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310 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 to 10 days).
- Other risk factors include mucositis; underlying disease and its status; intensity of chemotherapy; the use of biologic response modifiers, especially monoclonal antibodies, such as alemtuzumab or rituximab; presence of central venous catheter; and genetic factors.

Epidemiology and Etiology

- Epidemiology of bloodstream infections in neutropenia is constantly changing, and after years of the 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*, methicillin-resistant *Staphylococcus epidermidis*, or 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*, in turn caused by a widespread use of *Candida*-active fluconazole prophylaxis (the emergence of fluconazole-resistant strains is the natural consequence), whereas in solid-organ tumors, candidemia remains the most frequent IFD.

Prophylaxis (see Table 310-5)

- In general, antibacterial, antifungal, and antiviral prophylaxis is indicated in patients receiving induction chemotherapy for acute myelogenous leukemia (AML).
- Influenza and varicella vaccination of household contact and health care workers is recommended.
- Influenza and pneumococcal vaccination of patients, especially during less aggressive treatment phases, is recommended.
- Fluoroquinolones are recommended only for patients with prolonged (7 to 10 days) neutropenia in centers where resistance to fluoroquinolones is less than 20%.
- Primary antifungal prophylaxis in cancer patients is usually recommended if the incidence of IFD is higher than 15%.
  - Fluconazole is recommended as yeast-active prophylaxis in AML patients receiving anthracycline regimens.
  - Posaconazole as mold-active prophylaxis is recommended for patients receiving chemotherapy for AML or myelodysplastic syndrome.
- 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 or alemtuzumab.
- Antiherpes prophylaxis with acyclovir or valacyclovir should be offered to patients with acute leukemia or receiving alemtuzumab.
- Varicella postexposure prophylaxis with specific immunoglobulins or acyclovir is recommended for high-risk varicella-zoster virus–susceptible patients.
- Lamivudine is recommended for cancer patients with chronic inactive hepatitis B receiving high-dose chemotherapy, particularly if containing rituximab, and for selected patients with a resolved hepatitis B virus infection.

Management of Febrile Neutropenia (see Figs. 310-2 and 310-3)

- Blood cultures
- Assessment of the risk of severe infection (e.g., Multinational Association for Supportive Care in Cancer score; see Table 310-6)
- 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 the appropriate therapy
  - Oral versus intravenous
  - Inpatient versus outpatient setting
  - Escalation versus deescalation strategy
    - Escalation strategy usually starts with anti-*Pseudomonas* β-lactam monotherapy.
    - Deescalation strategy starts with a combination of anti-*Pseudomonas* β-lactam plus other agents covering the most probable resistant pathogens; these other agents should be discontinued if no resistant pathogen is isolated.
- 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 a chest computed tomography scan and fungal serum markers (galactomannan and β-D-glucan).
- In the era of increasing antibiotic resistance and few 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 (timely deescalation, appropriate dosing)
  - Establishing antibiotic regiments for empirical therapy appropriate for 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. It has been known for decades 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, rather, 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] Thus, an index—D-index or c-D-index—has been proposed to evaluate the area under the curve of the neutrophil count (combining depth and duration of neutropenia), for assessing the risk of late infections, particularly invasive fungal disease (IFD), in adult patients.[4] The other main factor that impacts the risk of infectious complications in these patients is mucositis, a situation that, by itself, can be the basis of severe and often polymicrobial infections, even in

KEYWORDS

antimicrobial stewardship; biologic response modifiers; deescalation strategy; empirical therapy; febrile neutropenia; fluoroquinolone prophylaxis; immunocompromised; invasive fungal disease; leukemia; multidrug-resistant (MDR) bacteria

the absence of neutropenia. Finally, new and peculiar aspects emerge with the use of biologic response modifiers, which have become part of many chemotherapeutic regimens and pose new challenges that should be considered.

However, compared with previous editions of *Principles and Practice of Infectious Diseases,* the most important change in the updated version of this chapter is represented by the phenomenon of growing antibiotic bacterial resistance worldwide, which also obviously impacts the management of infections in cancer patients. Antibiotic-resistant pathogens, such as Enterobacteriaceae resistant to third-generation cephalosporins (producers of extended-spectrum β-lactamases [ESBLs]) or carbapenems, multidrug-resistant (MDR) *Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-intermediate *Staphylococcus aureus* (VISA), and vancomycin-resistant enterococci (VRE), initially confined to intensive care units (ICUs), are now spreading to other wards in many countries, with a north-south/east-west gradient of endemicity and with sporadic cases or single wards affected everywhere in the world. This is radically changing our ability to prevent and cure infections in the immunocompromised. Very few new antibiotics are on the horizon, and the challenge is to ensure that an increasing antimicrobial resistance does not reverse the gains that have been made to improve survival outcomes for patients with cancer through targeted therapies or better surgical techniques.

As shown in Table 310-1, the clinical approach to a cancer patient with signs and symptoms of infection is multifactorial. Before planning a rational management intervention, physicians should answer several crucial questions about the type and stage of the underlying disease and the clinical presentation, to make a thoughtful and effective intervention. Among others, factors potentially associated with the presence of highly resistant bacterial strains should currently be very carefully considered.

Infections in cancer patients have often been considered nosocomial, despite the fact that these patients are often cared for as outpatients or even on a home-care basis. In fact, a study on infectious complications in 113 adults receiving treatment for acute hematologic malignancies showed that 91% of 223 infectious episodes were actually associated with the type of care patients had received, but only 42% of the episodes were truly "nosocomial" in origin.[5] For this reason, the terminology of health care–associated infections is more appropriate for describing infections in the cancer management field. In any case, even if developing in a hospital, infections in cancer patients should not necessarily be considered the result of bad clinical practice, and their rate cannot be necessarily decreased by exceptional infection control measures because most of the infectious pathogens come from an endogenous source.

In the following sections, the epidemiology and management principles of infections in cancer patients will be described. Risk factors and clinical presentations of specific infections, along with their treatment in non-neutropenic cancer patietns, will not be discussed here but dealt with in chapters focused on individual infectious agents. Similarly, infections in recipients of allogeneic hematopoietic stem cell transplant (HSCT) are discussed elsewhere (see Chapter 312), and we will only touch on these patients, especially in correlation with early infections during the preengraftment, neutropenic phase.

TABLE 310-1 What Should a Clinician Wonder 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, 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 (PMN <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. Any previous infections caused by resistant pathogens?	In patients at risk of infection caused by resistant bacteria, particularly if neutropenic, initial empirical therapy should cover these pathogens.
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 tumor)	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 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 and/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). Knowledge of local epidemiology, including susceptibility pattern, is mandatory for a correct diagnostic and therapeutic management.

HSCT, hematopoietic stem cell transplantation; PK/PD, pharmacokinetic/pharmacodynamic; PMN, polymorphonuclear neutrophils.

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 large 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 actual epidemiologic situation in real life. In addition, little information is available about non-neutropenic 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 wrong 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). Tables 310-2 and 310-3 report the epidemiology of febrile episodes, bacteremia, and invasive mycoses in cancer patients.[3-24] All 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 first-line treatments.[6,10] 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] 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's lymphomas, whereas the lowest rates are observed in solid tumors, although this may be largely dependent on antineoplastic treatment strategies. Patients with chronic leukemia or multiple myeloma may represent a peculiar group because of the role played by the use of the new biologic response modifiers (imatinib, desatinib, rituximab, alemtuzumab, etc.). These new drugs have the potential to modify the risk profiles for infectious complications, with an increasing risk of infections also caused by previously unusual pathogens, such as *Pneumocystis jirovecii* and various viruses.[26]

Neutropenia

Although the first scientist who showed, in pivotal studies, the direct relationship between infection and neutropenia was Gerald Bodey, from Houston in 1966, the first report in which the risk was reported in terms of infection rate was probably published in 1993 by Carlisle and colleagues,[27] who showed that the rate of infections in neutropenic cancer patients was 46.3 episodes per 1000 days of neutropenia (DN), with rates of 12.9 for bacteremia and 2.9 for invasive mycoses. More recent data from a prospective study in children and adults with neutropenia showed a median incidence of infectious complications of 43% and a rate of 22.8 episodes per 1000 DN; bacteremia was diagnosed in 21% of the episodes and mold infections in 5%, with rates of 10.2 and 2.4 for 1000 DN, respectively.[7] As shown in Table 310-2, the rate of infections is higher after high-intensity chemotherapies and lower after maintenance treatment. Although the epidemiology of infections has been studied more extensively in children, in general, data from adults report higher rates of infectious complications compared with pediatric populations. The majority of primary febrile episodes usually occur soon (a few days) after the onset of neutropenia.

