate of cytopenias, such as lymphopenia or neutropenia, due to combination with radioactive isotope. Cytopenia risk is higher if bone marrow is infiltrated by CD20+ hematologic malignancy. General safety profile probably similar to rituximab.
Anti-CD22 mAb Anti-CD22 mAb conjugated with the DNA-damaging agent calicheamicin Anti-CD22 mAb conjugated with *Pseudomonas* exotoxin A	Epratuzumab Inotuzumab ozogamicin Moxetumomab pasudotox	No significant increase in infections in placebo-controlled trials. Profile of infections similar to anti-CD20 mAbs: respiratory tract infections (viral and bacterial), pneumonia.
Anti-CD30 mAb conjugated with the microtubule disrupting agent monomethyl auristatin E	Brentuximab vedotin	Herpetic infections, including CMV; cases of PML and pneumocystosis.
Anti-CD33 mAb conjugated with a calicheamicin agent	Gemtuzumab ozogamicin	No significant increase in infections.
Anti-CD38 mAb	Daratumumab	Increased risk of VZV (prophylaxis warranted for 3 months after the end of treatment). Slightly higher risk of pneumonia and upper respiratory tract infections.
Anti-CD40 mAb	Dacetuzumab	Higher rate of neutropenia with dacetuzumab vs. placebo. Opportunistic infections similar to those observed in hyper-IgM syndrome (pneumocystosis, CMV reactivation, etc.) might be theoretically expected.
Anti-CD52 mAb	Alemtuzumab	Severe viral infections (particularly HSV, VZV and CMV, but also HHV6, BKV, parvovirus, adenovirus). Pneumocystosis and other fungal infections, toxoplasmosis, mycobacteriosis, reactivation or exacerbation of HBV infection, tuberculosis, listeriosis, infections due to acanthamoebae, *Balamuthia mandrillaris,* reactivation or worsening of chronic HBV infection have also been described.
Anti-CD139 (signaling lymphocytic activation molecule F7 [SLAMF7]) mAb	Elotuzumab	Lymphopenia and increased risk of opportunistic infections, particularly due to VZV.
Anti–C-C motif of chemokine receptor 4 (CCR4) mAb	Mogamulizumab	Infectious risk difficult to distinguish from the intrinsic effect of underlying diseases and concomitant lymphotoxic therapies. Pneumocystosis, HSV, VZV, HBV reactivation (risk of severe hepatitis in patients with high-level HBV DNA due to T-regulatory cell downregulation).
Tyrosine Kinase Inhibitors ***Breakpoint Cluster Region–Abelson Murine Leukemia (BCR-ABL) Signaling Pathway***		
Inhibitor of tyrosine kinase BCR-ABL, c-KIT, and platelet-derived growth factor (PDGF)-receptor	Imatinib	Febrile neutropenia has been reported. Cases of pneumocystosis and viral diseases, including reactivation of hepatitis.
Inhibitor of tyrosine kinase BCR-ABL	Nilotinib	Cases of pneumocystosis and viral diseases, including reactivation of hepatitis.
Inhibitor of tyrosine kinase BCR-ABL, SRC family, c-KIT, and others	Dasatinib	Cases of pneumocystosis and viral diseases, including reactivation of HBV. Noninfectious pleural effusions, less often pneumonitis (in differential diagnosis with infections).

Continued

TABLE 306.3 Selected Biologic Drugs for Treatment of Solid Tumors and Hematologic Malignancies and Possible Infectious Complications—cont'd

CLASS/SITE AND MECHANISM OF ACTION	DRUG	POSSIBLE INFECTIOUS COMPLICATIONS
Bruton Tyrosine Kinase Signaling Pathway		
Bruton tyrosine kinase inhibitor	Ibrutinib	Bacterial pneumonia, urinary tract infection and cellulitis, noninfectious pneumonitis, invasive fungal infections.
Janus Kinase–Signal Transducers and Activators of Transcription (JAK-STAT) Signaling Pathway		
Inhibitor of the JAK pathway (kinases 1 and 2)	Ruxolitinib	VZV reactivation, cases of tuberculosis, PML, pneumocystosis, cryptococcosis, and other opportunistic infections associated with T-cell dysfunction.
Phosphatidylinositol 3-Kinase (PI3K) Delta Isoform Signaling Pathways		
Inhibitor of PI3Kδ	Idelalisib	Pneumonia, sepsis (20%), opportunistic infections, along with noninfectious pulmonary and gastrointestinal inflammation. Prophylaxis of HBV reactivation and pneumocystosis and preemptive management strategy for CMV are warranted.
Others		
Multikinase inhibitors	Lapatinib Pazopanib Regorafenib	Possible skin infections because of skin toxicity. No significant data available for evaluation of the risk of severe infectious complications.
Vascular Endothelial Growth Factor (VEGF) Signaling Pathway		
Anti–human VEGF mAb	Bevacizumab	Infections in cases of chemotherapy-induced neutropenia: sepsis and pneumonia. Cases of intestinal perforation (with or without abscess formation), probably from the inhibition of endothelial cell proliferation and new blood vessel formation. Possible endophthalmitis due to intravitreal injections, but an increased risk of this type of infection has not been clearly demonstrated.
Recombinant protein circulating antagonist that prevents VEGF receptor binding	Aflibercept	Severe infections: incidence 7.3% (95% CI, 4.3–12.0%) with increased risk (RR, 1.87; 95% CI, 1.52–2.30). Mortality: 2.2% (95% CI, 1.5–3.1%), with increased risk (OR, 2.16; 95% CI, 1.14–4.11). The risk of infections with aflibercept substantially higher than with bevacizumab.
Inhibitor of tyrosine kinases on receptors for vascular endothelial growth factor (VEGFR), platelet-derived growth factor (PDGFR), and isoform B of tyrosine kinase (known as rapidly accelerated fibrosarcoma [B-RAF])	Sorafenib	Infections, as well as gastrointestinal perforations, are reported in less than 1% of treated patients.
Inhibitors of tyrosine kinases on PDGFRs and VEGFRs	Sunitinib	Cases of necrotizing fasciitis, respiratory infections, and sepsis.
Inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2), epidermal growth factor receptor (EGFR), and RET (rearranged during transfection) tyrosine kinase	Vandetanib	No significant increase in infections.
Tyrosine kinase inhibitor that inhibits angiogenesis blocking VEGFR-1– VEGFR-3, c-KIT, and PDGFR	Axitinib	No significant data available for evaluation of the risk of severe infectious complications.
Inhibitor of tyrosine kinases c-Met and VEGFR-2, and also AXL and RET	Cabozanitinib	No significant data available for evaluation of the risk of severe infectious complications.
Inhibitor of tyrosine kinases VEGFR-1–VEGFR-3	Lenvatinib	No significant data available for evaluation of the risk of severe infectious complications.
Epidermal Growth Factor (EGF) Signaling Pathway		
Anti–EGF receptor (ErbB1 or EGFR) mAb	Panitumumab (IgG2) Cetuximab (IgG1, chimeric)	Cases of necrotizing fasciitis, abscesses sepsis caused by *Staphylococcus aureus.* Important dermatologic toxicity, such as rash, skin drying and fissuring, or paronychial inflammation, with infectious complications (abscess, bacteremia) in up to 30% of patients, including sepsis caused by *S. aureus.* More severe infections have been described when combined with neutropenia-inducing chemotherapy.
	Nimotuzumab (humanized)	No significant data available for evaluation of the risk of severe infectious complications.
mAb against human EGF receptor 2 (human ErbB-2 or HER2)	Trastuzumab	Infections are generally mild and reported as URTIs or UTIs. Increased risk of infections has been described in combination with chemotherapy. Exacerbation of chemotherapy-induced neutropenia. Infection ≥ grade 3: 8.5% of patients (95% CI, 4.5–15.4), RR vs. control, 1.21 (95% CI, 1.07–1.37). Febrile neutropenia in the neoadjuvant/adjuvant and combination therapies: 12.0% (95% CI, 8.1–17.4), RR vs. control, 1.28 (95% CI, 1.08–1.52)
	Pertuzumab	>10% of febrile neutropenia, URTIs (associated with chemotherapy).

TABLE 306.3 Selected Biologic Drugs for Treatment of Solid Tumors and Hematologic Malignancies and Possible Infectious Complications—cont'd

CLASS/SITE AND MECHANISM OF ACTION	DRUG	POSSIBLE INFECTIOUS COMPLICATIONS
Inhibitor of epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI), possibly also of mutated JAK2	Erlotinib	Approximately 9% higher rate of infections compared to control arms for erlotinib.
Inhibitor of EGFR-TKI	Gefitinib	In a meta-analysis of over 6000 patients with NSCLC: any infection, 7% (95% CI, 4.7–10.3), severe infection, 2.1% (95% CI, 1.7–2.8), and fatal, 0.7% (95% CI, 0.4–1.0). There is a trend toward a higher risk with longer treatment.
Immune Checkpoints Inhibitors		
mAbs inhibiting programmed cell death protein 1 (PD-1)	Nivolumab	No significant increase in infectious complications but immune-mediated complications are frequent and should be considered in differential diagnosis (pneumonitis, colitis, hepatitis).
	Pembrolizumab	No significant data available for evaluation of the risk of severe infectious complications.
mAbs inhibiting programmed cell death ligand 1 (PD-L1)	Atezolizumab Avelumab Durvalumab	Cases of fever and UTIs. No significant data available for evaluation of the risk of severe infectious complications.
mAb inhibiting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)	Ipilimumab Tremelimumab	No significant data available for evaluation of the risk of severe infectious complications.
Immunomodulating Drugs		
Angiogenesis inhibitor	Thalidomide	Neutropenia and lymphopenia described, reported increased risk of infections (RR, 1.64; 95% CI, 1.40–1.92).
Apoptosis inducer in vivo, with antiangiogenic and osteoclastogenic effects	Lenalidomide	Described a 14% (95% CI, 12.08–16.90) incidence of severe infections, with RR 2.23 (95% CI, 1-71–2.91), with possible fatal events. May increase risk and duration of cytopenia if combined with chemotherapy.
Immunomodulatory, like thalidomide and lenalidomide, based on its use in multiple myeloma	Pomalidomide	Severe infectious complications in 23%, frequently in the absence of neutropenia. Pneumonia is the most frequently reported localization. Antibacterial prophylaxis has been recommended for patients receiving this drug, but fluoroquinolones could be contraindicated for the risk of drug interactions.
Activator of monocytes and macrophages	Mifamurtide	Fever frequently described, but no specific data on severe infectious complications.
Proteasome inhibitors	Bortezomib Carfilzomib	Increased risk of herpes zoster. Low risk of febrile neutropenia. Pneumonia (13%) and URTIs (28%) observed in patients receiving single-drug therapy, but approximately 2%–6% had severe infections.
	Ixazomib	Increased risk of herpes zoster. No significant data available for evaluation of the risk of severe infectious complications.
Others mAb against disialoganglioside (expressed on a variety of embryonal cancers (e.g., neuroblastoma, retinoblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma)	Dinutuximab (anti-GD2)	Fever is frequently observed, but there are data available for significant infectious complications.
Cyclopamine-competitive antagonist of the smoothened (a transmembrane protein) receptor that is a part of the hedgehog signaling pathway that is involved in proper cell differentiation	Vismodegib	No significant data available for evaluation of the risk of severe infectious complications.
Inhibitors of Histone Deacetylases		
Histone deacetylase (HDAC) inhibitor, induces intracellular increase of transcription factors important for the expression of genes needed to induce cell differentiation	Vorinostat	Neutropenia reported, but no data available for significant infectious complications.
Nonselective HDAC (pan-HDAC inhibitor).	Panobinostat	Pneumonia described in 13% of treated patients.
Selective inhibitor of HDACs	Romidepsin	No significant data available for evaluation of the risk of severe infectious complications.
Mammalian target of rapamycin (mTOR) inhibitors	Everolimus Temsirolimus	Infections attributable to mTOR inhibitors (mainly everolimus): any infection 9.3% (95% CI, 5.8–14.6%), severe infections 2.3% (95% CI, 1.2–4.4%). Important difference in the incidence depending on the type of cancer treated.

BKV, BK virus; *95% CI,* 95% confidence interval; *CMV,* cytomegalovirus; *CVC,* central venous catheter; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HHV6,* human herpesvirus 6; *HSV,* herpes simplex virus; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *NSCLC,* non–small cell lung cancer; *OR,* odds ratio; *PML,* progressive multifocal leukoencephalopathy; *RR,* relative risk; *URTI,* upper respiratory tract infections; *UTIs,* urinary tract infections; *VZV,* varicella-zoster virus.

a possible cutoff of 200 $CD4^+$ T-lymphocytes/mm^3) has been indicated as one of the most important factors related to the development of infections. Anti-CD20 compounds, the most widely studied being rituximab, cause a prolonged (2 to 6 months in median, but sometimes longer) suppression of immunoglobulin production.[62] Reactivation of hepatitis B virus (HBV) has been observed in 85% of hepatitis B surface antigen (HBsAg)–positive and in 41.5% of HBsAg-negative/hepatitis B core antibody (HBcAb)–positive lymphoma patients treated with chemotherapy that included rituximab.[63] More rarely, other severe viral infections (enteroviral infections, PML, parvovirus infections) have been reported.[62] Brentuximab, another monoclonal antibody targeting lymphocytes through CD30, has also been associated with severe infections. In particular, PML after brentuximab was found to develop earlier than with rituximab or natalizumab (2–3 months vs. 63 weeks vs. 26 months, respectively).[29,60,62,64,65] Therefore a low threshold for brain magnetic resonance imaging should be applied to patients treated with monoclonal antibodies who develop neurologic symptoms. Ruxolitinib was associated with varicella-zoster virus (VZV) reactivation and tuberculosis (TB), ibrutinib with invasive fungal diseases (IFDs), and idelalisib with herpes and cytomegalovirus (CMV) reactivations and with pneumocystosis. Last but not least, checkpoint inhibitors such as ipilimumab, which inhibits the cytotoxic T-lymphocyte–associated antigen 4 checkpoint, and nivolumab or pembrolizumab, which inhibit the programmed cell death protein 1 (PD1) checkpoint, are associated with severe immune-related adverse events, such as diarrhea, pneumonitis, or hepatitis. In these cases, differential diagnosis might be difficult and patients should always be tested for infectious etiologies, such as *Clostridioides difficile* (formerly *Clostridium difficile*) colitis, pneumocystosis, or viral hepatitis. Tyrosine kinase inhibitors seem to be associated with infectious complications similar to those observed with other immunosuppressive drugs affecting mechanisms of cell-mediated immunity. For these drugs, among the most frequently reported infections are pneumocystosis and reactivation of HBV (observed also in HBsAg-negative/HBcAb-positive patients). Finally, high-dose retinoic acid has been used for treatment of acute promyelocytic leukemia and some pediatric solid tumors (neuroblastoma). The dosages adopted in acute leukemia can induce fever and hepatotoxicity (vitamin A "intoxication"), while in patients with solid tumors, cases of skin and soft tissue infections, especially due to *S. aureus,* can be observed. Intravesical administration of Calmette-Guérin bacillus, a live strain of *Mycobacterium bovis,* is adopted as a treatment of non–muscle-invasive bladder cancer. Disseminated genitourinary or osteomuscular infections have been reported.[66]