Mucositis

As already mentioned, in addition to neutropenia, the severity of mucosal barrier injury may have an impact on infection rates. Indeed, it has been demonstrated that in patients receiving HSCT, the fever is

TABLE 310-2 Rates of Infectious Complications in Cancer Patients

PATIENT POPULATION	TYPE OF DISEASE	EPISODES PER 1000 DAYS AT RISK			REFERENCE
		Any Type of Infection or Febrile Episode	Bacteremia	Invasive Fungal Disease	
Children	Solid tumors, not analyzed in detail	13.7	—	—	Urrea, 2004
Children	Malignancies, not analyzed in detail	13.3	2.8	0.49	Ammann, 2008
Children	ALL, aggressive treatment	—	1.9	0.3	Castagnola, 2005
	ALL, less aggressive treatment	—	0.9	0.1	
	AnLL, aggressive treatment	—	2.7	0.5	
Children	ALL	27.1	—	—	Urrea, 2004
	AnLL	12.0	—	—	
	NHL	18.0	—	—	
Children	Solid tumors, not analyzed in detail, aggressive treatment	—	1.1	0.1	Haupt, 2001
	Solid tumors, not analyzed in detail, less aggressive treatment	—	0.2	0	
Children	Neutropenic AL/NHL, aggressive treatment	31.1	5.1	2.1	Castagnola, 2007
	Neutropenic AL/NHL, not aggressive treatment	12.8	1.1	0	
	Neutropenic solid tumor, aggressive treatment	24.7	1.5	0.1	
	Neutropenic solid tumor, not aggressive treatment	14.7	0.9	0.6	
	Neutropenic autologous HSCT	37.8	5.1	0.7	
Children	AnLL	—	2.6	0.84	Castagnola, 2010
Adults and children	Chemotherapy for hematologic malignancies, not analyzed in detail	—	10.2	2.4	Orasch, 2010
Adults	Neutropenic autologous HSCT	—	18.9	—	Dettenkofer, 2005
Adults	Hematologic malignancies and solid tumors	—	3.2	—	Velasco, 2006
Adults	Malignancies, not analyzed in detail, with MBL deficit	—	7.7	—	Vekemans, 2007
	Malignancies, not analyzed in detail, without MBL deficit	—	7.1	—	

—, data not reported; AL, acute leukemia; ALL, acute lymphocytic leukemia; AnLL, acute nonlymphocytic leukemia; NHL, non-Hodgkin's lymphoma; HSCT, hematopoietic stem cell transplantation; MBL, mannose-binding lectin.

TABLE 310-3 Infectious Complications in Cancer Patients

PATIENT POPULATION	TYPE OF DISEASE	PERCENTAGES OF PATIENTS OR PERIODS WITH INFECTIOUS COMPLICATIONS*					REFERENCE
		Any Type of Infectious or Febrile Episode	Bacteremia	Invasive Fungal Disease			
				Any (Proven, Probable, and Possible)	*Proven and Probable*		
					Yeasts	Molds	
Adults and children	Malignancies, not analyzed in detail	62	35	—	—	—	Gafter-Gvili, 2005
Adults	Malignancy or autologous HSCT, not analyzed in detail	—	18	0	—	—	Dettenkofer, 2005
Adults	High-risk acute leukemia	78	30	—	—	—	Bucaneve, 2005
	High-risk NHL or HSCT in solid tumors	73	23	—	—	—	
Adults	Acute promyelocytic leukemia	59	22	7.3	3	0.3	Girmenia, 2003
	Other AnLL	—	37	4.2	4	0.2	
Children	AnLL	94	25	4.2	0.6	1.6	Lehrnbecker, 2004
Children	ALL, aggressive treatment	—	30	10	—	—	Castagnola, 2005
	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, 2006
Adults	AnLL	—	—	—	6	11	Caira, 2008
Adults	New-onset hematologic malignancies	27	10	4	0.5	1.3	Pagano, 2012
Adults and children	Hematologic malignancies	—	21	5	—	—	Orasch, 2010
Children	AnLL: Incidence per patient Incidence per treatment course	—	51 32	16 10	—	—	Castagnola, 2010
Children	Aggressive treatment for solid tumor, including autologous HSCT	—	24	1.6	1	0.5	Haupt, 2001
	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, 2007
	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, 2007
	Neutropenic with AML, not receiving G-CSF	56	11	0	—	—	

*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's lymphoma; HSCT, hematopoietic stem cell transplantation; MBL, mannose-binding lectin; ST, solid tumor.

strictly related to the severity of mucosal barrier injury, independently of the severity and duration of myelosuppression. Mucositis is one of the most important factors predisposing to bloodstream infections, both caused by bacteria and by *Candida*. The damage of mucosal barrier allows colonizing pathogens to enter the bloodstream, where, in the absence of granulocytes, severe infection can rapidly develop, even in case of a low bacterial load. Mucositis, with or without neutropenia, might also be responsible for severe oral and intestinal infections. The pathogenesis and the role of mucositis after chemotherapy is described in detail elsewhere (see Chapter 309).

Central Venous Catheters

The presence of a central venous catheter (CVC) is another well-known factor facilitating infection in cancer patients and influencing the etiology of bacteremia. Table 310-4 reports the incidence of CVC-related complications in cancer patients.[20,28-35,36-38] Bacteremia represents the most frequent condition, whereas exit site, tunnel, and other types of CVC-related infections are less frequently reported. These complications are more frequent in partially implanted than in totally implanted catheters and also in double-lumen compared with single-lumen devices. It is noteworthy that in patients with totally implanted CVCs, infectious complications are more frequent in younger patients with hematologic malignancies than in other categories.[37] The number of CVC manipulations, which is mainly related with the intensity of antineoplastic chemotherapy and the severity of clinical conditions, represents the most important risk factor for the development of these infections.

A detailed description of complex problem of CVC-related infections is beyond the scope of this chapter and can be found elsewhere (see Chapter 302). The incidence of CVC-related infections should be kept at the minimum by several educational and organizational measures, such as repeated teaching sessions for patients, parents, and staff, or establishing teams dedicated to the insertion and maintenance of intravascular devices. Technical measures that have been suggested include the use of chlorhexidine-impregnated dressings or sponges and the antiseptic/antimicrobial coating of intravascular catheters, for example, with chlorhexidine and silver sulfadiazine. The benefit of their routine use depends on their cost, the observed rate and outcome of CVC infections, and, in case of antibiotic-impregnated devices, on the risk of inducing antimicrobial resistance.

Genetic Factors

The existence of genetic factors that are able to increase or decrease the susceptibility to infection in immunocompromised patients underlines an apparently trivial but important aspect, that is, all 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

TABLE 310-4 Epidemiology (Mean Values) of Infectious Complications Related to the Presence of Venous Access in Cancer Patients

TYPE OF INFECTION	TYPE OF DEVICE	INFECTIONS/100 DEVICES	INFECTIONS/1000 DEVICE-DAYS	NOTES	REFERENCE
Any, not further speciated	HB	14.5	0.6	Single-lumen catheters	Fratino, 2005
		34.6	1.40	Double-lumen catheters	
	HB with PASV	31	0.84		Fratino, 2005
	PICC	26	8	—	Cheong, 2004
Bacteremias	HB	—	4.8	—	Allen, 2008
		—	3.3	—	Simon, 2008
		22.5	1.6	Review (all patients, mainly hematology and oncology patients)	Maki, 2006
	HB with Groshong valve	21	0.98	—	Cogliati, 1995
	TIVAD	8	0.09	—	Hengartner, 2004
		—	1.8	—	Simon, 2008
		—	0.7		Allen, 2008
		3.6	0.1	Review (all patients, mainly hematology and oncology patients)	Maki, 2006
	Peripheral TIVAD	4.0	0.1	Review (all patients, including hematology and oncology patients), few specific data for cancer patients	Maki, 2006
	PICC	10	0.63	—	Abedin, 2008
		1.5	2.2	—	Harter, 2003
		3.1	1.1	Review (all patients, including hematology and oncology patients), few specific data for cancer patients	Maki, 2006
	Nontunneled CVC	—	5.2	—	Simon, 2008
		4.4	2.7	Review (all patients, including hematology and oncology patients), few specific data for cancer patients	Maki, 2006
	Midline	0.4	0.2		
	Medicated chlorhexidine–silver sulfadiazine CVC	2.6	1.6		
	Peripheral plastic catheter	2.0	8.6		
Exit site/tunnel	HB	1.6	—	—	Castagnola, 2007
	HB with Groshong valve	6	0.18	—	Cogliati, 1995
	PICC	1.6	0.1	—	Abedin 2008
Pocket	TIVAD	1.9	0.02	—	Hengartner, 2004
		4	—	Review (all patients, mainly hematology and oncology patients	Maki, 2006
Surgical site (within 30 days from catheter insertion)	HB	1.4	0.48	—	Castagnola, 2007
		3.7	1.34	—	Penel, 2007
	HB/TIVAD	—	0.19	—	Simon, 2008

—, data not available; CVC, central venous catheter; HB, Hickman-Broviac; PASV, pressure-activated safety valve; PICC, peripherally inserted central catheter; TIVADS, totally implanted venous access devices (Port-a-Cath).

protein were associated with an increased risk of infection (49.9 vs. 29.6/1000 days at risk, $P = .01$). This effect, less evident in the context of prolonged neutropenia, was not confirmed in all the studies. However, in a recent study of 269 children with cancer, mannose-binding lectin deficiency influenced both the incidence and the severity of febrile neutropenia.[39] 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.[40] The future will tell us whether genetic polymorphisms, alone or in combination, have an actual impact and might dictate prophylactic or therapeutic approaches.

Biologic Agents and Other New Drugs

As already mentioned, in recent years, monoclonal antibodies and other pharmaceutical compounds, specifically engineered for targeting cells or cytokines involved in the pathogenesis of specific diseases, have been introduced in the armamentarium of antineoplastic chemotherapy. These include biologic response modifiers and protein kinase inhibitors. Alemtuzumab is a monoclonal antibody against the CD52 receptor that is used in the treatment of acute or chronic lymphocytic leukemia or non-Hodgkin's lymphoma. This monoclonal antibody has a clear role in increasing the infection risk because it is associated with long-lasting and profound lymphopenia. Bacteremias, invasive fungal diseases (including pneumocystosis), several viral diseases, and tuberculosis have been all described in association with this drug. A low $CD4^+$ T-lymphocyte count (with a possible cutoff of 200 $CD4^+/mm^3$) has been indicated as one of the most important factors related to the development of infectious complications. Obviously, infections seem to be more common (with more severe clinical pictures) in patients previously treated with other antineoplastic protocols. Rituximab is an anti-CD20 (B-cell) antibody that causes a prolonged (2 to 6 months median, but sometimes more) suppression of immunoglobulin production. It has been associated with reactivation or acute exacerbation of viral hepatitis (both hepatitis B virus [HBV] and C virus [HCV]) and, more rarely, with disseminated parvovirus infections, enteroviral meningitis, progressive multifocal leukoencephalopathy, babesiosis, and pneumocystosis.[41] Bacterial and fungal diseases have also been described, usually when rituximab was administered in combination with other chemotherapeutic agents. For other anti-CD20 monoclonal antibodies, such as ibritumomab, tositumomab, ofatumumab, and ocrelizumab, less data on infectious complications exist. Such monoclonal antibodies were reported to cause severe myelosuppression, with a spectrum of infectious complications somewhat similar to those associated with classic cytostatic drugs. It is noteworthy that patients receiving antilymphocytic monoclonal antibodies (anti-CD52 and/or anti-CD20) for relapsing diseases (i.e., after previous prolonged chemotherapy cycles) present more frequent and severe complications

compared with those who receive front-line therapies. Bevacizumab is another monoclonal antibody that targets vascular endothelial growth factor and is used in colon, kidney, brain, or lung cancer. Febrile neutropenia and bacterial infections have been reported in approximately 10% of patients, usually when the drug was used in combination with other chemotherapeutic agents. Cetuximab (approved for colon, head, and neck cancer) and panitumumab (approved for colon cancer) both have the epidermal growth factor receptor as their main target of activity and cause important dermatologic toxicity, such as rash, skin drying and fissuring, or paronychial inflammation, with infectious complications in up to 30% of patients, including sepsis caused by *S. aureus*. Trastuzumab reacts with the human epidermal growth factor receptor 2 (HER2) and is administered, usually in combination with standard chemotherapies, for treatment of HER2-positive breast or gastric cancers. Infections associated with this compound are generally mild, though not infrequent, and they may exacerbate chemotherapy-induced neutropenia. Small molecules with protein kinase activity targeting oncogenic tyrosine kinase BCR-ABL (breakpoint cluster region–Abelson murine leukemia), such as imatinib, desatinib, and nilotinib, are used in patients with both acute and chronic leukemia and solid tumors, even for very long periods of time. Infectious complications seem to be similar to those observed with other immunosuppressive drugs affecting mechanisms of cell-mediated immunity, such as pneumocystosis and viral diseases, including reactivation of hepatitis. Because of the absence of major myelosuppression, there is no apparent increase in the rates of bacterial or fungal infections.[26] Finally, there are kinase inhibitors, such as sunitinib and sorafenib, that are used before nephrectomy for renal cell carcinoma and for hepatocellular carcinoma. These drugs apparently do not increase the risk of surgical infections, although one of them (sunitinib) has been associated with necrotizing fasciitis, respiratory infections, and sepsis.

Several problems impair our ability to understand the exact role of these new compounds on the risk of infection in cancer patients. Even in randomized, placebo-controlled trials and in large open-label studies, it is difficult to establish the rate of infectious complications. The main reason is that these trials were powered to measure efficacy but not safety, and if the effect is very rare, it might go undetected. Second, there are many confounding factors because new drugs are usually used together with old or classic therapies, making it difficult, if not impossible, to evaluate their respective role. In addition, the trials did not use the same definitions of infectious complications or simply did not pay enough attention to diagnosing them. Sadly, in some cases, there was a tendency toward minimization and covering. Finally, in some cases, there was not enough attention to forecast the risk of infection. This is the case of eculizumab used for paroxysmal nocturnal hemoglobinuria, which targets the C5 complement component. As widely known among infectious disease physicians dealing with infections in immunocompromised hosts, the inherited deficiency of the C5 complement component is associated with repeated episodes of meningococcal disease. Thus, this risk might have been forecast.

Oncologic 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 among oncologic versus nononcologic patients.[42,43] 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%,[42-44] with more than two infectious episodes per patient. 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.[45,46] In case of malignant biliary obstruction, early infectious complications after percutaneous biliary stent insertion were present in 6.5% of patients.[47] Similar incidence was reported in patients undergoing surgery for hepatocellular or metastatic carcinoma (3% to 11%), and this incidence was apparently lower than in surgery for nonmalignant conditions such as hepatolithiasis (24%).[48] The rate of infectious complications after hepatectomy for hepatocarcinoma was associated with surgical risk factors such as bile leakage and blood loss.[49] A similar incidence of surgical site infections was reported after elective colon and rectal surgery (9% and 18%, respectively),[50] and after orthopedic surgery (9.5%).[51] Of interest, in the latter study, the use of an implant or allograft did not represent a risk factor for infectious complications.[51] 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.

In conclusion, although not many data are available on infectious complications after surgery in solid tumors, it seems that surgical and ICU-related factors are more important than previous antineoplastic chemotherapy in determining the risk of infection. However, it must be noted that in patients with solid tumors, surgery, together with long hospital stay and use of third-generation cephalosporins and glycopeptides, has been associated with an increased risk of infections caused by MDR pathogens.[52]

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 are just as important because every center may have peculiarities related to the type of patient, type of care, and local historical antibiotic policies. Most of the available information concerns bacterial and fungal pathogens isolated in bloodstream, whereas the role of deep-seated infections is less known, as well as the impact of viral infections.

Bacterial Infections

In the last 30 years, gram-positive bacteria have been the most frequent pathogens in bloodstream infections in cancer patients. However, more recently, an increase in the frequency of bacteremias caused by gram-negative rods has been reported in many centers worldwide, with gram-negative pathogens becoming either predominant or at least as frequent as gram-positive pathogens. This trend has been observed also in the results from a recent literature review and European surveillance study performed in 2011 in 39 hematology centers from 18 countries for the Fourth European Conference of Infections in Leukemia (ECIL-4).[52a] As shown in Figure 310-1, gram-negative pathogens are almost as frequent as gram-positive ones, with the gram-positive versus gram-negative ratio in bloodstream infections at 60% versus 40% and 55% versus 45% in the literature review and ECIL-4 surveillance, respectively. The detailed etiology was similar (see Fig. 310-1) in the literature review and surveillance study, with slightly increased rates of enterococci and Enterobacteriaceae and a decreased rate of *P. aeruginosa* in the ECIL-4 surveillance study. These changes in etiology seemed to be accompanied by an important and alarming increase in the proportion of resistant pathogens, such as ESBL-producing Enterobacteriaceae, VRE, or, the most worrisome, carbapenem-resistant gram-negative pathogens, both *P. aeruginosa* and Enterobacteriaceae—mostly *Klebsiella pneumoniae*. Last but not least, in leukemia patients, most of staphylococci are resistant to methicillin, whereas most of gram-negative pathogens are fluoroquinolone resistant. Of note, the rates of resistance were generally higher in southern and eastern Europe than in northern and western Europe.