Chimeric Antigen Receptor T-Lymphocyte Therapy

Originally designed to treat lymphocyte-derived malignancies, chimeric antigen receptor (CAR) T-cell therapy is now being used in a wide range of solid tumors.[67] CAR T cells are derived from the patient's peripheral blood lymphocytes, which are transformed in vitro using a DNA construct that causes the lymphocyte to produce on its surface receptors that recognize a specific, selected tumor antigen. After CAR T cells are infused into the patient and encounter a cell with that antigen on its surface, the CAR T cells activate and become cytotoxic, thus killing the neoplastic cell. Potential adverse effects include killing of normal cells bearing the same antigen, as well as a cytokine release syndrome, which can cause high fever and multiorgan failure.[68] Little is known about infectious complications associated with CAR T-cell therapy. In cases of therapy of leukemia or lymphoma with CAR T cells targeting CD19, the incidence of infections was comparable to observations from clinical trials of salvage chemoimmunotherapies in similar patients.[69]

Surgery

Bacteremia, usually associated with surgical site infection and deep organ abscess, is not uncommon in urologic, gynecologic, and abdominal surgery in cancer patients, but it is difficult to say with certainty if this happens significantly more often in oncologic versus nononcologic patients.[70,71] Several studies reported the rates of postsurgery infections in different cancer populations. For example, among patients with peritoneal carcinomatosis undergoing peritonectomy and intraperitoneal hyperthermic chemotherapy, the proportion of infectious complications was rather high, varying from 24% to 36%, with more than two infectious episodes per patient.[70–72] The rate of infectious complications is lower in other oncologic surgeries. In breast cancer, surgical site infection is a complication in 4% to 8% of cases, depending whether breast reconstruction is performed in one or two steps and whether surgery follows previous chemotherapy cycles.[73,74] In case of malignant biliary obstruction, early infectious complications after percutaneous biliary stent insertion were present in 6.5% of patients.[75] Similar incidence was reported in patients undergoing surgery for hepatocellular or metastatic carcinoma (3%–11%), and this incidence was apparently lower than in surgery for nonmalignant conditions such as hepatolithiasis (24%).[76] The rate of infectious complications after hepatectomy for hepatocarcinoma was associated with surgical risk factors such as bile leakage and blood loss.[77] A similar incidence of surgical site infections was reported after elective colon and rectal surgery (9% and 18%, respectively), and after orthopedic surgery (9.5%).[78,79] Of interest, in the latter study the use of an implant or allograft did not represent a risk factor for infectious complications.[79] Finally, postoperative respiratory infections have been reported in nearly 4% of patients undergoing surgery for lung cancer, and they occurred more frequently in the presence of advanced age, impaired respiratory function, advanced pathologic stage, and induction chemotherapy.[80]

In conclusion, although not many data are available on infectious complications after surgery in solid tumors, it seems that surgical and intensive care unit–related factors are more important than previous antineoplastic chemotherapy in determining the risk of infection. Finally, in patients with solid tumors, surgery, together with long hospital stay and use of third-generation cephalosporins and glycopeptides, have been associated with an increased risk of infections caused by MDR pathogens.[81]

ETIOLOGY

Surveillance studies on pathogens causing infections in cancer patients are of the utmost importance for the implementation of management strategies. Large-scale studies are obviously crucial because they can provide information about worldwide trends, but single-center surveillance reports may be even more important, because every geographic region, country, or single center may have peculiarities related to the type of patient, type of care, and local previous antibiotic policies. Most of the available information concerns bacterial and fungal pathogens isolated in the bloodstream, whereas the role of deep-seated infections, as well as the impact of viral infections, are less known.

Bacterial Infections

Over the last 30 years, gram-positive bacteria were the most frequent pathogens causing bloodstream infections in cancer patients. However, more recently, an increase in the frequency of bacteremias caused by gram-negative rods has been reported, with gram-negative pathogens becoming either predominant or at least as frequently isolated as the gram-positives.[14,82,83] This trend has also been observed in a retrospective literature review and contemporary surveillance study performed in 2011 in 39 European hematology centers from 18 countries belonging to the network of the European Conference of Infections in Leukemia (ECIL).[84] As shown in Fig. 306.1, this study found that gram-negative pathogens were almost as frequently isolated as the gram-positives, with gram-positive/gram-negative ratios in bloodstream infections of 60%/40% and 55%/45%, in the literature review and the ECIL-4 surveillance, respectively. The detailed etiology was similar (see Fig. 306.1) in the literature review and the surveillance study, with a slightly higher rate of enterococci and Enterobacteriaceae and a decreased rate of *P. aeruginosa* in the surveillance study.[84] These changes in etiology seemed to be associated with an important and alarming increase in the proportion of resistant pathogens, such as ESBL-producing Enterobacteriaceae, VRE, MDR *P. aeruginosa,* and the most worrisome, carbapenem-resistant gram-negative pathogens. Last but not least, in leukemic patients, most staphylococci are resistant to methicillin, whereas most gram-negative pathogens are resistant to fluoroquinolones.[84]

Of note, the rates of resistance were generally higher in southern and eastern than in northern and western Europe, and this trend is also evident in the non–hematologic cancer population.[84,85] A recent

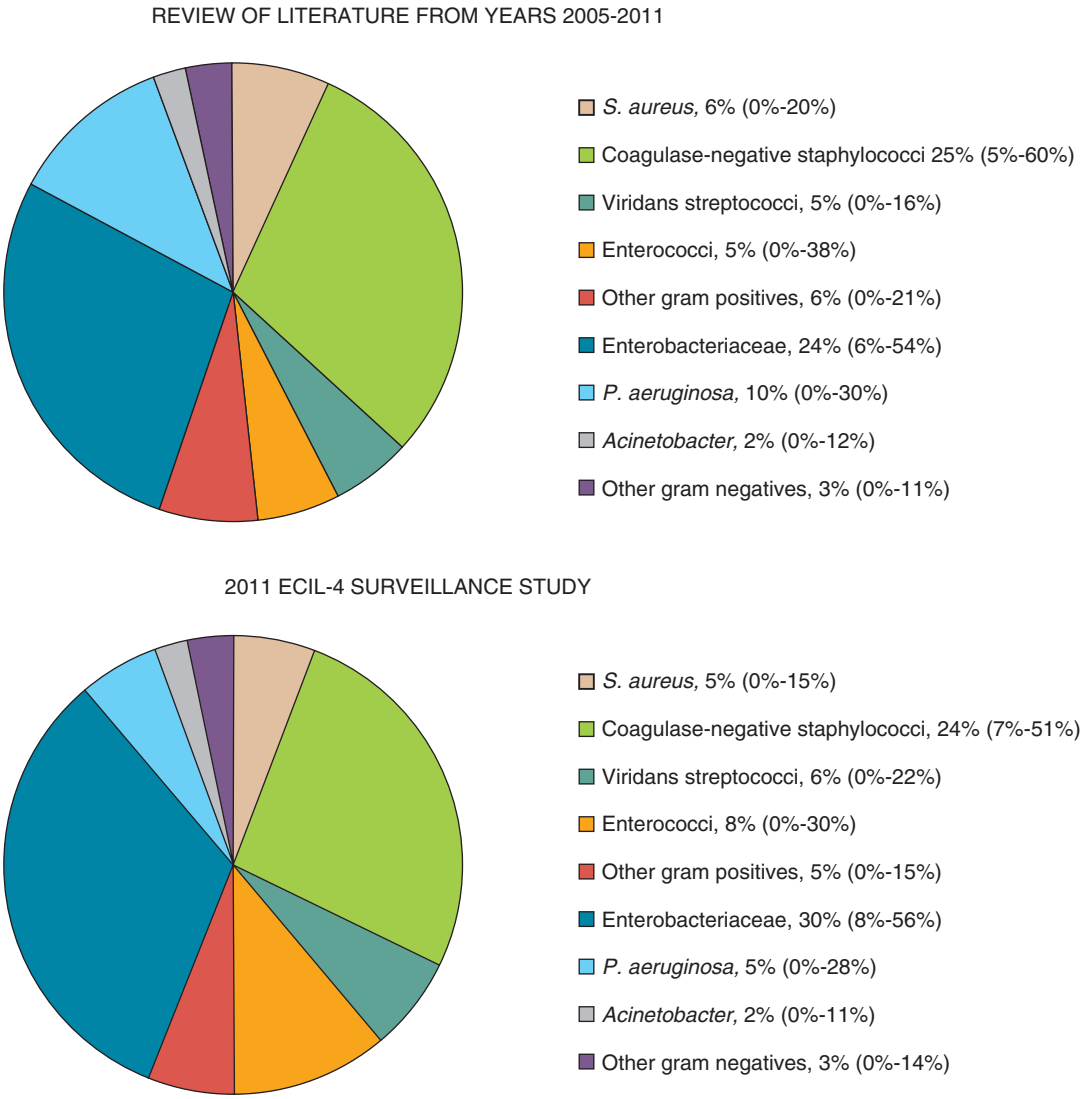

FIG. 306.1 Etiology of bloodstream infections in cancer patients. *Top,* Data from recent literature review. *Bottom,* Data from surveillance study for the Fourth European Conference of Infections in Leukemia (ECIL-4) in 2011. *(Modified from Mikulska M, Viscoli C, Orasch C, et al. Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients.* J Infect. *2014;68:321–331.)*

study in HSCT recipients has confirmed the alarming increase in resistance in this population as well, with increasing mortality rates.[86] The increase in infections caused by resistant strains usually follows an increase in colonization with these pathogens, because cancer patients typically first get colonized and then develop endogenous infection. Indeed, colonization with resistant bacteria is one of the most important risk factors for infection with resistant bacteria. The association between colonization and subsequent infection has been reported for VRE, ESBL-producing Enterobacteriaceae, *P. aeruginosa, Stenotrophomonas maltophilia,* and carbapenem- or colistin-resistant *K. pneumoniae.*[87–89] Obviously, the negative and positive predictive values of colonization are not 100% because not all the cases of MDR-BSI are preceded by documented colonization, whereas some colonized patients will not develop MDR-BSI. However, colonization may be the most easily identifiable risk factor, and screening protocols for drug-resistant bacteria should probably be implemented everywhere.

Anaerobic bacteria are isolated in less than 1% of positive blood cultures in cancer patients, but the proportion may increase to 3% among those undergoing abdominal surgery.[70] Anaerobes are usually isolated in polymicrobial bacteremias, especially together with gram-negative rods, with a rate that seems to be higher than that observed in nononcology patients undergoing similar surgery (0.597 vs. 0.033 per 1000 hospital days, respectively).[90] Differences in the etiology of bacterial infection between neutropenic and nonneutropenic cancer patients have been reported.[14]

CVC-related bacteremias are generally caused by gram-positive cocci (especially coagulase-negative staphylococci), which are isolated in more than 50% of the episodes compared with the rate of 25% to 40% for gram-negative rods.[9,91–98] As mentioned previously, the source of infection is likely to be partially different in cases of gram-positive and gram-negative CVC-related bacteremias. Infusate contamination is a rare but possible event, and in this case gram-negative rods, such as *Klebsiella, Enterobacter, Citrobacter, Achromobacter, Serratia, Ralstonia,* and *Pseudomonas* (other than *P. aeruginosa*), are more likely involved. Polymicrobial infections are not rare with a predominance of gram-negative bacteria, whereas fungi (mainly *Candida* spp.) are usually monomicrobial and infrequent.

Bacterial gastroenteritis caused by classic enteric pathogens (*Salmonella* and *Shigella*) is a rare event in patients with acute leukemia, involving less than 1% of acute enteritis after chemotherapy.[99] On the contrary, *C. difficile* is not unusual in cancer patients, with an incidence that is twofold higher than in the noncancer population.[100] *Helicobacter pylori* has also been described as a possible cause of gastrointestinal disease in cancer patients.

Legionellosis and nocardiosis are rare but potentially life-threatening infections, with *Legionella* pneumonia sometimes presenting with unusual

radiologic patterns. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have been rarely described as a cause of pneumonia in cancer patients, but it is possible that their incidence is underreported. Similarly, TB is probably underestimated and underdiagnosed in cancer populations, although there are data showing that the rate approximates 90 cases per 100,000 persons (i.e., ninefold higher than in the general population in developed countries).[101] Patients from high-endemicity countries account for most of the cases. Infections caused by nontuberculous mycobacteria are rare, outside of the already mentioned rare occurrence of local or even disseminated *M. bovis* infections in patients receiving Calmette-Guérin bacillus immunotherapy for bladder cancer.

Fungal Infections

Aspergillus spp. and *Candida* spp. are the most common fungal pathogens in cancer patients, with the former now seen more frequently than the latter. Other fungal pathogens include *P. jirovecii,* cryptococci, and molds such as *Mucorales* or *Fusarium.*

Among yeasts, *Candida* is the most frequently isolated organism, usually in BSIs, with an increasing proportion of non-*albicans* strains, probably due to the extensive use of prophylactic fluconazole. This phenomenon, known since 1999, was confirmed in a more recent European Organization for Research and Treatment of Cancer (EORTC) study, which reported that in cancer patients the overall incidence of fungemia was 2.3%, with *C. albicans* responsible for 72% of candidemia cases in the whole study population, but only 27% in patients with hematologic malignancies.[102,103] Of note, in this study only 38% of fungemias occurred during neutropenia. In general, yeasts belonging to the *Candida parapsilosis* complex are usually associated with CVC contamination, whereas other *Candida* species are supposed to come from the gastrointestinal tract after selection and translocation. *Candida glabrata* is the species increasing in frequency and resistance, not only to fluconazole but also to echinocandins.[104] Additionally, *Candida auris* is a recently identified species that caused outbreaks worldwide.[105] It is characterized by resistance to numerous antifungals, mainly fluconazole, less frequently voriconazole and amphotericin B. Therefore echinocandins are the mainstay of treatment. *Candida auris* has a potential for clonal outbreaks, and is associated with 40% to 50% mortality due to patients' poor general conditions, antifungal resistance, and its ability to form biofilm and cause persistent infection.[105]

Among molds, *Aspergillus* represents the most frequently isolated or suspected organism. The majority of episodes are caused by *Aspergillus fumigatus,* although some centers report a predominance of infections caused by *Aspergillus flavus* and *Aspergillus terreus.*[106,107] *Aspergillus* species are ubiquitous molds whose primary ecologic niche is represented by decomposing vegetable material, including potted plants, soil, flowers, and carpets. In healthy individuals, *Aspergillus* conidia are trapped in the upper respiratory tract, and only a small proportion of them enter the lower airways where *Aspergillus* may become an allergen. In immunocompromised patients, especially those with hematologic malignancies or after allogeneic HSCT, spores can germinate and cause an invasive disease. Thus invasive aspergillosis in patients with malignancy or receiving HSCT is an endemic disease, which is usually community acquired and endogenous, although epidemic outbreaks of exogenous infection associated with massive environmental exposures (in and outside the hospital) can occur. The incidence of invasive aspergillosis depends on the patient's age (lower in those younger than 10 years), the underlying malignancy, and its treatment, being the highest in patients with prolonged neutropenia, followed by those receiving high doses of steroid therapy. In a multicenter Italian study, the incidence of aspergillosis among hematologic cancer patients varied from 7.9% in acute nonlymphoblastic leukemia to 4.3% in acute lymphoblastic leukemia, 2.3% in chronic myelogenous leukemia, and less than 1% in chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma, and multiple myeloma.[106] A recently described risk group is represented by patients with chronic lymphoproliferative disorders, probably as a result of introducing more intensive treatment protocols.[107] Additionally, the risk of aspergillosis in patients with acute lymphoblastic leukemia was reported as high as 11.7%.[108] The incidence of invasive aspergillosis after autologous HSCT is low (0.3%–2%), and it occurs during preengraftment neutropenia.[109]