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.[42] Anaerobes are usually isolated in polymicrobial bacteremias, especially together with gram-negative rods,[53] with a rate that seems to be higher than that observed in nononcologic patients undergoing similar surgery (0.597/1000 vs. 0.033/1000 hospital days, respectively). Of interest, in non-neutropenic febrile cancer patients, gram-negative pathogens are the most frequently isolated, followed by gram-positive pathogens, yeasts, and filamentous fungi, probably in relation to severe gastrointestinal mucositis.[54] CVC-related bacteremias are generally caused by gram-positive

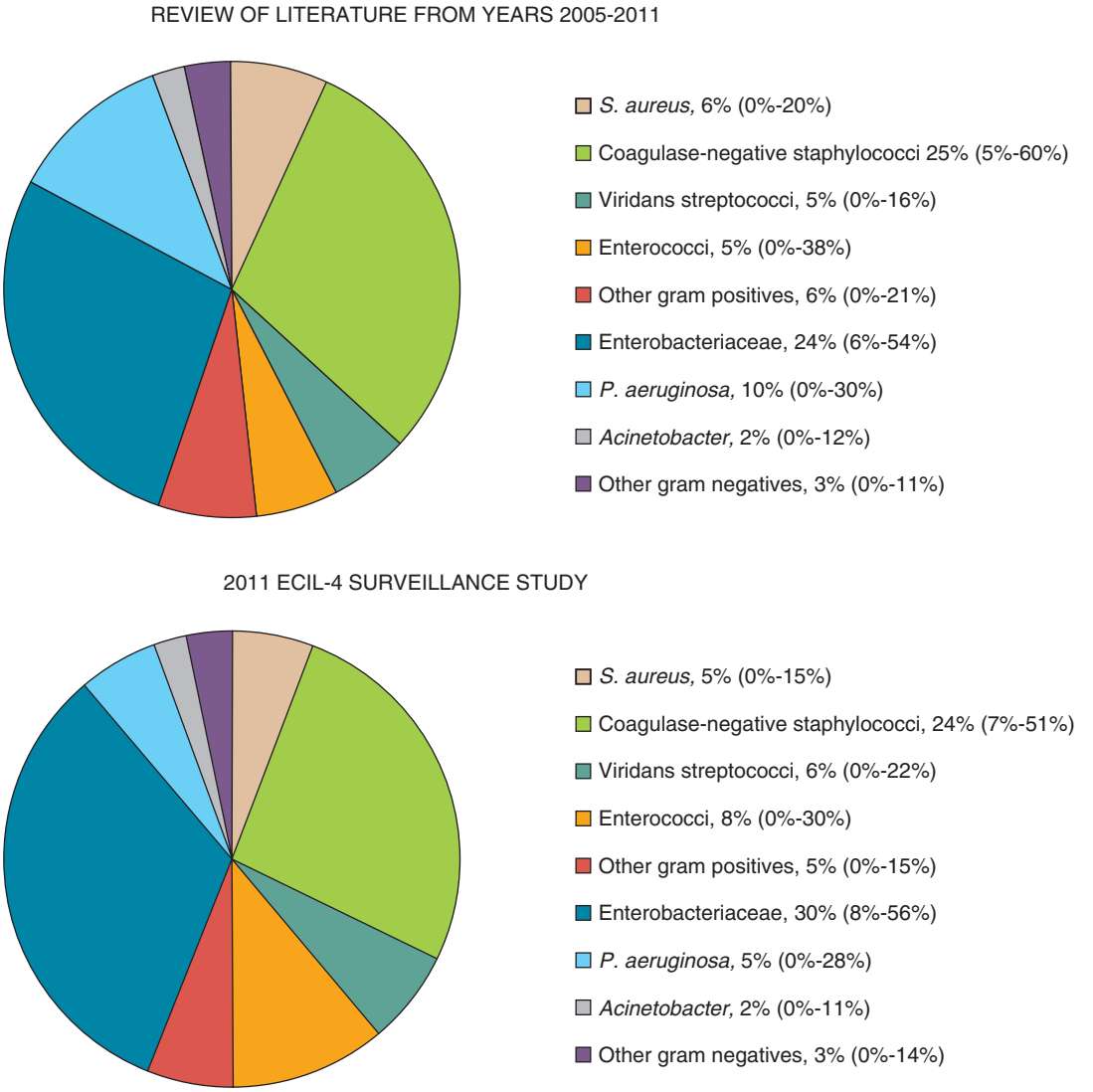

FIGURE 310-1 Etiology of bloodstream infections in cancer patients. *(Data from recent literature review* (top) *and surveillance study for the Fourth European Conference of Infections in Leukemia (ECIL-4) in 2011* (bottom). *Modified from Mikulska M, Viscoli C, Orasch C, et al. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients.* J Infect. *2014;68:321-331.)*

cocci (especially coagulase-negative staphylococci) that are isolated in more than 50% of the episodes, compared with the rate of 25% to 40% for gram-negative rods. The source of infection is likely to be partially different between gram-positive and negative CVC-related bacteremias. In both cases, contamination of skin or hub caused by incorrect catheter management is pivotal, although many gram-positive cocci come directly from the patient's skin flora. Infusate contamination is a rare but possible event, and in this case, gram-negative rods, such as *Klebsiella, Enterobacter, Citrobacter, Achromobacter, Serratia,* and *Pseudomonas* (other than *P. aeruginosa*), are more likely involved. Polymicrobial infections are not rare (8% to 49% of the episodes), with a predominance of gram-negative bacteria, whereas fungi (mainly *Candida* spp.) are usually isolated in no more than 10% of CVC-related bloodstream infections.[20,29-35,38]

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.[55] On the contrary, *Clostridium difficile* is not unusual in cancer patients, with an incidence that is twofold higher than in the noncancer population.[56] *Helicobacter pylori* has also been described as possible cause of gastrointestinal (GI) disease in cancer patients.

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, tuberculosis 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).[57] Patients from high-endemicity countries or belonging to racial and ethnic minorities account for most of the cases. On the contrary, infections caused by nontubercular mycobacteria are rare. Of note, disseminated tuberculosis caused by *Mycobacterium bovis* may occur in patients receiving Calmette-Guérin bacillus immunotherapy for bladder cancer.

Fungal Infections

The etiology of fungal infections in cancer patients is shown in Table 310-3. *Aspergillus* spp. and *Candida* spp. are the most common fungal pathogens, with the former now being 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 bloodstream infections. There is an increasing proportion of non-*albicans* strains, at least partly in correlation with the extensive use of prophylactic fluconazole, to which some non-*albicans* strains are resistant or less susceptible. Already, in a 1999 European Organisation for Research and Treatment of Cancer (EORTC) study, *C. albicans* was responsible for only 35% of candidemias in patients with hematologic malignancies and for 70% of episodes in those with solid tumors.[58]

Similarly, recent EORTC data from 297 patients with fungemia, presented at the 2012 European Congress of Clinical Microbiology and Infectious Diseases, reported an overall incidence of 2.3%, with *C. albicans* responsible for only 40% of monomicrobial infections.[58a] Of note, only 38% of fungemias occurred during neutropenia.

In general, yeasts belonging to the *Candida parapsilosis* complex are usually associated with CVC contamination, whereas the other *Candida* species are supposed to come from the GI tract after selection and translocation.

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*.[23,59] *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 transplantation, 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 patients varied from 7.9% in acute nonlymphoblastic leukemia; 4.3% in acute lymphoblastic leukemia; 2.3% in chronic myelogenous leukemia; to less than 1% in chronic lymphocytic leukemia, Hodgkin's disease, non–Hodgkin's lymphoma, and multiple myeloma.[23] A recently described risk group is represented by patients with chronic lymphoproliferative disorders, probably resulting from more intensive treatment protocols.[59] The incidence of invasive aspergillosis after autologous HSCT is low (0.3% to 2%), and it occurs during neutropenia preceding the engraftment.[23,60-62]

P. jirovecii is a well-known cause of pneumonia in cancer patients not receiving specific prophylaxis, especially in association with high-dose and prolonged steroid therapy. Attack rates vary from 6.5% to 43% in acute lymphoblastic leukemia, 4% to 25% in rhabdomyosarcomas, and nearly 1% in Hodgkin's disease and primary or metastatic central nervous system tumors.[63]

In some centers, there have been increasing reports of mucormycosis; however, it is unclear whether this represents a general trend, is influenced by local factors, or that these infections are simply diagnosed more often because of an increased clinical awareness. Other fungi, such as *Cryptococcus, Fusarium*, *Blastoschizomyces, Trichosporon,* and *Scedosporium,* have been reported sporadically. Finally, infections or reactivations of dimorphic fungi, such as *Histoplasma* or *Coccidioides,* are possible in patients who live 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 cytomegalovirus (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.[64] For this reason, routine monitoring of CMV reactivation and preemptive therapy is 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, particularly alemtuzumab.[65,66]

Community-acquired respiratory viruses, such as respiratory syncytial virus (RSV), influenza and parainfluenza viruses, 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.[67] 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.[68] Almost half of these patients had pneumonia, and the mortality was 14%.[68] 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).[68a]

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 GI 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 of hepatotropic viruses (HBV and HCV) represents an important problem in areas of high endemicity. HBV reactivation is not infrequent in cancer patients with chronic inactive HBV infection (hepatitis B surface antigen [HBsAg] positive, with negative or low-level serum HBV DNA), but it can occur also in patients with an occult HBV infection (HBsAg negative, hepatitis B core antibody [HBcAb] positive, or with low-level serum HBV DNA), particularly in association with the use of rituximab.