The main challenge in the current management of invasive aspergillosis, which consists of voriconazole or isavuconazole as first-line therapy and prophylaxis with posaconazole in high-risk patients, is the increasing problem of primary resistance to azoles in *A. fumigatus.*[110] Azole-resistant isolates harboring the *TR34/L98H* or the *TR46/Y121F/T289A* mutations have been found in the environment due to a widespread use of azoles in the agriculture industry in some countries. Patients may inhale spores of these strains and develop primary azole-resistant disease despite no previous antifungal therapy. The prevalence of resistant strains is only about 3% among 3788 isolates screened in Europe and differs highly between regions.[111] Data on high prevalence of resistant strains in patients with hematologic malignancies in the Netherlands and Germany have been reported, but methodologic issues, including the choice of denominator to evaluate resistance rate, are crucial.[112] Despite the fact that the phenomenon is so far relatively limited in most of the settings, knowledge of the frequency of azole resistance at the country and hospital level and within different patient groups is warranted. Secondary azole resistance, with different genetic patterns, has been reported in patients with chronic fungal infection after prolonged treatment, particularly in the case of suboptimal blood levels or high fungal burden.[113]

Mucormycosis is being increasingly reported by some centers, especially in the US. It is unclear whether this represents a general trend, if it is influenced by local factors, or if these infections are simply diagnosed more often because of an increased clinical awareness or improved patient survival. Other fungi, such as *Cryptococcus, Fusarium*, *Trichosporon, Saprochaete (Magnusiomyces/Blastoschizomyces),* and *Scedosporium,* have been reported sporadically, but it is likely that previously uncommon organisms may appear more frequently because they are being selected by the widespread use of mold-active antifungal prophylaxis.[114]

Pneumocystis jirovecii is a well-known cause of pneumonia in cancer patients not receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, especially if treated with high-dose and prolonged steroid therapy or certain antineoplastic drugs such as fludarabine or temozolomide. Attack rates vary from 6.5% to 43% in acute lymphoblastic leukemia, 4% to 25% in rhabdomyosarcomas, and nearly 1% in Hodgkin lymphoma and primary or metastatic central nervous system tumors.[115,116]

Finally, infections or reactivations of dimorphic fungi, such as *Histoplasma* or *Coccidioides,* are possible in patients who live in or used to live in endemic areas.

Viral Infections

Apart from herpes simplex virus (HSV) reactivation, which occurs in up to 60% of HSV-seropositive patients with acute leukemia, other viral infections are rather infrequently reported outside the setting of allogeneic HSCT.[3] For example, a positive pp65 antigenemia for CMV has been reported in 9% of non-HSCT recipients and in 12% of patients undergoing autologous HSCT, without necessarily being accompanied by CMV disease.[117] For this reason, routine monitoring of CMV reactivation and preemptive therapy were not considered necessary in cancer patients other than HSCT recipients. However, the risk of viral reactivation might change significantly with the increasing use of novel T-cell–suppressing agents or drug combinations, such as alemtuzumab or idelalisib or a combination of bendamustine and rituximab.[62,118–120]

Community-acquired respiratory viruses, such as influenza, parainfluenza, respiratory syncytial virus (RSV), metapneumovirus, adenoviruses, rhinoviruses, and coronaviruses, are a frequent cause of respiratory disease in cancer patients and are probably underestimated as a cause of fever. Whereas most cancer patients would experience self-limited upper respiratory illness, those with a severe immune deficit, such as those treated for leukemia, are at increased risk for progression from upper respiratory tract infection to pneumonia, with possible respiratory failure and fatal outcome.[121] The incidence rate of viral respiratory infections in patients with acute lymphocytic and acute myelogenous leukemia is estimated to be 68 and 31 infections per 1000 new admissions, respectively.[122] Almost half of these patients had pneumonia, and the mortality was 14%.[122] In cancer patients with a viral respiratory disease, deferral of chemotherapy could be considered. Specific treatment is warranted for influenza and in some cases of RSV infection (e.g., in leukemic patients with risk factors for RSV-related mortality) (see Chapter 158).[121]

Viral gastroenteritis, mainly caused by rotavirus but also norovirus or sapovirus, may be a frequent complication in pediatric oncology, with a potential to cause outbreaks in cancer centers because of persistent gastrointestinal shedding in immunocompromised hosts. Both adenoviruses and parvovirus B19 have been reported as rare causes of severe gastrointestinal disease in cancer patients.

Finally, the reactivation/exacerbation of infections due to hepatotropic viruses (HBV and hepatitis C virus) represents an important problem in areas of high endemicity. HBV reactivation is frequent in cancer patients with chronic inactive HBV infection (HBsAg positive, with negative or low-level serum HBV DNA), but it can occur also in patients with an occult HBV infection (HBsAg negative, HBcAb positive, or with low-level serum HBV DNA), particularly in association with the use of rituximab (up to 40% of patients).[63] The possibility of chronic hepatitis E virus infection due to genotype 3, which is endemic in certain industrialized regions, has been recently reported in patients with hematologic malignancies and transplant recipients.[123,124] Repeated transfusions might be a risk factor for hepatitis E virus infection.[125]

Other Pathogens

The risk of rare infections or reactivations caused by protozoa (leishmaniasis, South American trypanosomiasis, and malaria), helminths (strongyloidiasis), endemic fungi and other tropical diseases should be considered in patients who lived in endemic areas. Obtaining a history to identify potential exposure is the most important screening, with additional serology to document past exposure. However, in the case of strongyloidiasis, for example, the suboptimal performance of stool examination or serologic screening may warrant empirical treatment with ivermectin in patients who present with unexplained eosinophilia and who lived in endemic areas, such as the tropics, the subtropics, or the southeastern United States and Europe.

PREVENTION OF INFECTIONS IN CANCER PATIENTS

Prevention is obviously a desirable goal, given the remarkable mortality and morbidity associated with infections in cancer patients. Table 306.4 summarizes different regimens for primary chemoprophylaxis and other approaches that have been considered appropriate in cancer patients based on clinical trials and guidelines. In the following sections, advantages and disadvantages of different procedures are discussed.

Prevention of Bacterial Infections

Antibacterial Chemoprophylaxis

The use of antibiotics to prevent bacterial infections should be weighed against their efficacy, their toxicity, and especially their impact on the development of resistance. In general, to evaluate the cost-effectiveness

TABLE 306.4 Suggested Prophylaxis for Infections in Cancer Patients

	DRUG	SCHEDULE	COMMENTS
Antibacterial	Ciprofloxacin Levofloxacin	500 mg bid 500 mg once daily	Use of FQs should be based on local epidemiology and careful evaluation of potential drawbacks of FQ prophylaxis. Probably not active anymore in many sites. Some studies showed possible effects on increasing resistance. Traditionally administered to adults receiving chemotherapy for acute leukemia with expected neutropenia >7–10 d; starting with chemotherapy and continuing until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia.
Antifungal	Posaconazole	100-mg tablets: 3 tablets twice daily on the first day, then 3 tablets daily As alternative, oral solution 200 mg tid orally with a (fatty) meal or acidic drink	Patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Therapeutic drug monitoring is warranted.
	Fluconazole	400 mg once daily	Patients receiving chemotherapy for acute myelogenous leukemia with cytarabine plus anthracycline regimens (administered for 7 and 3 d, respectively) and high-dose cytarabine-containing regimens.
	Other		Secondary prophylaxis according to isolated pathogen, clinical presentation, or both.
Anti–*Pneumocystis jirovecii*	Trimethoprim-sulfamethoxazole (TMP-SMX)	One double-strength tablet (160/800 mg) three times weekly, *or* 25 mg/kg TMP-SMX (5 mg/kg of TMP), max. 1920 mg (2 double-strength capsules) in 2 divided doses for 3 consecutive days/wk	All patients receiving chemotherapy with steroids, including those with solid tumors (e.g., brain cancer).
	Dapsone	2 mg/kg/d (max. 100 mg), on alternate days three times/wk	In patients who cannot tolerate TMP-SMX.
	Aerosolized pentamidine	300 mg once a month with nebulizer	In patients who cannot tolerate TMP-SMX; effective, but it is more difficult to administer.
	Atovaquone	750 mg twice daily or 1500 mg once daily	In patients who cannot tolerate TMP-SMX.
Antiviral	Acyclovir *or*	40 mg/kg in children in 2 divided doses In adults >40 kg: 800 mg twice daily	Patients with positive anti-HSV antibodies and severe mucositis or receiving treatment for acute leukemia.
	Valacyclovir	For HSV or VZV prophylaxis: 500 mg twice daily or 1000 mg daily For VZV exposure: 1 g three times daily (see text)	VZV-susceptible patients exposed to chickenpox who did not receive prompt administration of specific immunoglobulins.
	Lamivudine	100 mg once daily	Patients with chronic inactive HBV infection (HBsAg positive, HBV DNA low level or negative). Patients with resolved HBV infection (HBsAg negative and HBcAb positive), particularly if receiving rituximab or allogeneic HSCT.
	Entecavir	0.5 mg daily	HBsAg-positive patients treated with rituximab with HBV DNA <2000 IU/mL.

Continued

TABLE 306.4 Suggested Prophylaxis for Infections in Cancer Patients—cont'd

	DRUG	SCHEDULE	COMMENTS
Antituberculosis	Isoniazid	5 mg/kg (max. 300 mg) in adults, 10 mg/kg (max. 300 mg) once daily in children once daily for 6–9 mo	Patients with latent tuberculosis. Efficacy not specifically evaluated in cancer patients. See Chapter 249 and text for other regimens to treat latent tuberculosis.
Anti–CVC-associated infection	None	Good skin preparation and the use of sterile technique at time of device insertion. Good maintenance procedures.	All patients with indwelling central venous catheter.
Others	Growth factors	Filgrastim either subcutaneously or as an intravenous infusion over at least 1 h, *or* pegylated filgrastim	For the prevention of febrile neutropenia in patients who have a high risk of this complication based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. Secondary prophylaxis with G-CSFs recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in whom a reduced dose of chemotherapy may compromise disease-free or overall survival or treatment outcome. Efficacy not fully demonstrated for pegylated filgrastim.
	Immunoglobulins	Polyclonal immunoglobulins: 400 mg/kg every 21–28 d	Patients with chronic lymphocytic leukemia after the second episode of severe bacterial infection. Patients with leukemia or lymphoma with hypogammaglobulinemia (<400g/dL) and severe bacterial infections (reasonable, but not proved).
		Specific anti-VZV (VariZIG): 125 IU for every 10 kg of body weight (max., 625 IU)	In high-risk contact with a negative history of varicella preferably within 96 h after exposure to chickenpox.
	Vaccines	Influenza	Influenza vaccination of patients, especially during less aggressive treatment phases. Vaccination of household contact and health care workers.
		Varicella	VZV-seronegative household contacts and health care workers.
		Pneumococcus	Conjugated 13-valent antipneumococcal vaccine.
	Isolation procedures	Perform hand hygiene with an alcohol-based hand rub or by washing hands with soap and water if soiled, before and after all patient contacts or contact with the patients' potentially contaminated equipment or environment. Use contact precautions (gowns and gloves). Ensure adherence to standard environmental cleaning with an effective disinfectant.	Patients colonized or infected with multidrug-resistant pathogens (such as VRE, CRE, etc.) or infected with other pathogens for which contact isolation precautions are advisable (*C. difficile,* norovirus, etc.); of note, alcohol-based hand rubs are not cidal against *C. difficile* or norovirus.

CRE, Carbapenem-resistant Enterobacteriaceae; *CVC,* central venous catheter; *FQ,* fluoroquinolone; *G-CSFs,* granulocyte colony-stimulating factors; *HBcAb,* hepatitis B core antibody; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HSCT,* hematopoietic stem cell transplantation; *HSV,* herpes simplex virus; *IU,* international unit; *max.,* maximum; *VRE,* vancomycin-resistant enterococci; *VZV,* varicella-zoster virus.

of a prophylactic protocol, one should know, in every center, the rate of the complication to prevent and, consequently, the number of patients needed to treat to prevent the occurrence of a single infectious episode and attributable death. The safety—that is, the number needed to harm—should be also taken into consideration. Chemoprophylaxis for the prevention of bacterial infections was first proposed in clinical practice based on the discovery that 80% of the bacterial pathogens causing infection in neutropenic cancer patients were originating from the endogenous flora, but that approximately half of the pathogens were acquired during the hospital stay. The first approach relied on the oral administration of nonabsorbable antibiotics (gentamicin, vancomycin, and nystatin) aimed at totally (including anaerobes) or partially (excluding anaerobes) suppressing the intestinal bacterial flora and preventing the acquisition of exogenous organisms (gut decontamination). Subsequently, absorbable drugs such as TMP-SMX, usually given in combination with oral nystatin and then fluoroquinolones (FQs), were introduced. Several studies and meta-analyses were performed on the effectiveness of quinolone prophylaxis in cancer patients. The last and the largest one was published in 2012 and showed that antibacterial prophylaxis, especially with quinolones, was able to reduce in a statistically significant way both overall and infection-related mortality, in addition to preventing bacterial infections.[126] The number needed to treat (NNT) to prevent one death was around 50 and was higher than in a previous meta-analysis (NNT = 24), and there was apparently no untoward effect in terms of induction of resistance, although the issue was only partially studied because of undeniable difficulties.[127] Therefore most of the guidelines recommended FQ prophylaxis for adult patients with expected neutropenia longer than 7 days. It is important to note that these results were based on studies published between 1973 and 2011, thus before the spread of bacterial resistance.[128]

Following an alarming increase in bacterial resistance worldwide, two issues need to be addressed: (1) whether the benefit of FQ prophylaxis can still be expected, and (2) what is the contemporary impact of routine prolonged administration of broad-spectrum agents such as FQ on the selection of resistant strains and local epidemiology. A recent literature review on studies of FQ prophylaxis published in the last decade, in an era of increased resistance, did not confirm any effect on mortality, although prophylaxis was still associated with lower rates of BSI and febrile episodes.[128] The reason for that might be that the sample size could be insufficient to show a difference in mortality. However, a more

clinical explanation could be proposed: that the infections that quinolones were still able to prevent were those caused by susceptible organisms, in which mortality was very low in any case, because of the effective and timely empirical treatment.[129] Indeed, as in other settings, the mortality in neutropenic patients with BSI is most importantly influenced by the time between the onset of infection and the administration of appropriate antibiotic therapy.[130] As demonstrated recently by several studies, BSI-associated mortality is mainly driven by MDR pathogens, which are unlikely to be prevented by FQs.[86,131,132] This might explain the fact that FQ prophylaxis may no longer have any effect on overall mortality, despite their ability to prevent some infections (i.e., those due to organisms that are effectively treated with classic empirical therapy).[128,129]

As far as the impact of FQ prophylaxis on antibiotic resistance is concerned, data were scarce and discordant, but some studies reported an increase in ESBL-producing or MDR bacteria. There was no association with the rate of background resistance to FQs and the efficacy of FQ prophylaxis, but the NNT to prevent one BSI in the last decade was twice as high as reported in the meta-analysis from 2005.[128] For all previously mentioned reasons, some recent guidelines, considering the limited clinical benefit (mortality rates low and not improved by FQs, high NNT) and potential negative impact of FQs (toxicity and selection of resistant strains), do not support the use of FQ prophylaxis.[133,134] In patients with solid tumors, who usually experience low rates of BSI and shorter (<7 days) neutropenia, FQ prophylaxis is not recommended given no difference in the incidence of severe infections or both infection-related and overall mortality.[20]

In conclusion, FQ prophylaxis of febrile neutropenia has probably lost part of its efficacy because of the decreasing quinolone activity related to increasing resistance rates. Countries and centers with no or negligible resistance might still benefit from prophylaxis, while in others the advantage is likely to be minimal. The global situation of antibiotic usage has changed substantially in recent years, thus calling for a change in the way we look at indications that were apparently consolidated. Every center should review its prophylactic approach according to its own data. The world is facing a global crisis in terms of increased antibiotic resistance and spread of MDR pathogens, which are resistant to almost all available therapeutic options. This calls for new responsibilities of every specialist concerning proper use of antibiotics. Fluoroquinolones should be used cautiously in patients receiving cyclophosphamide since they were reported to cause significantly lower exposure to 4-hydroxycyclophosphamide (the active metabolite of cyclophosphamide) in patients with non-Hodgkin lymphoma.[135]

In children with acute leukemia, single studies on the use of amoxicillin/clavulanate, ciprofloxacin, or levofloxacin showed a reduction of fever episodes.[136–138]

Decolonization for Prevention of Infections Due to Resistant Bacteria, Including Fecal Microbiota Transplantation

Colonization with an MDR pathogen is a well-established risk for BSI due to the same strain, and the rate of BSI due to carbapenem-resistant *K. pneumoniae* was over 30% in allogeneic HSCT recipients colonized with such a pathogen.[131,139] Therefore attempts at decolonization by oral administration of nonabsorbable molecules such as gentamicin or colistin have been carried out and were reviewed in 2014.[139] Briefly, the decolonization rate varied from 37% to 68%, at the expense of a risk of developing resistance to the used drug (frequently the only therapeutic option in cases of subsequent MDR infection) as high as 45%. However, the applicability of this strategy before prolonged periods of neutropenia might be reevaluated in light of the availability of new antibiotics that might be used if an MDR breakthrough infection occurs.

Stemming from observations that alterations of intestinal microbiota can represent an important risk factor for development of bacteremia in cancer patients, fecal microbiota transplantation (FMT) could represent a strategy for prevention of infections due to antibiotic resistant pathogens. Indeed, a recent prospective trial in 20 patients with hematologic malignancies (40% of whom were neutropenic) colonized with MDR bacteria showed that 25 intraduodenal FMT procedures resulted in complete and partial decolonization in 60% and 80%, respectively.[140] The FMT procedure was more effective in the absence of concomitant antibiotic administration (79% vs. 36%), and no severe adverse events were observed.[140] Further studies are warranted to determine all the potential benefits and real-life applications of manipulation of gut microbiota.

Prophylaxis of Tuberculosis

Latent TB may reactivate during immunosuppression after antineoplastic chemotherapy. No specific study on latent TB treatment in cancer patients has been performed. The data on efficacy come from other immunocompromised patients, mostly human immunodeficiency virus (HIV) positive, and show that daily isoniazid monotherapy for 6 to 9 months, or rifapentine and isoniazid weekly for 3 months, or rifampin daily for 4 months are effective in treating a latent TB infection and preventing TB.[141,142] This approach should be considered in cancer patients with a positive TB skin test or a positive interferon-γ release assay (T-SPOT TB test [Oxford Immunotech, Marlborough, MA] or QuantiFERON-TB Gold In-Tube test [Qiagen, Valencia, CA]) and in cases of household exposure to TB or history of inadequately treated TB. Attention should be paid to potential interactions between rifampin and antineoplastic drugs and possible hepatotoxicity associated with all the regimens.

Prevention of CVC-Related Infections (See Chapter 300)

Prevention of CVC-related infections lies mainly in the correct insertion and manipulation of the devices, not only by health care workers but also by caregivers who perform CVC-maintenance procedures (and sometimes drug infusions) at home. Aseptic bundles during insertion and postinsertion care, bundles that include assessment of need for CVC, daily assessment of the site of insertion, change of dressing at least weekly or whenever wet or soiled, use of chlorhexidine gluconate–impregnated sponges, application of alcohol scrub for 15 seconds before each access of the line, and hand hygiene are effective measures to prevent infectious complications.[41] Continuous education and regular audits of bundle implementation represent other helpful activities.[143] Antibiotic catheter flushing has also been suggested to reduce the risk of infections, but this could represent a risk for selection of resistant bacteria. On the contrary, taurolidine lock has been associated with a significant reduction of CVC-related BSI, even if the susceptibility of gram-positives and gram-negatives to taurolidine are indeterminate due to limited data.[144]

Prevention of Fungal Infections

Primary Antifungal Chemoprophylaxis

Although fungal infections usually represent no more than 10% of all infections (see Table 306.2), their associated mortality is very high. Therefore preventing invasive fungal infections has always been considered a desirable approach. Two main drugs have been used in recent years for antifungal prophylaxis in acute leukemia patients: fluconazole (active against yeasts such as *Candida* but not molds) and posaconazole (mold-active prophylaxis). Meta-analyses showed that the use of fluconazole is effective in preventing *Candida* infections in allogeneic HSCT and in acute myeloid leukemia patients and suggest some possible benefit in other populations, if the incidence of invasive candidemia is higher than 7% to 10%.

As far as mold-active prophylaxis is concerned, in 2007 a study of oral posaconazole (oral solution) in adults receiving multiple cycles of chemotherapy for acute myeloid leukemia or myelodysplastic syndrome showed a statistically significant advantage in terms of mortality and a 6% absolute reduction in the relative risk of invasive mycosis, from 8% to 2% (primary end point), with a significant reduction also in the cumulative risk of infection compared with standard prophylaxis (fluconazole or itraconazole).[145] In this study, it was impossible to confirm the difference in mortality in a multivariate analysis including all baseline and time-dependent factors potentially able to affect survival, thus substantially limiting the likelihood of the survival benefit. Given the reduction in the incidence of fungal infections and the incidence observed in the control group, the NNT to prevent one case of proven/probable invasive mycosis was 16, and the NNT to prevent one fungal infection–related death was 27.[146] However, if the of incidence of invasive mycoses is lower than 8%, the NNT to prevent

one infection would be higher, and this observation underlines the need for every center to obtain accurate information on the local epidemiology of invasive mycosis and to tailor the results of clinical trials to the local situation. Until recently, posaconazole was only available as an oral solution and absorption was highly variable, depending heavily on ingestion of a fatty meal or an acidic drink, on subdividing the daily dose (three to four times a day), and on maintaining gastric acidity (no proton pump inhibitors). Thus therapeutic drug monitoring of serum levels has been recommended.[147] The recent introduction of an intravenous formulation and a new oral formulation (oral delayed-release tablets whose absorption is not influenced by gastric pH) resolved the problem of the low bioavailability, resulting in adequate plasma levels in most patients. Indeed, blood levels were sometimes too high, with some cases of toxicity.[148] As shown in Tables 306.4 and 306.5, particular attention is warranted if oral formulations are interchanged, since the dosing is different (200 mg tid for oral solution vs. 300 mg bid on the first day and then 300 mg daily for tablets). Of note, posaconazole has also been effective in reducing the incidence of invasive fungal infections in allogeneic HSCT recipients with graft-versus-host disease.[149]

Voriconazole, another mold-active azole, has never been studied for and is not approved for prophylaxis in acute leukemia. It has been tested in two trials in the setting of allogeneic HSCT, including the neutropenic preengraftment phase.[150,151] In the first study, the primary end point (survival) was not met, but voriconazole prophylaxis reduced the incidence of invasive aspergillosis, although in a non–statistically significant way.[150] Of note, efficacy was more evident among patients undergoing transplantation for acute myeloid leukemia as an underlying disease. In the second study, voriconazole was superior to itraconazole in a composite end point, in which the main driver of success was better tolerability and not efficacy. Unfortunately, the design of the voriconazole studies was suboptimal because, in both cases, both low- and high-risk patients were included, with consequent dilution of the possible benefit of prophylaxis. Issues related to therapeutic drug monitoring are also relevant for voriconazole, because of its erratic metabolism. In addition, triazoles (especially voriconazole) have many pharmacokinetic interactions with other drugs metabolized via the cytochrome P-450 system, with the risk of reducing the efficacy of treatments and increasing the incidence of (severe) adverse events.[152,153]

Finally, prophylaxis with nebulized liposomal amphotericin B plus systemic fluconazole, compared with fluconazole only, was demonstrated effective in reducing proven/probable IFD during repeated periods at risk after chemotherapy for acute leukemia in adults (a 10% reduction in IFD events).[154] A systemic antifungal prophylaxis with liposomal amphotericin B at 2.5 mg/kg twice weekly was found feasible and safe in high-risk pediatric cancer patients, compared with a historical control

TABLE 306.5 Antibacterial and Antifungal Agents Usually Used in Cancer Patients

PATIENTS' TYPE OF THERAPY	DRUG	ROUTE OF ADMINISTRATION	DAILY PEDIATRIC DOSAGE	USUAL DAILY ADULT DOSAGE	NO. OF DAILY DIVIDED DOSES
Antibacterial, intravenous	Piperacillin-tazobactam	IV	400 mg/kg (as piperacillin)	13.5–18 g (as piperacillin)	3–4 in adults, 4 in children; preferably in prolonged or continuous infusion with a loading dose
	Ceftazidime	IV	100 mg/kg	6000 mg	3
	Cefepime	IV	100 mg/kg	6000 mg	3
	Meropenem	IV	60 mg/kg	3000–4000 mg	3, infuse over 3–6 h
	Ceftolozane-tazobactam	IV	ND	4500 mg (as both drugs) 9000 mg in studies on nosocomial pneumonia (off-label dosage)	3
	Ceftazidime-avibactam	IV	ND	7500 mg (as both drugs)	3, infuse over 2 h
	Ceftaroline	IV	2 mo to <2 yr: 8 mg/kg every 8 h ≥2 yr to <18 yr (≤33 kg): 12 mg/kg every 8 h ≥2 yr to <18 yr (>33 kg): 400 mg every 8 h or 600 mg every 12 h	1200 mg	2, infuse over 5–60 min
	Ceftobiprole	IV	ND	1500 mg	3
	Imipenem-cilastatin	IV	60–100 mg/kg (as imipenem)	2000–4000 mg (as imipenem)	3–4
	Meropenem-vaborbactam	IV	ND	12 (as both drugs)	3, infuse over 3 h
	Ciprofloxacin	IV	15–30 mg/kg	800–1200 mg	2–3
	Ceftriaxone	IV	80 mg/kg	2000 mg	1
	Amikacin	IV	20 mg/kg	1000–1500 mg	1
	Vancomycin	IV	40–60 mg/kg	2000 mg	2 or as continuous infusion after a loading dose
	Teicoplanin	IV; not available in United States	10 mg/kg (loading dose of 10 mg/kg bid on first day of treatment)	600–1200 mg (loading dose of 600 mg bid on first day of treatment)	1 (2 on first day of treatment)
	Daptomycin	IV	10 mg/kg	6–8 mg/kg	1
	Linezolid	IV (also available oral)	30 mg/kg in three doses if <12 yr, then 20 mg/kg	1200 mg	2
	Tedizolid	Oral/IV	ND	200 mg	1
	Tigecycline	IV	2.4 mg/kg loading dose, then 2.4 mg/kg (proposed)	100 mg loading dose, then 100 mg	2
	Colistimethate sodium (colistin)	IV	150,000–200,000 IU/kg loading dose, then 150,000–200,000 IU/kg[a]	9,000,000 IU loading dose, then 9,000,000 IU[a]	2
	Polymyxin B	IV	Infants: up to 40,000 U/kg Children: 15,000–25,000 U/kg	15,000–25,000 U/kg (= 1.25–2.5 mg/kg, 1 mg = 10,000 U; a loading dose might be indicated)	
	Fosfomycin	IV; not available in United States	300 mg/kg	15–24 g	3–4

TABLE 306.5 Antibacterial and Antifungal Agents Usually Used in Cancer Patients—cont'd

PATIENTS' TYPE OF THERAPY	DRUG	ROUTE OF ADMINISTRATION	DAILY PEDIATRIC DOSAGE	USUAL DAILY ADULT DOSAGE	NO. OF DAILY DIVIDED DOSES
Antibacterial, oral	Amoxicillin-clavulanate	Oral	60–80 mg/kg (as amoxicillin)	2–3 g (as amoxicillin)	2–3
	Ciprofloxacin	Oral	30 mg/kg	1000–1500 mg	2
	Cefixime	Oral	6–8 mg/kg	400 mg	2–3
	Moxifloxacin	Oral, IV	Based on age, 4–6 mg/kg twice daily[225]	400 mg	1
Antifungal	Amphotericin B deoxycholate[b]	IV	0.5–1 mg/kg	0.5–1 mg/kg	1
	Liposomal amphotericin B	IV	3 mg/kg	3–5 mg/kg	1
	Amphotericin B lipid complex	IV	5 mg/kg	5 mg/kg	1
	Caspofungin	IV	50 mg/m^2 for age <17 yr	70 mg the first day, then 50 mg the following days	1
	Micafungin	IV	2–4 mg/kg	100 mg	1
	Anidulafungin	IV	3 mg/kg q24h the first day, then 1.5 mg/kg q24h	200 mg the first day, then 100 mg the following days	1
	Voriconazole	IV, oral	9 mg/kg bid the first day, then 8 mg/kg bid[c]	6 mg/kg bid the first day, then 4 mg/kg bid	2
	Fluconazole	IV, oral	10 mg/kg	400 mg	1
	Posaconazole[d]	Oral solution (doses are different for tablets and IV)	If >12 yr, dose as adults	800 mg (with a fatty meal or acidic carbonated drink)	4
		Oral delayed-release tablets	Not approved for <18 yr but PK/PD data available for per-kg dosing[226,227]	600 mg/d divided in 2 doses, then 300 mg daily	1
	Isavuconazole	IV/oral	ND	200 mg q8h for 6 doses, then 200 mg daily (372 mg if ordered as isavuconazonium sulfate)	3 during the first 48 h, 1 thereafter

[a]An important and potentially confusing characteristic is colistin's dosage expression. Colistin is available in two salt forms, colistin sulfate and colistimethate sodium. In Europe, colistimethate sodium (salt) is available, and dosing is expressed usually in international units (IU), and sometimes in milligrams of colistimethate sodium, whereas in the United States, the dosage of US Food and Drug Administration–approved colistimethate sodium is defined in milligrams of colistin base activity. Thus particular attention should be paid to avoid dosage errors. Approximate dose conversion: 1,000,000 IU = 80 mg of colistimethate sodium = 30 mg colistin base.[228] The optimal dosing of colistin remains to be established. Recent studies in adults with normal renal function reported the use of 6,000,000 to 9,000,000 IU daily, with pharmacologic analyses supporting the use of loading dose of 9,000,000 IU, followed by 4,500,000 IU every 12 hr.[229–231] See Chapter 32 for recommended doses in the United States, which are 5 mg colistin base/kg loading and then 5 mg colistin base/kg/d in two or three divided doses. If ordered as colistimethate, the dose per day would be 13.3 mg/kg, divided into two or three doses.