Other Pathogens

The risk of unusual infections or reactivations caused by protozoa (leishmaniasis, South American trypanosomiasis, and malaria), helminths (strongyloidiasis), 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 tool. For example, for strongyloidiasis, the suboptimal performance of stool examination or serologic screening warrants empirical treatment in patients who present with unexplained eosinophilia and who lived in endemic areas, such as the tropics, subtropics, or the southeastern United States and Europe.

PROPHYLAXIS OF INFECTIONS IN CANCER PATIENTS

Prevention is obviously a desirable goal, given the remarkable mortality and morbidity associated with infections in cancer patients. Table 310-5 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 will be discussed.

Antibacterial Chemoprophylaxis

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

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 originated from the patient's endogenous flora, but that approximately half of infections were acquired during the hospital stay. The first approach relied on the administration of nonabsorbable antibiotics aimed at totally (including anaerobes) or partially (excluding anaerobes) suppressing the intestinal bacterial flora and preventing the acquisition of exogenous organisms. Oral gentamicin, vancomycin, and nystatin were used. Subsequently, absorbable drugs—first, trimethoprim-sulfamethoxazole (TMP-SMX), usually given in combination with oral nystatin or amphotericin B—and then fluoroquinolones, were introduced. A meta-analysis published in 2005 showed that prophylaxis during neutropenia with absorbable drugs, especially quinolones, significantly reduced the risk of death and the rates of both

TABLE 310-5 Suggested Prophylaxis for Infections in Cancer Patients

	DRUG	SCHEDULE	COMMENTS
Antibacterial	Ciprofloxacin Levofloxacin	500 mg bid 500 mg once daily	Adults receiving chemotherapy for acute leukemia or autologous HSCT; starting with chemotherapy and continuing until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia
	Amoxicillin-clavulanate	25 mg/kg (max., 1000 mg) bid	Children receiving chemotherapy for acute leukemia
Antifungal	Posaconazole	Oral solution 200 mg tid orally with a (fatty) meal	Patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome
	Fluconazole	400 mg once daily	Patients receiving chemotherapy for acute myelogenous leukemia with cytarabine plus anthracycline regimens (administered for 7 and 3 days, respectively) and high-dose cytarabine-containing regimens
	Other		Secondary prophylaxis according to isolated pathogen and/or clinical presentation
Pneumocystis jirovecii	Trimethoprim-sulfamethoxazole	One-double strength tablet (160/800 mg) three times weekly, *or* 25 mg/kg of TMP-SMX (5 mg/kg of TMP), max., 1920 mg (two 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/day (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*	2000 mg (40 mg/kg in children) in 4-5 divided doses or in adult >40 kg: 800 mg twice daily	Patients with positive anti-HSV antibodies and severe mucositis or receiving treatment for acute leukemia
	Valacyclovir	500 mg twice daily for HSV prophylaxis 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) if receiving rituximab or allogeneic HSCT
Tuberculosis	Isoniazid	300 mg once daily	Patients with latent tuberculosis Efficacy not specifically evaluated in cancer patients
Central venous catheter	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 300 μg/day (in children: 5 μg/kg/day) either subcutaneously or as an intravenous infusion over at least 1 hr, or pegylated filgrastim, 6 mg every 14 days	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 is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which 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 days	Patients with chronic lymphocytic leukemia after the second episode of severe bacterial infection Patients with leukemia or lymphoma with hypogammaglobulinemia (<400 mg/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 within 96 hours after exposure to chickenpox
	Vaccines	Influenza Varicella	Influenza and varicella (negative contacts) vaccination of household contact and health care workers Influenza vaccination of patients, especially during less aggressive treatment phases
		Pneumococcus	Conjugated-polysaccharide 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, KPC, etc.) or infected with other pathogens for which contact isolation precautions are advisable (*Clostridium difficile*, norovirus, etc.); of note, alcohol-based hand rubs are not sporicidal

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; KPC, *Klebsiella pneumoniae* carbapenemase; max., maximum; TMP-SMX, trimethoprim-sulfamethoxazole; VRE, vancomycin-resistant enterococci; VZV, varicella-zoster virus.

unexplained fever and documented bacterial infections.[15] No significant increase in the rate of fluoroquinolone resistance was found, although no study was designed to evaluate any impact on resistance rates. As is the case in many meta-analyses, an important limitation to this conclusion was the poor quality of some studies included and the fact that many of them had been performed decades ago, when the situation in terms of bacterial epidemiology and resistance patterns was completely different. Soon after this meta-analysis was performed, the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA)[13] published a randomized clinical trial of 760 consecutive patients with acute leukemia or lymphoma (only 6% of patients had other solid tumors) that confirmed the value of quinolone prophylaxis in reducing the number of bacterial infections. The difference in survival was not statistically significant, although a trend favoring prophylaxis was observed. The proportion of resistant strains did not change over time when comparing two studies performed by the same group in different years, and the authors concluded that the pressure exerted by the use of fluoroquinolone prophylaxis might have been counterbalanced by the decreased need to use empirical antibacterial therapy, thus limiting the risk of emergence of resistance to the drugs used for empirical therapy. These data were encompassed in a new meta-analysis, published in 2012, that included 190 trials (involving 13,579 patients) conducted between 1973 and 2010. The results confirmed that antibiotic prophylaxis significantly reduced the risk of death from all causes and the risk of infection-related death when compared with placebo or no intervention.[69] The estimated number needed to treat (NNT) was 34 to prevent one death for all-cause mortality and 48 for infection-related mortality. Prophylaxis also significantly reduced the occurrence of fever and clinically or microbiologically documented infections. Again the question regarding antibacterial resistance selection was not answered. In fact, data on this pivotal topic were available for only six trials (3%) and 336 patients (2%). Finally, it must be stressed that no study evaluated the effects of repeated cycles of prophylaxis administered during the whole course of antineoplastic chemotherapy. All the aforementioned data and considerations on chemoprophylaxis are valid for patients with hematologic malignancies or undergoing HSCT because these populations represented the vast majority of patients enrolled in these clinical trials.

The issue of prophylaxis was also addressed in low-risk patients undergoing standard chemotherapy for solid tumors, with some advantage in minor end points, but no difference in the incidence of severe infections or both infection-related and overall mortality.[18] Consequently, many guidelines recommend the prophylactic administration of fluoroquinolones only when the expected duration of post-chemotherapy neutropenia is longer than 7 to 10 days.[70]

Unfortunately, as already mentioned, quinolone resistance, likely related to the very large and sometimes improper use of these drugs in human and veterinary medicine, is increasing worldwide, and more importantly, quinolone resistance may lead to the emergence of bacteria displaying cross-resistance to β-lactams and aminoglycosides. For this reason, international guidelines now recommend the implementation of systematic surveillance for monitoring rates of quinolone resistance among gram-negative pathogens. Some authors recommend that fluoroquinolone prophylaxis should be abandoned because it is probably ineffective—when resistance rates among *Escherichia coli* is greater than 20%.[70,71] Unfortunately, this is exactly the case in many hematologic centers throughout the world.

In conclusion, the use of quinolones as antibacterial prophylaxis of febrile neutropenia has advantages and disadvantages and may still represent a valid option in centers with low incidence of resistance and if susceptibility trends are closely monitored. In centers with high rates of resistance, quinolone prophylaxis makes little sense.

Antifungal Chemoprophylaxis

Primary Antifungal Prophylaxis

Invasive mycoses are severe complications of antineoplastic chemotherapy, especially in patients with acute leukemia, and their role has increased in recent years. Although fungal infections usually represent no more than 10% of all infections (see Tables 310-2 and 310-3), 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 but not molds) and posaconazole (mold-active prophylaxis). Meta-analyses showed that the use of fluconazole is effective in preventing fungal infections in allogeneic HSCT and in acute myeloid leukemia and suggest some possible benefit in other populations, if the incidence of invasive fungal disease is higher than 15%. Fluconazole reduced the incidence of *Candida* infections (*albicans* and non-*albicans*) but obviously did not diminish the risk of aspergillosis. In recent years, a study of oral posaconazole 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).[72] The fact that the difference in mortality was not confirmed in a multivariate analysis including baseline and time-dependent factors potentially able to affect survival, limits substantially the certainty of the effect of posaconazole on survival benefit. Given the reduction in the incidence of fungal infections and the incidence observed in the control group, the number needed to prevent one proven/probable invasive mycosis was 16, and the number needed to prevent one fungal infection–related death was 27.[73] However, with lower infection rate and lower mycosis-related mortality, the number needed to prevent one infection or one death would be higher, and this observation underlines the need for every center to obtain accurate information on the local epidemiology of invasive mycosis and therefore 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 on subdividing the daily dose (three to four times a day). Moreover, GI side effects were not unusual, although administration through a nasogastric tube in patients who cannot swallow was associated with a reduction of plasma levels. Whether or not there is a need for therapeutic drug monitoring with posaconazole is still controversial. Recent introduction of two new formulations of posaconazole (i.e., intravenous and oral capsules of which absorption is not influenced by gastric pH) might resolve the problem of bioavailability of the oral solution. Of note, posaconazole has been also effective in reducing the incidence of invasive fungal infections in allogeneic HSCT recipients with graft-versus-host disease.[74] Similarly, voriconazole, another mold-active azole, has also been studied in the setting of allogeneic HSCT, including the neutropenic preengraftment phase.[75,76] In the first study, primary end point (survival) was not met, but voriconazole prophylaxis reduced the incidence of invasive aspergillosis, although not in a statistically significant way.[75] 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, not efficacy. Unfortunately, the design of the voriconazole studies was suboptimal because, in both cases, low- and high-risk patients were included, with consequent dilution of the possible prophylactic effect. Issues related to therapeutic drug monitoring are also relevant for voriconazole, in this case not caused by problems with oral absorption but as a result of its complex and variable metabolism. In addition, triazoles (especially voriconazole) are a known cause of complex drug 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.[77]

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).[78] Recently, 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 children, compared with a historical control group.[79]

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.[80] 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 primary infection, 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–human immunodeficiency virus (HIV) patients.[81] The risk is particularly high in patients with acute (especially lymphoblastic) leukemia, non-Hodgkin's lymphoma, Waldenström's macroglobulinemia, multiple myeloma, and chronic lymphocytic leukemia treated with standard chemotherapy or undergoing autologous transplantation. 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.[81] 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, rarely with rituximab, and, in one case, also with the multikinase inhibitor desatinib. However, it is not clear whether these biologic drugs may be solely 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.

The duration of risk after treatment discontinuation is not known, nor is the exact dose and duration of steroid therapy that is sufficient to predispose to this infection. 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 bone marrow transplantation. Because the efficacy and tolerability of 960 mg of TMP-SMX given three or seven times a week are comparable, one double-strength 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 271).

Antiviral Prophylaxis

With the exclusion of acyclovir or valacyclovir for the prevention of herpes simplex virus reactivation in HSV-positive patients during therapy for acute leukemia or in recipients of HSCT, no other primary antiviral chemoprophylaxis is currently recommended for patients with solid tumors, lymphomas, or acute or chronic leukemias. However, new drugs pose new challenges. For this reason, all patients included in alemtuzumab clinical trials received antiviral prophylaxis (acyclovir, 200 mg three times a day; famciclovir, 500 mg two times a day; or valacyclovir, 500 mg two times a day) for at least 2 months after completion of therapy. Other than in this study, the recommended dose of acyclovir for prophylaxis against HSV for adults weighing more than 40 kg is approximately 2000 mg/day orally, given as 400 mg two to five times daily or 800 mg twice daily or 250 mg/m^2 intravenously, or valacyclovir, 500 mg orally two times daily. It has been postulated, but never proven, that acyclovir prophylaxis, by reducing the severity of oral stomatitis, may also reduce the incidence of bacterial infections originating from the oral flora.

Regarding CMV, routine prophylaxis is not recommended, although regular screening with polymerase chain reaction or pp65 antigen until 2 months after the end of treatment could be beneficial in patients at high risk of CMV infection.[65]

Varicella may have a severe clinical course in patients receiving antineoplastic chemotherapy. Thus, intravenous administration of anti–varicella-zoster virus (VZV) immunoglobulins within 72 to 96 hours of the exposure represents the recommended prophylactic approach, although protection is not guaranteed. If anti-VZV immunoglobulin is not available or in case of delayed notification of the risk contact, valacyclovir, 1 g three times daily for adults weighing more than 40 kg, is an option, although efficacy is not established. Prophylactic chemotherapy should be started on the third day after contact and continued for 22 days after exposure. If anti-VZV immunoglobulin (VariZIG) is given, valacyclovir should be continued for 28 days after exposure because the incubation period can be significantly prolonged in case of passive immunization.

Lamivudine, 100 mg/daily, started 4 weeks before chemotherapy (when possible) and continued for at least 6 months after the end of chemotherapy, should be offered to patients with inactive HBV infection (HBsAg positive, HBV DNA negative or low level). In addition, prophylaxis of HBV reactivation could be useful in patients with a resolved HBV infection (HBsAg negative, HBcAb positive) in case of allogeneic HSCT or rituximab administration.

Prophylaxis of Tuberculosis

Latent tuberculosis (TB) may reactivate during immunosuppression after antineoplastic chemotherapy. Although no specific study in cancer patients has been performed, data from other immunocompromised patients, mostly HIV-positive, show that daily isoniazid monotherapy for 6 to 9 months, or alternatively, rifapentine and isoniazid weekly for 3 months, are both effective in treating a latent TB infection.[82,83] Prophylaxis of latent TB should be considered in cancer patients with a positive skin test, positive interferon-γ release assays (IGRAs; T-SPOT TB test [Oxford Immunotech, Marlborough, MA] or QuantiFERON-TB Gold In-Tube test [Qiagen, Valencia, CA]), household exposure, previous Calmette-Guérin bacillus immunotherapy, or history of inadequately treated tuberculosis.

Role of Colony-Stimulating Factors in Prophylaxis

Colony-stimulating factors are used with the aim to facilitate more dose-intense treatments and to decrease treatment-related 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.[84] 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.[85] 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.[86] 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).[87] 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.[87]

In children, a study performed in 157 patients with solid tumors during 595 neutropenic periods, showed that the risk of fever during repeated episodes of neutropenia was not influenced by the use of G-CSF.[88]

Role of Immunoglobulins in Prophylaxis

Based on the experience in patients with primary immunodeficiency syndromes, the administration of immunoglobulins has been recommended in patients with secondary, iatrogenic immunoglobulin deficiencies, such as in patients with acute and chronic lymphocytic leukemia or non-Hodgkin's lymphoma and in those receiving rituximab. Keeping the immunoglobulin G level greater than 600 mg/dL has been associated with a reduction of infectious episodes, provided the treatment could be given for at least 6 months.[89] This treatment reduced bacterial infections but had no effect on viral and fungal

diseases. There is no defined monitoring schedule regarding how often immune globulin levels should be checked.

Other Prophylactic Measures

Isolation, Food, and Lifestyle

For patients with chemotherapy-induced cytopenia, it is not clear whether staying at home or in hospital may have an impact on the development of chemotherapy-related complications. In a hospital, keeping the patient in reverse isolation represents an important tool for reducing colonization with pathogens. Practical guidelines for preventing the diffusion of infectious diseases in health care facilities have been published[90] and should be implemented in any ward where cancer patients are admitted. Because aspergillosis and other mold infections are acquired via the respiratory route, the use of high-efficiency particulate air filters in rooms or wards where leukemic and transplant patients are hospitalized is recommended.[91] The use of masks with adequate filtration power (free-flow pressure 2 [FFP2]) could reduce *Aspergillus* colonization and infections when the patient is moved from the protective environment. This approach has been demonstrated effective, together with other physical barriers, during building renovations.[92] In addition, personal masks could also prevent the diffusion of other respiratory diseases, such as influenza or respiratory syncytial virus infection. 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 providers to care for them properly.

A low-bacterial-count diet seems not to offer any benefit compared with a normal diet.[93,94] However, some precautions should be recommended, such as avoiding unpasteurized milk; unpasteurized or mold cheese products; raw or undercooked meat, fish, tofu, or eggs; and unpeeled fruits and salads, unless properly washed at home. *Listeria* colonization and infection has been described in association with dairy products, whereas raw vegetable sprouts have been associated with outbreaks of *E. coli* and *Salmonella* infection. 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.

Cancer patients, especially during less intensive treatment, may seek information on the safety of traveling or other recreational activities. Although few data exist that quantify the risk of travel or recreational activities, a few considerations can be made. First, the assessment of the underlying conditions should be made with particular attention to the stability of clinical condition and patient's 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 against yellow fever or *Salmonella typhi*) might be contraindicated, whereas effectiveness of other vaccines, such as 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 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 the quality of life.

Vaccination

The use of inactivated vaccines has been demonstrated safe and could be effective, especially during nonaggressive treatments. Although poor immunologic response may occur, safety is not of concern. Influenza vaccination is strongly recommended for household contacts during each influenza season, as well as for patients not receiving intensive chemotherapy. Pneumococcal vaccination is very important in immunocompromised patients, although, again, response to vaccine may be suboptimal.