[b]Contraindicated in the presence of risk factors for renal toxicity (e.g., impaired renal function at baseline; nephrotoxic comedication, including aminoglycoside antibiotics; and history of previous toxicity).

[c]In patients 2 to 12 yr of age, and 12 to 14 yr if weighing less than 50 kg; otherwise, dose as for adults if 12 yr of age and older. Therapeutic drug monitoring is highly recommended. Children metabolize voriconazole more rapidly than adults.

[d]Therapeutic drug monitoring might be useful to assess if trough levels are in the range for efficacy in case of oral solution.

ND, No established dosing for children; *PK/PD,* pharmacokinetic/pharmacodynamic.

group.[155] On the other hand, a randomized controlled trial that included 355 adult patients undergoing remission-induction chemotherapy for newly diagnosed acute lymphoblastic leukemia demonstrated a high incidence of IFD in this population, but failed to demonstrate the efficacy of liposomal amphotericin B at 5 mg/kg twice weekly (IFD 7.9% in prophylaxis arm vs. 11.7% in placebo arm).[156]

Secondary Antifungal Prophylaxis

Patients with a history of invasive mycosis are at high risk of reactivation when undergoing further chemotherapy. The recurrence of invasive aspergillosis after HSCT has been associated with less than 1 month of antifungal therapy and with persistence of radiologic abnormalities after treatment.[157] Therefore secondary antifungal prophylaxis is recommended during HSCT or high-intensity chemotherapies for patients with previous IFD. The drug for secondary prophylaxis should be chosen according to the etiology of the original IFD, the localization, the drugs available and their formulations, and risks of interactions with other therapies, especially those for the treatment of the underlying disease.

Prophylaxis Against *Pneumocystis jirovecii*

In recent years, *P. jirovecii* pneumonia has been described with increasing frequency in non-HIV patients.[158] The risk is particularly high in patients with acute (especially lymphoblastic) leukemia, non-Hodgkin lymphoma, Waldenström macroglobulinemia, multiple myeloma, and chronic lymphocytic leukemia treated with standard chemotherapy or undergoing autologous transplantation.[116] Other patients at risk for this complication are those with central nervous system solid tumors, in correlation with the prolonged use of high-dose steroids and the alkylating agent temozolomide, or those receiving bendamustine for breast cancer.[158] Several other drugs affecting cell-mediated immunity have also been associated with the risk of *P. jirovecii* pneumonia, including fludarabine, ara-C (cytarabine), methotrexate, D-actinomycin, bleomycin, and L-asparaginase. In addition, pneumocystosis has been associated with administration of alemtuzumab, which causes profound depletion of T lymphocytes; with rituximab if used in combination with bendamustine or CHOP (cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisolone) chemotherapy every 14 days; and with idelalisib, ibrutinib, and, in two cases, with the tyrosine kinase inhibitor dasatinib.[62,116] It remains to be determined whether novel biologic drugs are responsible for an increased infection risk or whether other concomitant or previous treatments (purine analogues, alkylating agents, or steroids) contribute significantly to the risk of pneumocystosis, and the duration of risk after treatment discontinuation is not known. Indications for prophylaxis of pneumocystosis include certain diseases (e.g., acute lymphoblastic leukemia) and treatments (e.g., fludarabine, alemtuzumab, or corticosteroid at the dose of >20 mg of prednisone daily for at least 4 weeks).[159] An absolute CD4$^+$ lymphocyte count of 200/mm^3 or less, or a proportion of 15% or less (or similar age-related values for children), has been suggested as an indication for prophylaxis, at least after HSCT. Because the efficacy and tolerability of 160/800 mg of TMP-SMX given three or seven times a week are comparable, one 160/800 mg TMP-SMX tablet three times weekly remains the best prophylactic option, provided the patient is strictly compliant with the prescription. Other drugs, such as daily oral dapsone

or atovaquone or monthly aerosolized pentamidine, have demonstrated efficacy and are alternative options in patients who cannot tolerate TMP-SMX (see Chapter 269).[159]

Prevention of Viral Infections

For the prevention of HSV or VZV reactivation, antiviral prophylaxis with acyclovir or valacyclovir is recommended for seropositive patients undergoing HSCT, therapy for acute leukemia, or treatment with certain new agents such as bortezomib, alemtuzumab, idelalisib, or daratumumab. In patients not on active prophylaxis who are exposed to varicella, intravenous administration of anti-VZV immunoglobulins (VariZIG) within 72 to 96 hours of the exposure is recommended, although protection is not guaranteed (see Chapter 136). If anti-VZV immunoglobulins are not available or in case of delayed notification of the risk contact, prophylaxis with valacyclovir (1 g three times daily for adults weighing more than 40 kg) or acyclovir (in children per os 20 mg/kg per dose, administered four times per day, with a maximum daily dose of 3200 mg; in adults 800 mg five times a day) is an option, although the efficacy has not been established. Prophylactic chemotherapy should be started on day 7 after exposure and continued for 7 days thereafter.

Routine CMV prophylaxis is not recommended outside of the transplantation setting. Despite that, it seems worthwhile to report that letermovir, a new antiviral with significantly fewer side effects than (val)ganciclovir or foscarnet, has been recently shown to reduce the clinically significant CMV infection rate in adult allogeneic HSCT recipients from 61% to 38%.[160] CMV DNA testing should be performed in all cancer patients with signs or symptoms compatible with CMV reactivation (cytopenias, unexplained fever) or disease (gastroenteritis, pneumonia, retinitis, hepatitis, encephalitis) (see Chapter 137).[119] In certain settings, such as patients receiving alemtuzumab for hematologic malignancies, idelalisib, rituximab and bendamustine, and possibly also brentuximab, the risk of CMV reactivation and subsequent disease may warrant routine, usually weekly, CMV monitoring.[119]

All cancer patients should be screened for an active or past HBV infection (with at least HBsAg and HBcAb) before starting chemotherapy because viral reactivation and acute hepatitis, with consequences ranging from delaying chemotherapy to fatal fulminant infection, can occur in patients receiving chemotherapy. Patients with chronic hepatitis should receive antiviral treatment, while those with inactive infection (i.e., HBsAg-positive, HBV DNA negative) should receive prophylaxis to prevent reactivation if they are scheduled to receive intensive chemotherapy, particularly including rituximab. Lamivudine (100 mg/day) used to be the mainstay of antiviral prophylaxis. Very limited data on new antivirals are available in this setting, with only one recent randomized, open-label trial showing entecavir (0.5 mg/day) to be superior to lamivudine in preventing clinical hepatitis in Chinese patients with chronic inactive HBV infection undergoing chemotherapy, including rituximab with CHOP (R-CHOP), for lymphoma (rate of reactivation, respectively, 4 of 61 [7%] vs. 18 of 60 [30%]).[161] Nevertheless, based on data from immunocompromised patients treated for a chronic HBV infection, most guidelines recommend agents with a high genetic barrier (such entecavir or tenofovir in any of the two formulations) for prophylaxis in HBsAg-positive patients.[63] Prophylaxis should be started before chemotherapy if possible, but chemotherapy should not be delayed because of it, and prophylaxis should be continued for at least 6 to 12 months after the end of chemotherapy (18 months for rituximab), depending on the predicted duration and intensity of immunosuppression.

HBV reactivation is also possible, although less likely, in patients with resolved HBV infection (HBsAg negative, HBcAb positive). The risk of reactivation can be as high as 42% in patients with lymphoma treated with rituximab, and 20% in chronic lymphocytic leukemia, 13% in T-cell leukemia, and 5% in multiple myeloma patients.[63] The options are either to provide lamivudine prophylaxis in those with high risk (i.e. >10%) of reactivation (e.g., patients receiving anti-CD20 agents) or to monitor them closely for HBV DNA appearance and treat at the first sign of reactivation.

Vaccination against influenza is the most effective preventive measure globally. Additionally, during community or nosocomial outbreaks of influenza infection, prophylaxis with oseltamivir 75 mg once daily for 10 days should be considered, especially in severely immunocompromised patients, because of the risk of severe infection and its complications.

Other Prophylactic Measures

Role of Colony-Stimulating Factors in Prophylaxis

Colony-stimulating factors are used with the aim of facilitating dose-intense treatments and decreasing infectious complications by preventing the development of neutropenia or reducing its duration. In solid tumors, studies using prophylactic granulocyte colony-stimulating factor (G-CSF) have consistently demonstrated a decrease in the length and severity of neutropenia and a decrease in the incidence of febrile neutropenia.[162] On the contrary, in patients with hematologic malignancies, G-CSF significantly reduced the duration of severe neutropenia, but without any significant reduction in febrile complications, duration of hospitalization, or survival.[163] Only two studies have compared antibiotics and G-CSF in the prevention of febrile neutropenia. When assessed together in a meta-analysis, a non–statistically significant difference favoring antibiotics was demonstrated.[164] Several guidelines consistently recommend the prophylactic use of G-CSF in adult cancer patients receiving a chemotherapy regimen associated with more than a 20% risk of febrile neutropenia or in patients at lower risk but with relevant comorbidities (older age, advanced underlying disease).[134] Finally, patients with solid tumors who experienced neutropenia and fever during previous cycles may benefit from prophylactic administration of G-CSF during subsequent cycles of chemotherapy.[134]

Role of Immunoglobulins in Prophylaxis

Based on the experience in patients with primary immunodeficiency syndromes, the administration of immunoglobulins has been recommended in those with secondary, iatrogenic immunoglobulin deficiencies, such as in patients with acute and chronic lymphocytic leukemia or non-Hodgkin lymphoma and in those receiving rituximab. Indeed, keeping the immunoglobulin G (IgG) level higher than 600 mg/dL has been associated with a reduction of infectious episodes due to bacteria, provided the treatment could be given for at least 6 months, but had no effect on viral and fungal diseases.[165] Similarly, a meta-analysis of studies in patients with chronic lymphocytic leukemia or multiple myeloma receiving immunoglobulins reported a reduction in the occurrence of infections, but without any impact on mortality.[166] Patients considered to deserve regular IgG replacement therapy are those with chronic lymphocytic leukemia and recurrent infections (mainly pneumonia or sinusitis) and an IgG level less than 500 mg/dL.[167]

Infection Control: Isolation and Antimicrobial Stewardship

In consideration of the growing antimicrobial resistance and shortage of new antibiotics, infection control and antimicrobial stewardship programs should be implemented in all cancer centers.[168] Infection control practices include surveillance, promoting and auditing the use of standard and transmission mode–based precautions, appropriate screening for colonization with resistant pathogens, and preventive measures, such as proper hand hygiene and contact precautions for patients colonized or infected with resistant bacteria (see Chapter 298). Active surveillance—for example with rectal swabs for colonization with carbapenemase-producing *K. pneumoniae* or VRE—should be performed in institutions where these pathogens are regularly encountered. Additional transmission mode–based precautions include the use of high-level masks/respirators for health care personnel, such as N95 or higher level or free-flow pressure 3 (FFP3) masks. These *airborne precautions* should be applied, for example, in cases of active TB or measles. *Contact precautions* (hand hygiene, use of disposable gowns and gloves) are indispensable when caring for a patient colonized or infected with MDR bacteria. In these cases, patients should be isolated in single rooms, possibly with staff cohorting. If single rooms are not available, then patient cohorting is recommended. In addition, in cases of patient transfer to another ward or hospital, it is of utmost importance to notify promptly and completely the receiving unit about the carrier status and the need for precautions. *Droplet precautions,* including disposable gown and gloves and a surgical mask, should also be applied

in cases of infection with respiratory viruses such as influenza. For all precaution measures, regular monitoring of adherence is warranted and the facilities should ensure access to adequate hand hygiene stations (sinks, alcohol-based rubs, etc.) and personal protective equipment.

For neutropenic patients, it is not clear whether staying at home or in a hospital may have an impact on the development of chemotherapy-related complications. In a hospital, keeping the patient in a reverse isolation/protective environment is believed to reduce colonization or infection with various pathogens. Unlike for transmission-based precautions, there is no universal consensus on the appropriate protective environment for neutropenic patients, and standards may vary between institutions. However, they usually include single rooms and, for people entering the room, surgical masks (to prevent mainly respiratory viruses) and in some institutions also disposable gloves and gowns (to prevent contamination with contact-transmitted pathogens). General guidelines for preventing the diffusion of infectious diseases in health care facilities should be followed in any ward where cancer patients are admitted.[169] Additionally, since aspergillosis and other mold infections are acquired via the respiratory route, the use of high-efficiency particulate air (HEPA) filters in rooms or wards where leukemic or transplant patients are hospitalized is recommended.[170] The use of masks with adequate filtration power (FFP3 or free-flow pressure 2 [FFP2] or N95 respirators) could reduce *Aspergillus* colonization and infection when the patient is moved from the protective environment. This approach has been demonstrated effective, together with other physical barriers, during building renovations.[171] The use of laminar airflow rooms is not deemed necessary and does not impact substantially on the rate of infection. On the contrary, it impacts negatively on patients' quality of life and on the possibility for the health care providers to care for them properly.

Antimicrobial stewardship (see Chapter 51) should include four main aspects: (1) local surveillance of antibiotic resistance, antibiotic consumption, and patient outcomes; (2) development and regular update of protocols and algorithms for the diagnosis, prevention, and treatment of infections; (3) prompt reporting of microbiologic results by the laboratory, allowing timely deescalation of broad-spectrum empirical regimens and shortening of antibiotic therapy; and (4) optimization of dosing regimens. All these aspects call for a multidisciplinary approach and close collaboration between the treating oncologist and hematologists; the microbiology laboratory; the infectious diseases consultation service, including infection control unit; and the hospital pharmacy.

Food and Lifestyle

A low-bacterial-count diet seems not to offer any benefit compared with a normal diet.[172,173] However, some precautions should be recommended, such as avoiding unpasteurized milk; unpasteurized or mold cheese products; raw or undercooked (including insufficiently reheated) meat, fish, shellfish, tofu, or eggs; and unpeeled fruits and salad ingredients, unless properly washed at home. *Listeria* colonization and infection has been described in association with unpasteurized dairy products and ready-to-eat deli meats, whereas raw vegetable sprouts have been associated with outbreaks of *E. coli, Salmonella,* and *Listeria* infection. Transmission of toxoplasmosis can also occur with raw meat and vegetables contaminated with cat feces. Although probiotics (foods with live yeast cultures) are advertised as useful in reducing the risk of antibiotic-associated diarrhea, bloodstream infections from probiotic administration have been reported. Food safety practices for food handling should be followed, and specific information for cancer patients is available online.[174] Diet recommendations that are too restrictive may have a negative impact on the patient's nutritional status or quality of life, or both.

Cancer patients, especially during less intensive treatment, may seek information about the safety of traveling or other recreational activities. Although few data exist that quantify the risk of travel or recreational activities, some considerations can be made. First, the assessment of the underlying conditions should be made, with particular attention to the stability of the patient's clinical condition and his or her potential need for rapid access to health care facilities (in that case, remote destinations or cruises are not recommended). In addition, evaluation of any ongoing treatment that might constitute a contraindication to the disease prevention measures recommended for the proposed destination, such as vaccines or antimalaria prophylaxis, is necessary. In immunocompromised hosts, live-attenuated vaccines (such as those against yellow fever or *Salmonella typhi*) might be contraindicated, whereas effectiveness of other vaccines, such as that against hepatitis A, might be reduced.

Cancer patients should not be advised to part with their pets, although some precautions are necessary; for example, a different household member should be assigned to scoop cat litter, because of potential *Toxoplasma* cyst exposure. Aquariums should not be touched or maintained by patients because water in fish tanks may be contaminated with atypical mycobacteria, whereas *Salmonella* can be acquired directly from reptiles or from fomites; thus patients should avoid contact with a reptile's food or aquarium. Finally, large pet birds should be avoided because they may transmit *Chlamydia psittaci.* In general, the potential benefit of recommendations on safety of food, pet care, travel, and other lifestyle measures should be weighed against the unclear value of such recommendations and their potential to have a negative impact on patients' nutritional intake and quality of life.

Vaccination

The use of inactivated vaccines in cancer patients has been demonstrated to be safe and effective, especially during nonaggressive/maintenance treatment phases, with the only pitfall that the immune response can often be poor, especially with certain drugs. International recommendations are available for vaccination of patients with hematologic malignancies and HSCT recipients.[175,176] Influenza vaccination with inactivated vaccines is strongly recommended for all immunocompromised patients, with the possible exception of those treated with intensive chemotherapy (e.g., a remission induction regimen for acute leukemia) and those who received rituximab within the previous 6 months, not because of safety concerns but because the probability of responding is very low. Both unvaccinated and vaccinated but severely immunocompromised patients should be offered empirical antiviral treatment in cases of clinical signs or symptoms of influenza during the influenza season. Influenza vaccination is also recommended for household contacts and health care personnel caring for cancer patients.

Pneumococcal vaccination is also strongly recommended for immunocompromised patients, although, again, response to vaccine may be suboptimal. Pneumococcal conjugate vaccine (PCV13) is thought to elicit better response than the pneumococcal polysaccharide vaccine (PPSV23).

In some cases—for example, for varicella—vaccination is recommended for seronegative household contacts. However, it has been suggested that prejudice about safety in those to be vaccinated is the major difficulty for implementing a varicella vaccination program targeted at seronegative household contacts to prevent varicella in immunocompromised children.[177]

TREATMENT OF COMPLICATIONS IN NEUTROPENIC CANCER PATIENTS

Empirical Antibacterial Therapy of Fever During Neutropenia

Fever during neutropenia has always been considered a medical emergency and should always be considered as due to infection, unless proven otherwise. Febrile episodes during the course of neutropenia are classified according to the presence or absence of a microbiologic or clinical documentation of infection, as (1) microbiologically documented infections with bacteremia (isolation of a significant pathogen from one or more blood cultures); (2) microbiologically documented infections without bacteremia (isolation of a significant pathogen from a well-defined site of infection, usually urine or respiratory secretions obtained with sterile procedures or fluid aspiration); (3) clinically documented infections, in the presence of a clinical picture clearly and objectively infectious in nature but without any microbiologic proof; and (4) unexplained fever or fever of unknown origin, when both clinical and microbiologic proof is lacking, but the clinical course is compatible with an infection. For the purpose of starting empirical antibiotic therapy, fever is usually defined as an axillary temperature greater than 38°C at three different times within a 12-hour period or as a temperature greater than 38.5°C in a single measurement. In a

neutropenic cancer patient, the development of fever or other signs of infection (e.g., altered mental status, hypotension, skin or mucosal lesions, respiratory failure) without fever or even with hypothermia should always raise the suspicion of an infection and must receive prompt attention, which involves diagnostic procedures (at least blood cultures) and empirical antibacterial treatment.

The effectiveness of the empirical therapy approach has been clearly demonstrated, and empirical antibiotic therapy has certainly contributed substantially to the impressive reduction in mortality from infectious complications observed during the last decades.[178] Unfortunately, some recent studies on infection in acute leukemia and HSCT patients seem to show that the mortality rate associated with infections due to gram-negative rods, and possibly also VRE, may be increasing, mainly driven by MDR isolates with peaks as high as 70% in BSI due to carbapenem-resistant *K. pneumoniae* in allogeneic HSCT recipients.[130,139,179,180] Indeed, in the era of bacterial resistance and shortage of new antibiotics, especially those active against gram-negative rods, infectious complications might once again significantly compromise the success of cancer treatment. Bacterial epidemiology and patterns of resistance may vary from patient to patient (in cases of individual colonization with resistant pathogens), from center to center (in cases of environmental colonization), and from country to country (different endemicity of resistant strains). Therefore for each patient, the risk of a severe and complicated clinical course and the risk of infection caused by resistant pathogens should be evaluated individually and the treatment chosen accordingly.[181] Fig. 306.2 summarizes a possible initial approach to a patient with febrile neutropenia. Table 306.5 summarizes the major antibiotics used for empirical or targeted therapy in febrile neutropenia.

Patients at Low Risk

An important change in the natural history of infections in cancer patients has been the increasing number of patients with solid tumors and nonleukemic hematologic diseases who are treated with high-dose chemotherapy and therefore may develop neutropenia and fever. However, patients with solid tumors rarely receive regimens that make them neutropenic for more than 7 to 8 days, and neutropenia is seldom

TABLE 306.6 Factors Associated With Low Risk of Severe Infection or an Uncomplicated Clinical Course in Febrile Neutropenic Cancer Patients

	MASCC SCORE	
	Clinical Parameters	**Score[a]**
Clinical data available at onset of febrile neutropenia or soon after admission	1. Burden of illness: no or mild symptoms[b]	0, 3, or 5
	2. No hypotension	5
	3. No chronic obstructive pulmonary disease	4
	4. Solid tumor or hematologic malignancy with no prior fungal infection	4
	5. No dehydration	3
	6. Outpatient status	3
	7. Patient's age <60 yr	2

[a]The maximal theoretical score is 26. Low-risk patient: score ≥21.
[b]No or mild symptoms = 5, moderate = 3, severe or morbid = 0.
MASCC, Multinational Association for Supportive Care in Cancer.

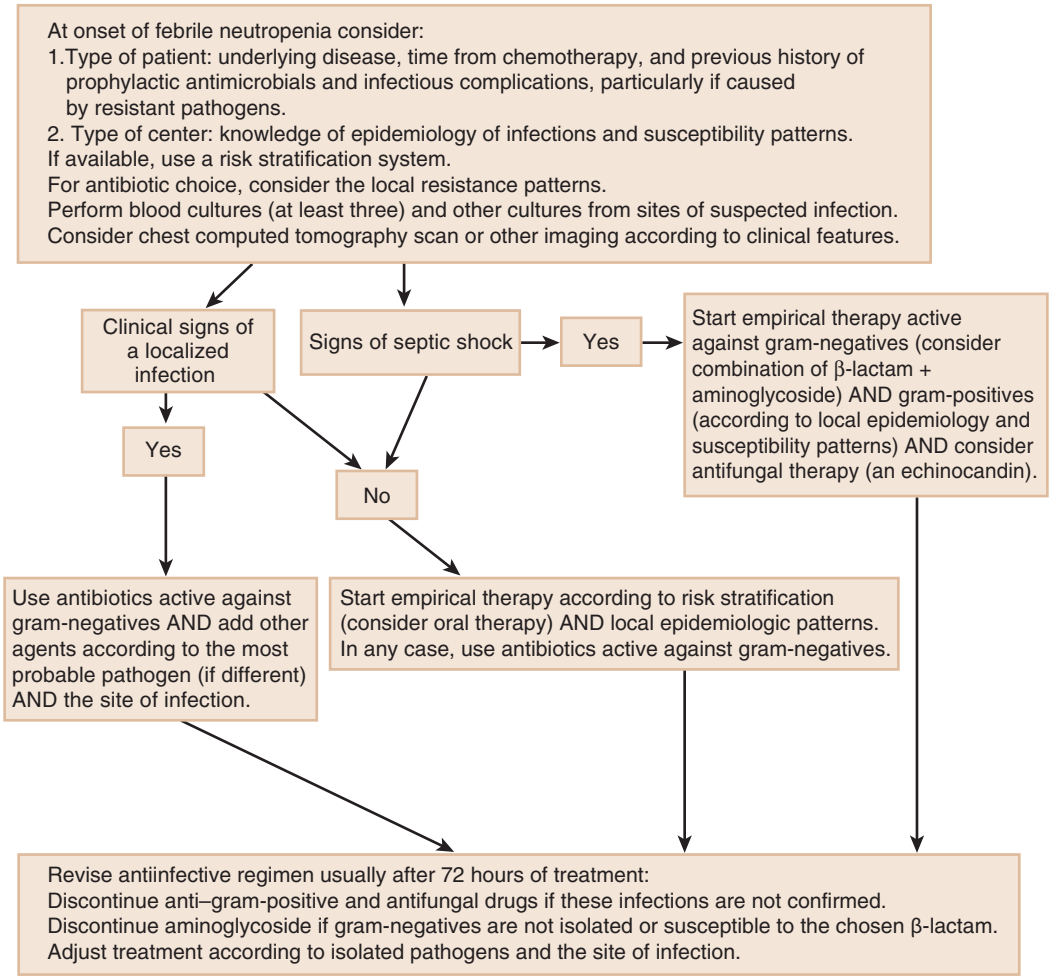

FIG. 306.2 Possible initial approach to a patient with febrile neutropenia.

severe. In most cases, these patients are clinically stable within 48 hours after the appearance of fever and are without fever within 3 to 4 days. On the basis of this concept, the Multinational Association for Supportive Care in Cancer (MASCC) score has been shown to be an acceptable tool to identify patients with low probability of complicated febrile neutropenia (Table 306.6). A risk-index score greater than 21 identified low-risk patients, with positive and negative predictive values of 91% and 36%, respectively. At this threshold, sensitivity and specificity were 71% and 68%, respectively, with a 30% misclassification rate. Studies in children evaluating the risk of complicated outcome were less successful. Although six pediatric stratification systems for identifying low-risk patients were established in a retrospective analysis, none of them could be validated in separate data sets.[182]

If low-risk patients can be reliably identified, the next logical step would be to try to discharge these patients early or even to treat them as outpatients or at home. The mandatory conditions for home or outpatient treatment include the presence of a reliable caregiver at home, a stable intravenous access, hospital proximity and adequate transportation, and the necessary facilities (telephone, running water, heating, and refrigeration). Antibiotic choices for oral therapy in the absence of risk factors for resistant pathogens include ciprofloxacin plus amoxicillin-clavulanate combination therapy, moxifloxacin monotherapy, or intravenous antibiotics such as ceftriaxone plus amikacin once daily.[183,184] In neutropenic patients with fever of unknown origin, switching therapy from intravenous to oral (e.g., ciprofloxacin or cefixime) has been also demonstrated to be a safe practice. Recent developments in antibiotic therapy suggest that skin and soft tissue infections due to gram-positive cocci might be safely treated with a single administration of 1.5 g of dalbavancin, thus allowing outpatient treatment of infections due to resistant gram-positive bacteria, although there is no experience in neutropenic patients.[185]

Despite still being only partially valid, these data and recommendations should be put in a more modern context. First of all, as previously mentioned, targeted therapies and biologic response modifiers have partially changed the spectrum of infecting pathogens and put patients at a risk that is higher than and different from what was previously realized. Second, all these studies were performed in times when antibiotic resistance was not a major problem and the risk for a bacterial infection caused by an ESBL-producing and/or quinolone-resistant gram-negative rod was low or absent. The current situation might be different, because the increasing resistance phenomenon does not necessarily affect only high-risk patients but can be present in specific settings, hospitals, or countries in low-risk patients as well, although the shorter duration and severity of neutropenia should still mitigate the clinical course. Therefore once again, every center should make its own choices based on its local epidemiology and every patient should be evaluated separately.

Patients at High Risk

As already mentioned, the practice of administering empirical antimicrobial therapy very early at the onset of fever during neutropenia has probably been the main driver of the undeniable progress obtained in this field. However, in recent years, because of the decreasing activity of the classic antibiotics used for fever during neutropenia and the shortage of new molecules, choices and strategies have been rediscussed. Indeed, physicians have been forced to diversify empirical regimens based on colonization, local epidemiology, antibiotic policies, and patient-related factors such as clinical presentation, organ failure, and status of the underlying disease. Currently, two strategies for empirical therapy have been envisaged: the escalation approach and the deescalation approach, as first suggested by us in the 7th edition of the present text in 2010 and then expanded in the ECIL guidelines, published in 2013.[181,186] In both strategies, there are two key time points: the day of onset of fever or suspected infection (day 0), when the patient is initially evaluated, cultures are drawn, and antibiotic therapy is started; and the day in which everything should be reevaluated, based on clinical conditions and availability of microbiologic results (days 2–4, depending on the performance of local laboratories). Being ready to review the composition of empirical therapy is mandatory in both cases, in light of the possible need to widen or restrict the antibiotic coverage or focus on a specific pathogen.

The escalation approach consists of starting with piperacillin-tazobactam or a third-generation cephalosporin (a choice that used to be broad spectrum and active against *P. aeruginosa* 20 years ago, but it is not so any more in many places) and then adjusting therapy if necessary. This approach seems to be still appropriate in many countries and centers, especially when resistance rates are low among pathogens commonly causing infections in neutropenia. With this approach, the carbapenems are used as second-line therapy either in patients failing the initial therapy or in case of a documented infection.[181,187] In this clinical situation, combining an aminoglycoside with a β-lactam is not deemed necessary because of more toxicity and no clinical advantage. This was clearly shown by a double-blind, placebo-controlled clinical trial comparing piperacillin-tazobactam with placebo versus the same drug with amikacin, and was confirmed in subsequent meta-analyses.[188] The empirical use of an anti–gram-positive antibiotic such as vancomycin, teicoplanin, linezolid, or daptomycin is not recommended by any guideline, either as initial therapy or in persistently febrile patients, unless a MRSA or a penicillin-resistant pneumococcus or enterococcus is isolated, or the patient has signs and symptoms suggesting a gram-positive etiology (e.g., CVC involvement or pneumonia).[183] The escalation approach avoids universal, and usually unnecessary, up-front use of antibiotics with the broadest spectrum, such as carbapenems or combinations with aminoglycosides or glycopeptides, and consequently minimizes potential disadvantages, such as selection of resistant pathogens or toxicity. However, in light of increasing resistance, there is a growing concern with this approach, because it has been shown that if the initial regimen fails to cover the pathogen responsible for infection, the outcome can be fatal.[189] For this reason, a new approach has been suggested, which has been called "deescalation empirical therapy."