Vaccination, with adequate precautions in the case of live-attenuated vaccines, is also recommended for other transmissible diseases, such as varicella. In this case, it is noteworthy that the observation from a small study that the major difficulties in implementing a varicella vaccination program targeted at negative household contacts of immunocompromised children were attributable to the attitude of pediatric oncologists and parental refusal because of fears of adverse events (in those to be vaccinated, not in the patient!) when VZV vaccination was not part of the general vaccination program.[95]

TREATMENT OF INFECTIOUS COMPLICATIONS IN CANCER PATIENTS

Fever during Neutropenia

Fever during neutropenia has always been considered a medical emergency and should always be regarded as caused by 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. On this basis, febrile complications in neutropenic cancer patients are classified as (1) microbiologically documented infections (MDIs) with bacteremia (isolation of a significant pathogen from one or more blood cultures); (2) MDIs without bacteremia (isolation of a significant pathogen from a well-defined site of infection (urine, respiratory secretions obtained with sterile procedures, or fluid collection); (3) clinically documented infections, that is, in the presence of a clinical picture clearly and objectively infectious in nature but without microbiologic proof (such as sepsis, meningitis, pneumonia, or neutropenic enterocolitis); and (4) unexplained fever or fever of unknown origin, when clinical and microbiologic proof is lacking and the clinical course is merely 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. The development of fever or signs of infection without fever (see definition of systemic inflammatory response syndrome in Chapter 4) in a neutropenic cancer patient must always raise the suspicion of an infection and should result in a prompt diagnostic and therapeutic intervention. The reliability of empirical therapy 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. Pure epidemiologic studies that include all patients, not just those eligible to enter a clinical trial, show slightly higher but still acceptable (considering the increased intensity of chemotherapeutic regimens) mortality rates (5% for gram-positive, 18% for gram-negative, and 13% for polymicrobial bacteremias).[96] Unfortunately, there are recent data showing that the increasing proportion of infections caused by resistant pathogens, such as ESBL-producing Enterobacteriaceae, carbapenem-resistant *P. aeruginosa* or *K. pneumoniae,* and VRE, raises mortality in neutropenic patients.[97-99] Indeed, in the era of bacterial resistance and the limited number of new antibiotics available, especially against gram-negative rods, infectious complications might once again start to compromise the success of cancer treatment.

It was well known in the past that not all cancer patients were the same, and therefore, some of them were suitable for home care and oral therapy in case of fever, whereas others required prompt hospitalization. The differences among cancer patients are even more evident currently because bacterial epidemiology and pattern of resistance may vary from patient to patient (in case of individual colonization with resistant pathogens), from center to center (in case of environmental colonization), and from country to country (different endemicity of resistant strains). Therefore, for each patient, the risk of severe infection, a complicated clinical course, and infection caused by resistant pathogens should be evaluated individually and treatment chosen accordingly.[99a] Figure 310-2 summarizes a possible initial approach to a patient with febrile neutropenia.

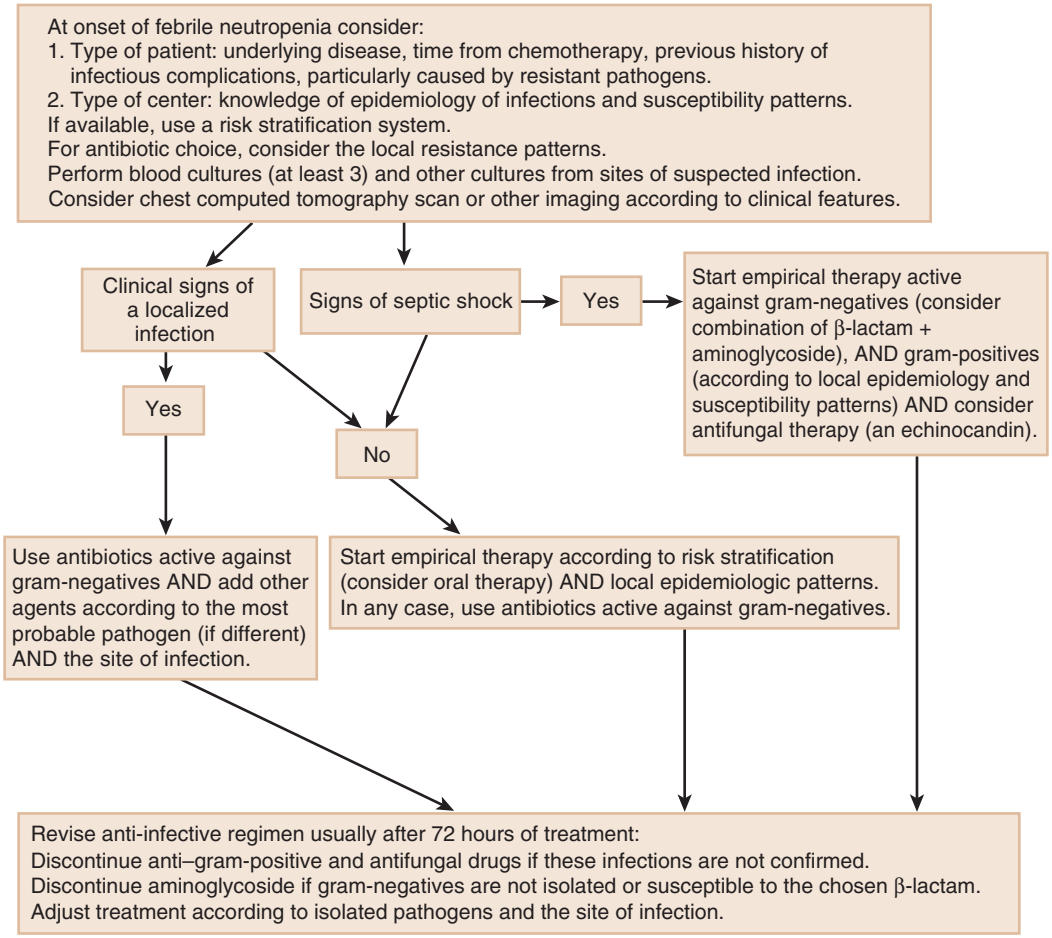

FIGURE 310-2 Possible initial approach to a patient with febrile neutropenia.

Patients at Low Risk of Severe Infections

An important change in the natural history of infections in cancer patients has been the increasing number of patients with solid tumors who are treated with high-dose chemotherapy and therefore 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 rarely severe. In most cases, these patients are clinically stabilized within 48 hours after the appearance of fever and are without fever within 3 to 4 days. According to these observations, the empirical therapy of febrile neutropenia in cancer patients should not be the same in every situation and in every patient but should be modulated according to individual risk factors. On the basis of this concept, several studies have been performed with the aim of identifying a priori, in a scientific way and not empirically, the patient populations at low risk of a severe infection. The Multinational Association for Supportive Care in Cancer (MASCC) score has been shown suitable to identify patients with low probability of complicated febrile neutropenia (Table 310-6). 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. No study addressed the issue of identifying patients at high risk, although one might infer that in the MASCC score, subjects with a low index are not low-risk patients. Studies in children evaluating risk of complicated outcome were less successful. Although six pediatric stratification systems for identifying low-risk patients were determined in a retrospective analysis, none of them could be validated in separate data sets. Thus, at present, no recommendation of a single low-risk prediction rule can be made for predicting specific outcomes in children, although locally derived risk stratification strategies can be incorporated into routine clinical management.[100] 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 of febrile neutropenia include 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/amoxicillin-clavulanate combination, moxifloxacin monotherapy, or intravenous antibiotics such as ceftriaxone plus amikacin once daily.[70,101] In neutropenic

TABLE 310-6 Factors Associated with Low Risk of Severe Infection or Associated with an Uncomplicated Clinical Course in Febrile Neutropenic Cancer Patients

	MASCC SCORE	
	Clinical Parameters	**Score**
Clinical data available at onset of febrile neutropenia or soon after admission	1. Burden of illness: no or mild symptoms	5
	2. No hypotension	5
	3. No chronic obstructive pulmonary disease	4
	4. Solid tumor or no previous fungal infection	4
	5. No dehydration	3
	6. Outpatient status	3
	7. Burden of illness: moderate symptoms	3
	8. Patient's age <60 yr	2

MASCC, Multinational Association for Supportive Care in Cancer.
Points attributed to the variable "burden of illness" are not cumulative. The maximal theoretical score is therefore 26.
Low-risk patient: score ≥21.

patients with fever of unknown origin, switching therapy from intravenous to oral (e.g., ciprofloxacin or cefixime) has also been demonstrated to be a safe practice. In the next section, the management of a high-risk patient and the new challenges presented by MDR pathogens will be discussed. However, it should be emphasized that increasing resistance does not necessarily affect only high-risk patients but can be present in specific settings, hospitals, or countries in low-risk patients as well.