The deescalation approach consists of starting with a very broad initial empirical regimen, chosen based of the severity of the patient's clinical presentation, the presence of colonization with MDR bacteria, risk factors for harboring MDR bacteria, and the local bacterial epidemiology. Examples of deescalation empirical therapy include:

1. Starting with carbapenem or ceftolozane-tazobactam (no experience in neutropenic patients for the latter at the time of this writing), to cover ESBL-producers and MDR *P. aeruginosa*;
2. Up-front use of vancomycin in patients colonized with MRSA, methicillin-resistant *Staphylococcus epidermidis,* or penicillin-resistant gram-positive cocci or in centers with high incidence of infections due to these pathogens;
3. Up-front use of ceftazidime-avibactam, meropenem-vaborbactam, or a combination including colistin, if a patient is colonized with carbapenem-resistant Enterobacteriaceae;
4. Addition of daptomycin, tigecycline, or linezolid in the presence of colonization with MDR gram-positive pathogens (Table 306.7).

In the deescalation approach, the key issues are (1) to safeguard the patient and to avoid the risk of undertreating his or her infection, which has the potential to be overwhelming; and (2) to reduce as much as possible the unnecessary use of precious drugs (e.g., carbapenems

TABLE 306.7 Risk Factors for Infections Caused by Resistant Bacteria in Cancer Patients

1. Previous infection or previous or current colonization by resistant bacteria, in particular:
   - Enterobacteriaceae resistant to third-generation cephalosporins or carbapenems
   - Multidrug-resistant, nonfermenting, gram-negative rods: *Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*
   - Vancomycin-resistant enterococci
   - Methicillin-resistant *Staphylococcus aureus*
2. Previous exposure to broad-spectrum antibiotics, in particular to third-generation cephalosporins
3. Health care–related infection
4. Prolonged hospital stay and/or repeated hospitalizations
5. Presence of urinary catheter
6. Older age
7. Intensive care unit stay

or vancomycin) by reassessing the antibiotic treatment after 48 to 96 hours and by streamlining therapy, based on microbiologic results, whenever possible. For example, in our center, where an increase in the incidence of BSIs caused by ampicillin-resistant enterococci and ciprofloxacin-resistant/ESBL-producing gram-negative rods (around 60% of gram-negative pathogens) was noted, piperacillin-tazobactam was the standard therapy when the clinical presentation allowed watchful waiting. However, patients presenting with severe sepsis, septic shock, or suspected bacterial pneumonia and those known to be colonized by resistant pathogens may be started with meropenem plus vancomycin and then deescalated to piperacillin-tazobactam or ceftazidime with vancomycin stopped, if a susceptible pathogen is isolated. In patients with colonization or previous infection with an MDR gram-negative pathogen, empirical antibiotic therapy targeting this strain is decided upon and noted in the chart at hospital admission to be started at the onset of fever. It frequently contains a combination regimen of ceftazidime-avibactam or colistin, plus an aminoglycoside, tigecycline, or other suitable molecule.[83]

The bottom line is that knowledge of local epidemiologic data represents pivotal information for deciding whether to start with an escalation or a deescalation approach and deciding on the type of drugs to be administered, as recently suggested in a pediatric study, as well.[190] Data from neutropenic cancer patients in an intensive care unit, and more recently from neutropenic HSCT recipients, showed that the deescalation approach is safe and feasible.[191–193]

Duration of Antibacterial Treatment

Another traditional practice that has been challenged by the ECIL guidelines is the need for empirical antibiotics to be continued until neutrophil recovery, with the idea that this is the way to avoid infection relapse and superinfections and to reduce mortality. This recommendation was based on a very small, open-label, randomized trial published in 1979.[194] The ECIL position was that antibiotics can be safely discontinued after 72 or more hours of intravenous therapy in patients who are and have been hemodynamically stable since the onset of fever, and are without fever for 48 or more hours, irrespective of the granulocyte count and the expected duration of neutropenia. Obviously, very careful clinical monitoring was recommended in order to immediately restart antibiotics at first signs of infection relapse or novel infection. In microbiologically documented infection, the recommendation was to treat for at least 7 days. The rationale for this revolutionary recommendation was based on acknowledging that, as already forecast a long time ago, alteration of a patient's microbiota leads to an increased risk of intestinal colonization by resistant pathogens, which, in turn, increases the risk of infection.[195,196] Thus antibiotics, which are the main drivers of dysbiosis, may be not protective but in fact harmful if used unnecessarily. Decreasing the antibiotic selective pressure is crucial for future generations and should be pivotal in modern medicine. Contrary to what is commonly believed, controversies about the dogma that antibiotic therapy should be continued until the end of neutropenia can be traced back to 1988, and the 2008 Infectious Diseases Society of America guidelines left some room for the possibility of stopping empirical therapy before recovery of neutropenia in a clinically stable patient, although providing the shortcut of resuming quinolone prophylaxis.[183,197] Was there any validation of the discontinuation recommendation? Actually not much. Only two prospective randomized studies in low-risk children found that discontinuation of antibiotics before marrow recovery did not result in deaths caused by bacterial infections or in an increased rate of the recurrence of fever.[198,199] Other observational studies performed in high-risk patients with prolonged neutropenia had confirmed that discontinuation of antibiotics was associated with relapse of fever in a few patients but without an increase in mortality, providing that antibacterial treatment was restarted immediately.[200,201]

Since going against a dogma is always controversial, the ECIL approach was promptly criticized. In 2014, Micol and colleagues prospectively assessed their version of a discontinuation approach (different from the ECIL one) in high-risk acute myeloid leukemia patients with neutropenic fever of unknown origin.[202] According to their criteria, treatment was discontinued in only 7 of 59 episodes of fever during neutropenia in 38 acute myeloid leukemia patients. In this observational study, 3 of 7 patients had relapsing fever due to severe infections. The conclusion was that discontinuing therapy was probably unethical and, in any case, allowed to spare only 3 days of antibiotics. The ECIL answer was that these results were based on too low numbers to draw any conclusion and that, more importantly, the criteria for discontinuation were different from those recommended by the ECIL group.[203]

More recently, in the first and so far only open-label, multicenter, randomized trial, a Spanish group addressed the issue of whether or not a clinically oriented approach was superior to a standard end-of-neutropenia approach for discontinuing empirical antibacterial therapy in patients with fever and neutropenia, according to the ECIL guidelines.[204] The hypothesis was that the experimental approach would have been able to increase the number of antibiotic-free days with respect to the standard approach during a 28-day period. Mortality and days of fever during the follow-up were secondary end points. The results of the study in the intention-to-treat analysis show that the clinically oriented approach significantly increased the number of antibiotic-free days from 13.6 to 16.1, without impacting on mortality and days of fever. Indeed, the rate of fever recurrences and fungal or bacterial superinfections in the two groups was basically the same and so was the outcome, likely due to timely and adequate interventions.

In conclusion, in the face of the antibiotic crisis and the increasing recognition of the importance of maintaining as much as possible the integrity and diversity of the human microbiota, we are forced to rationalize antibiotic intervention in hematologic patients. This rationalization includes four main aspects:

1. To review antibiotic prophylaxis measures
2. To adopt stringent criteria for driving empirical choices at the onset of fever and neutropenia and on day 3 to 4 after starting treatment
3. To be acquainted with the concept that a planned progressive succession of antibiotics in fever and neutropenia does not exist, and every patient and every episode should be evaluated separately
4. To accept the idea that in neutropenic patients with fever of unknown origin, empirical antibiotics could be discontinued even before neutropenia recovery, provided close clinical observation as inpatients is maintained with a high level of suspicion for restarting treatment.

Empirical and Preemptive (Diagnostic-Oriented) Antifungal Therapy

The empirical antifungal therapy approach consists of administering an antifungal drug in a persistently febrile neutropenic cancer patient after a variable period of empirical antibacterial therapy (usually 4–7 days), in the absence of any clinical, microbiologic, or radiologic documentation of a fungal infection. This practice is based on autopsy studies showing fungal infections undetected during life and on two randomized studies that enrolled, in total, less than 200 patients.[205–208] These studies were not double blind or placebo controlled and did not actually conclude that there was an unequivocal advantage of the empirical antifungal approach. In both randomized studies, the statistical power of the observed results was very small. Nevertheless, empirical antifungal therapy in persistently febrile neutropenic patients without a documented infection has become common practice in many cancer centers worldwide, and numerous drugs have been tested for this indication. Except for the first studies, which used persistence of fever and survival as the main end points, almost all other studies used a composite end point that included five criteria: defervescence, no discontinuation for toxicity, treatment of baseline fungal infections, prevention of breakthrough fungal infections, and survival. In general, no drug has been demonstrated significantly more effective than others, and differences were only based on lower toxicity. Of interest, a meta-analysis of the six trials in which empirical treatment was compared with no treatment or preemptive therapy confirmed that empirical antifungal treatment was associated with a lower rate of (diagnosed) invasive fungal diseases, but gave no significant advantage in terms of overall mortality.[205] The aim of empirical therapy was to treat as early as possible both candidiasis and aspergillosis. However, when fluconazole prophylaxis became widely used and reduced

the incidence of *Candida* infections, it became evident that empirical therapy was mainly directed against *Aspergillus*.

In recent years, awareness has grown that the empirical approach results in a tremendous overtreatment of just one symptom (fever) and has encouraged development of a preemptive or, maybe better named, diagnostic-driven approach aimed at treating a fungal disease when highly suggestive, although not conclusive, diagnostic criteria are present (not just fever). In the diagnostic-driven strategy, clinical considerations (fever, thoracic pain, cough), biologic markers (e.g., *Aspergillus* galactomannan in serum or bronchoalveolar lavage fluid, cytologic detection of fungal hyphae, or positive culture of sputum or bronchoalveolar lavage fluid), and imaging data (e.g., chest computed tomography [CT], with whole-volume scanning with thin-slice reconstruction preferable to high-resolution CT scanning) are combined together to obtain the highest possible diagnostic likelihood of aspergillosis and consequently to start therapy. Whether or not any pulmonary infiltrate is enough or typical radiologic signs of invasive aspergillosis are required to start antifungal therapy is a matter of debate.

Some studies analyzed the feasibility of this approach in adult patients. The first one concluded that the diagnostic-driven approach was feasible, associated with less use of antifungal therapy, and without increased mortality with respect to historical controls. Of particular interest, in this study, 10 patients who were diagnosed with positive galactomannan and CT scanning would have not received any antifungal therapy with the classic empirical approach because of absence of fever.[209] In the first randomized noninferiority trial that compared the empirical and preemptive approaches (defined differently from the previous study), no difference was found in the primary end point (survival). As expected, in the arm of preemptive therapy, in which an active diagnostic workup was performed, there were more fungal infections than in the other arm. In this study, patients were stratified by status of underlying disease, and the lower limit of the confidence interval of the difference in survival between the two strategies, among patients in first remission-induction therapy (the highest risk period), was exactly at the 8% predefined delta limit, thus leading the investigators to conclude that noninferiority was not demonstrated in this subgroup.[210] Other studies compared the two strategies, with results that were consistently in favor of the diagnostic-driven approach.[211]

There are some pitfalls in using the diagnostic-driven approach. The first is the need for a readily available CT scan with skillful radiologists who are willing to collaborate. The second is the availability of different antigen detection assays, of which galactomannan is the most important. The third is the turnaround time, which should be no more than 2 to 3 days to allow timely intervention. Finally, it had been demonstrated that a mold-active prophylaxis might lead to a reduction in the sensitivity and specificity of the galactomannan test, therefore lowering its reliability. Indeed, due to low pretest probability, screening with galactomannan in this setting is unhelpful, but targeted testing in case of suspicion of breakthrough invasive aspergillosis has been shown effective.[212]

In conclusion, in our opinion, the empirical and diagnostic-driven strategies are not mutually exclusive. Some combination of the two (e.g., lung CT scanning combined with a fever-driven approach) is probably the wisest integrated clinical approach to mold infections in cancer patients. For example, empirical antifungal therapy could be started at clinical suspicion while awaiting the results of diagnostic procedures but then discontinued if the results are not confirmatory. Fig. 306.3 summarizes the possible approaches to a patient with persistent febrile neutropenia. Table 306.5 lists drugs indicated for empirical or targeted antifungal therapy. Drugs approved for empirical therapy include liposomal amphotericin B, caspofungin, and itraconazole, whereas there is no drug approved specifically for preemptive treatment. In cases of preemptive treatment, the indirect diagnostic tests, such as galactomannan or (1→3)-β-D-glucan, or radiologic imaging may suggest a possible etiology. Therefore the preemptive antifungal treatment is the same as that recommended for first-line therapy. For example, for aspergillosis, it usually has been voriconazole or liposomal amphotericin B. Recently, isavuconazole has been approved for treating invasive aspergillosis and mucormycosis, following the results of a large randomized study that demonstrated noninferior efficacy and better tolerability compared to voriconazole for treatment of aspergillosis, and data of similar efficacy (survival) in 21 patients with mucormycosis compared to 33 treated with amphotericin B.[213,214] The management of specific fungal infections is beyond the purposes of this chapter.

Finally, a new issue of the choice of an antifungal treatment in case of failing mold-active prophylaxis warrants some consideration. Failure of mold-active prophylaxis is suspected when a patient develops signs and symptoms suggestive of a fungal infection without microbiologic documentation (e.g., a lung infiltrate unlikely caused by bacterial superinfection, with negative galactomannan, or the appearance of liver/spleen nodules) while receiving posaconazole or voriconazole prophylaxis. Four possible explanations include (1) the patient was not taking prophylaxis (lack of compliance); (2) the drug was not absorbed (posaconazole) or was metabolized too fast (voriconazole), as shown by inadequate blood levels; (3) the "new" fungal infection is due to a non-*Candida*/non-*Aspergillus* fungus intrinsically resistant to azoles; or (4) the "new" fungal infection is due to an azole-resistant *Candida* or *Aspergillus* species. In the first two cases, adjusting dosages without changing therapy seems an adequate option, whereas in the third and fourth cases, shifting to another drug family (caspofungin for *Candida* and lipid amphotericin B for *Aspergillus*) seems the only possible option.

It has been proposed that in centers with resistance to azoles among *A. fumigatus* exceeding 10%, the first-line therapy could consist of a combination of an azole and echinocandin or liposomal amphotericin B.[215]

Management of a Neutropenic Patient With a Localized Infection

Catheter-Related Infection

It is likely that the role of indwelling catheters in causing fever and infection in neutropenic patients might have been overestimated. The suspicion that the catheter is actually involved should only be raised in case of septic shock, endocarditis, rapidly progressive bacterial infection, fever with concomitant signs of infection at the catheter site (including the subcutaneous tunnel), persistence of positive blood cultures in the absence of any other detectable site of infection (although this might have explanations as well), and fever developing concomitantly with catheter flushing. In addition to clinical criteria, there are some microbiologic criteria (time to blood culture turning positive, differential colony count between peripheral and catheter-drawn blood culture, and absolute very high colony count in a catheter-drawn blood culture) that could be used, although most of them require quantitative evaluation systems. When a catheter-related infection is proven or suspected, the first thing to do is to establish whether or not the catheter is still indispensable. If not, the catheter should be removed and treatment administered, if possible, through a peripheral line.

In terms of therapy, the choice of the antibiotic regimen should be based on the epidemiology of CVC-related infections in every individual center and on the pharmacokinetic/pharmacodynamic characteristics of the available antibiotics. As a general rule, an anti–gram-positive drug should always be included in the initial regimen, although the choice should not necessarily be vancomycin, except for centers with a high rate of methicillin-resistant staphylococci. On the other hand, in centers where staphylococci with high minimal inhibitory concentration values for vancomycin (≥2 μg/mL) have been isolated, daptomycin or linezolid might be considered. Moreover, because gram-negative organisms are not infrequent in single-agent or polymicrobial CVC bacteremias, an anti–gram-negative coverage is recommended in all cases. In contrast, the empirical inclusion of an antifungal drug seems not to be appropriate, considering the relatively low incidence of fungal infections in this clinical setting. Once the causative pathogen is identified, treatment should be tailored according to its susceptibility pattern.

Treatment of CVC-related bacteremias requires the use of antibiotics that can be administered systemically (possibly through the infected line to improve the possibility of its "sterilization") but that also can (and sometimes must) be administered "locally", as catheter lock, in order to increase "local" (i.e., within the device) antibiotic concentrations to overcome resistances and penetrate into the biofilm.[41] Many drugs have been proposed for catheter lock, and their use depends on both the antimicrobial spectrum and chemical stability.[216,217]

Duration of treatment varies according to etiology, presence or absence of complications, and whether the catheter has been removed

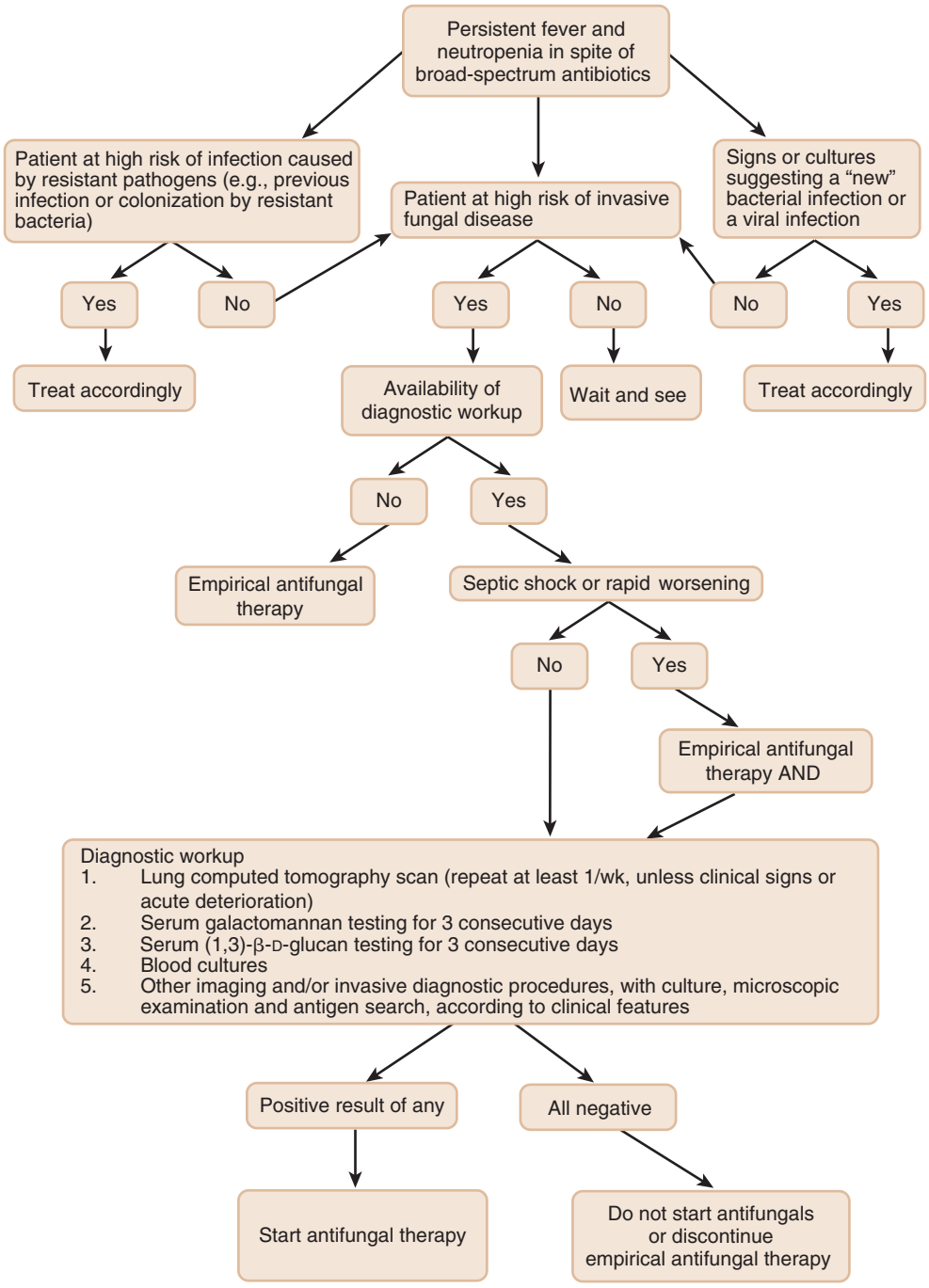

FIG. 306.3 **Management of a persistently febrile neutropenic patient.**

or not. According to some guidelines, "day 1" of treatment should be counted as the day of the first negative blood culture.[218] Follow-up blood cultures (at least once a day until documented negativization) should therefore be used to document response to treatment. If a patient has persistently positive blood cultures up to 72 hours after initiation of appropriate therapy, the catheter should be removed.[41] The possibility to remove the catheter relies mainly on general clinical conditions, availability of other vascular access, adequate platelet counts, and ability to achieve adequate hemostasis.

Pneumonia

The choice of empirical therapy in neutropenic patients with a pulmonary infiltrate should be based on the type of infiltrate, the time of appearance of the infiltrate with respect to the onset of fever, and epidemiologic and anamnestic data. For example, viridans-group streptococci have been associated with acute respiratory distress syndrome in neutropenic patients with severe oral mucositis. If pneumonia is evident since the beginning of the febrile episode, a bacterial etiology should be suspected, and the same antibiotic regimen commonly used for febrile neutropenia in high-risk patients should be used, with necessary modifications if the risk of resistant pathogens is present. On the contrary, if pneumonia apparently occurs as a breakthrough infection in a patient already receiving broad-spectrum antibiotics, a fungal etiology is more likely and antifungal therapy is logical, although a resistant (e.g., ESBL- or carbapenemase-producing) or atypical bacterial pathogen, such as *Legionella* or *M. pneumoniae,* is also a possibility. Tuberculosis should be taken into account in countries or in people coming from countries with high endemicity for tuberculosis. Interstitial pneumonia is relatively rare during neutropenia, but it does occur. In this case, pneumocystosis and influenza are the most likely etiologies, followed by CMV, *Mycoplasma*

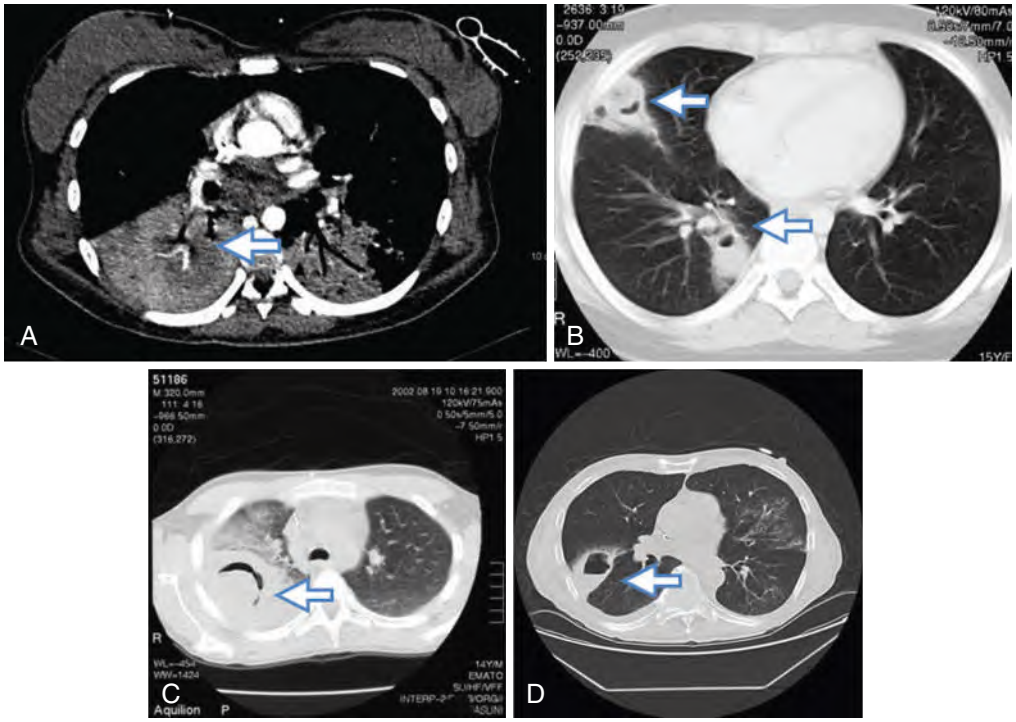

FIG. 306.4 Pulmonary cavitary lesions resulting from different etiologies, in the presence and absence of neutropenia. (A) Neutropenic patient with hemoptysis and pulmonary cavitation *(arrow)* in the presence of *Klebsiella pneumoniae* bacteremia. (B) Neutropenic patient with pulmonary cavitation *(arrows)* in the presence of methicillin-susceptible *Staphylococcus aureus* bacteremia. (C) Air crescent *(arrow)* in a no-longer neutropenic patient with pulmonary aspergillosis. (D) Cavitary lesion *(arrow)* in a no-longer neutropenic patient with *Pseudomonas aeruginosa* bacteremia.

and *Chlamydia,* other respiratory viruses, or noninfectious causes. The appropriate diagnostic measures should be implemented, and treatment should be tailored accordingly. In any case, it is important to remember that the presence of a cavitary lesion in a febrile and neutropenic patient with acute leukemia should raise the suspicion of a bacterial infection, especially in the presence of positive blood cultures (e.g., *S. aureus* or gram-negative rods) (Fig. 306.4). Indeed, fungal lesions in neutropenic patients usually present with the typical halo sign or with nodular lesions and not with cavitary lesions that become apparent only after neutrophil recovery.[219]

Abdominal Infections

Febrile neutropenic patients may present with gastrointestinal signs and symptoms, such as abdominal pain, nausea, vomiting, and diarrhea, in addition to fever. In these patients, an initial conservative management with bowel rest, intravenous fluids, total parenteral nutrition, and broad-spectrum antibiotics with antianaerobic activity should be immediately implemented. In some cases (3%–6%), especially in patients receiving aggressive treatment for acute leukemia, full-blown neutropenic enterocolitis may develop, with high fever, severe abdominal pain, and even hemorrhagic diarrhea evolving into acute abdomen and septic shock. *Clostridioides* or CMV colitis should be taken into account in the diagnostic workup, and treated accordingly (see Chapter 243). Surgical intervention is usually not indicated but may be recommended in the setting of obstruction, perforation, persistent gastrointestinal bleeding despite correction of thrombocytopenia and coagulopathy, and clinical deterioration.

OTHER TREATMENTS

Granulocyte Transfusions

Granulocyte transfusions from donors stimulated with growth factors have been proposed in desperate cases of life-threatening bacterial and fungal infections in patients with persistent neutropenia unlikely to recover promptly. The evidence for clinical efficacy is limited to that of case reports and small series, and the results are not uniform.[220]

Improved methods of harvesting granulocytes from normal volunteer donors has made this technique, though resource consuming, a potential bridge for infected patients whose neutrophil recovery is not expected soon, to prevent death from fungal infection. Technical issues include matching for blood type, CMV serology, and in the case of future stem cell transplant candidates, also for human leukocyte antigen; the dose; and in cases of repeated infusion the possibility of allosensitization (11% of patients in one series).[221]

A recent randomized trial, which included 114 patients who in the intervention arm received a median of five transfusions, with a mean transfusion dose of 54.9×10^9 granulocytes, reported no benefit on the primary end point, survival plus microbial response at 42 days after randomization (42% vs. 43%).[222] In a post hoc analysis, subjects who received an average dose per transfusion of 0.6×10^9 granulocytes/kg or greater tended to have better outcomes than those receiving a lower dose.[222] However, even if short-term benefit is observed, the success of granulocyte transfusion in cases of IFD depends ultimately on subsequent patient marrow recovery.[223]

Colony-Stimulating Factors

Many case reports have noted the effectiveness of growth factors in the treatment of severe, life-threatening bacterial or fungal infections. However, a meta-analysis published in 2002 suggested the lack of efficacy of systematic, widespread use of G-CSF for the treatment of febrile neutropenia.[224] In any case, the use of G-CSF may be an option in patients with fever and neutropenia who are at high risk for infection-associated complications or with prognostic factors of complicated outcome, such as prolonged (>10 days) and profound ($<0.1 \times 10^9$/L) neutropenia, age older than 65 years, uncontrolled primary disease, pneumonia, hypotension, and multiorgan failure. In patients with pulmonary aspergillosis, a very rapid granulocyte recovery has been associated with the development of severe complications, such as pneumothorax or fatal hemoptysis.

CONCLUSIONS

The management of fever and infection during neutropenia remains a challenging exercise for clinicians. The shortage of new antibiotics and the emergence of various degrees of resistance to traditional antibiotics active against gram-negative bacteria (third-generation cephalosporins,

piperacillin-tazobactam and other penicillins, quinolones, and carbapenems) have again increased mortality rates and made the treatment of gram-negative infections very difficult. It should be acknowledged that this problem is more evident in some countries and less in others, probably due to past antibiotic policies. At the same time antineoplastic treatments are changing, with consequent need to maintain a high level of attention for unexpected etiologies and unusual clinical presentations. Although not dealt with in this chapter, diagnostic microbiology methods are also changing substantially, with the possibility of speeding up pathogen identification and susceptibility assessments and consequent possibility of earlier and more appropriate antibacterial and antifungal therapies. In the future, the progressive recognition of the pivotal role played by the human microbiota will probably introduce extensive innovations in our ability to understand many pathogen-host interactions and immunological mechanisms of immunotolerance and aggression.

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