Patients at High Risk of Severe Infections

The specific composition of the regimen for empirical therapy of febrile neutropenia in high-risk patients remains controversial and subject to change. Although the results of clinical trials play a pivotal role in the choice of an effective regimen, other factors to be considered include local bacterial epidemiology and resistance patterns, local antibiotic policies, antibiotic toxicity, and cost. In recent years, antibiotic resistance, local stewardship policies, cost, and shortage of new antibiotics, especially against gram-negative organisms, have dramatically complicated treatment choices and forced physicians to diversify empirical regimens based on colonization, local epidemiology, antibiotic policies, and, last but not least, patient safety. Patient-related factors, such as clinical presentation, organ failure, status of the underlying disease, and expected duration of neutropenia, are all extremely important in this therapeutic diversification. The key time points for managing the high-risk neutropenic patient with fever and infection are day 0, when the patient is evaluated, cultures are drawn, and antibiotic therapy is started, and day 3 or 4, when results come back from the laboratory and the patient is reevaluated. This time line does not indicate that empirical regimen needs to be left unchanged for 3 days, but it highlights mandatory reevaluation and, if applicable, discontinuation of a part of empirical strategy that has not been confirmed necessary. In fact, empirical antibiotic regimen should be modified anytime, based on patient's clinical conditions (need for broader coverage and deescalation strategy in case of sudden deterioration) and microbiologic results.

Escalation therapy (i.e., starting with a relatively narrow-spectrum coverage and then adjusting therapy if necessary) seems appropriate in the setting where resistant bacteria are infrequent (the majority of experts consider as infrequent if less than 10% to 20% of species are resistant) because it covers most Enterobacteriaceae and *P. aeruginosa* except for MDR strains. Monotherapy with an anti-*Pseudomonas* β-lactam antibiotic (ceftazidime, cefepime, or piperacillin-tazobactam) probably represents the most rational approach in clinical centers without evidence of resistance phenomena, with the carbapenems used as second-line therapy in failing patients with or without documented infections. In a standard clinical situation, combining an aminoglycoside with a β-lactam is not deemed necessary because of possible increased toxicity and no clinical advantage in efficacy. This was clearly shown in a double-blind, placebo-controlled clinical trial comparing piperacillin-tazobactam with placebo versus the same drug with amikacin.[102] The escalation approach avoids universal, and usually unnecessary, upfront 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 the light of increasing resistance, there is a growing concern that if the initial regimen fails to cover the pathogen responsible for infection, the prognosis is worsened significantly.

Deescalation therapy—that is, starting with a very broad initial empirical regimen, such as a carbapenem, which covers ESBL-producing Enterobacteriaceae and some resistant *P. aeruginosa,* with or without vancomycin for MRSA, MRSE, or penicillin-resistant gram-positive cocci—may be appropriate in clinical centers with a high incidence of infections caused by resistant bacteria or in patients with risk factors for resistant pathogens (Table 310-7). Because use of carbapenems and vancomycin has been associated with emergence of carbapenem-resistant Enterobacteriaceae and VISA, the key point of the deescalation strategy is reassessing the antibiotic treatment after 48 to 96 hours and downgrading therapy to a narrow-spectrum regimen whenever possible. The very broad coverage is discontinued by deescalating once the susceptibility of the isolated pathogen is known and/or patient clinical conditions improve. Examples of an extreme initial regimen in a deescalation strategy regimen include the use of colistin, daptomycin, tigecycline, or linezolid, if a patient is colonized with MDR gram-negative or gram-positive pathogens. The use of a drug active against resistant gram-positive pathogens (vancomycin, linezolid, daptomycin, or others, depending on local factors) might be recommended in case of suspected infections caused by resistant gram-positive pathogens, such as skin and soft tissue or CVC-related ones.

TABLE 310-7 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

Such an individualized approach has been adopted in the hematology and transplantation unit of our institution, where an increase in the incidence of bacteremias caused by ampicillin-resistant enterococci and ciprofloxacin-resistant and ESBL-producing gram-negative pathogens was noted.[103] These results led to a change in the empirical therapy, with a diversified deescalating approach tailored to the clinical presentation: meropenem plus vancomycin represent the empirical therapy in patients presenting with severe sepsis, septic shock, or suspected bacterial pneumonia, to avoid inadequate treatment of bacteremia—for example, caused by ESBL-positive Enterobacteriaceae—and to provide adequate treatment for enterococci and methicillin-resistant staphylococci. Then, vancomycin is discontinued within 3 days if not necessary, and meropenem is changed to piperacillin-tazobactam or ceftazidime if a susceptible pathogen is isolated. Colistin and/or aminoglycosides are included in the initial regimen in case of previous infection or colonization with an MDR gram-negative pathogen, whereas linezolid is used in case of staphylococcal or enterococcal pneumonia. In less severe conditions (i.e., fever, no pneumonia, and stable hemodynamic conditions), the escalating approach is still used, with piperacillin-tazobactam as the first-line empirical monotherapy.

In empirical therapy, antibiotics should be administered at the maximal dosage and according to their best infusion schedule, based on pharmacokinetic/pharmacodynamic parameters. Many experts use β-lactams in continuous or prolonged (over 3 hours) infusion because, in this way, serum concentrations remain substantially higher than the minimal inhibitory concentration (MIC) of the majority of pathogens during the treatment period, although the universal value of such administration scheme has been questioned.[104,105] Table 310-8 summarizes the major antibiotics used for empirical or targeted therapy in febrile neutropenia.

In consideration of growing antimicrobial resistance and scarcity of new antibiotic molecules, infection control and antimicrobial stewardship should be implemented in all cancer centers.[105a] Infection control practices include surveillance, containing appropriate screening for resistant pathogens, and preventive measures, such as proper hand hygiene and contact precautions for patients colonized or infected with resistant bacteria. Active surveillance, for example, with rectal swabs for carbapenemase-producing *K. pneumoniae* or VRE, should be performed in institutions where these pathogens are regularly encountered. The knowledge of proper hand hygiene techniques is not sufficient for effective prevention of pathogen spread, and should be supplemented with regular monitoring of adherence, and facilities should ensure access to adequate hand hygiene stations (sinks, alcohol-based rubs, etc.). Contact precautions includes hand hygiene, use of disposable gowns and gloves when caring for a colonized or infected

TABLE 310-8 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	300 mg/kg (as piperacillin)	12-16 g (as piperacillin)	3-4
	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
	Imipenem-cilastatin	IV	60-100 mg/kg (as imipenem)	2000-4000 mg (as imipenem)	3-4
	Ciprofloxacin	IV	15-30 mg/kg	800-1200 mg	2
	Ceftriaxone	IV	80 mg/kg	2000 mg	1
	Amikacin	IV	20 mg/kg	1000-1500 mg	1
	Vancomycin	IV	40 mg/kg	2000 mg	2
	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
	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 IU/kg loading dose, then 150,000 IU/kg*	9,000,000 IU loading dose, then 9,000,000 IU*	2
	Fosfomycin	IV; not available in United States	300 mg/kg	15-24 g	3-4
Antibacterial, oral	Amoxicillin-clavulanate	Oral	60 mg/kg (as amoxicillin)	2-3 g (as amoxicillin)	2-3
	Ciprofloxacin	Oral	30 mg/kg	1000 mg	2
	Cefixime	Oral	6-8 mg/kg	400 mg	2-3
	Moxifloxacin	Oral	—	400 mg	1
Antifungal	Amphotericin B deoxycholate†	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
	Itraconazole	IV	5 mg/kg	400 mg	2
	Micafungin	IV	2-4 mg/kg	100 mg	1
	Anidulfungin	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§	6 mg/kg bid the first day, then 4 mg/kg bid	2
	Fluconazole	IV, oral	10 mg/kg	400 mg	1
	Posaconazole‡	Oral solution (doses are different for tablets and IV)	If >12 yr, dose as adults	800 mg (with a fatty meal or acid carbonated drink)	4

*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 IU, and sometimes in mg of colistimethate sodium, whereas in the United States, the dosage of U.S. Food and Drug Administration–approved colistimethate sodium is defined in mg of colistin base activity. Thus, particular attention should be paid to avoid dosage errors (see http://www.ashp.org/DocLibrary/Policy/PatientSafety/NANAlert-Colistimethatesodium.aspx). Approximate dose conversion: 1,000,000 IU = 80 mg of colistimethate sodium = 30 mg colistin base.

The optimal dosing of colistin remains to be established. Recent studies in adults 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.[117-119] See Chapter 31 for recommended doses in the United States, which are 5 mg colistin base/kg loading and then 5 mg colistin base/kg/day 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.

†Contraindicated in the presence of risk factors for renal toxicity (e.g., impaired renal function at baseline, nephrotoxic co-medication, including aminoglycoside antibiotics, and history of previous toxicity).

‡Therapeutic drug monitoring might be useful to assess if trough levels are in the range for efficacy.

§In patients aged 2 to 12 years and 12 to 14 years if weighing less than 50 kg; otherwise, dose as for adults if aged 12 years and older; therapeutic drug monitoring is highly recommended. Children metabolize voriconazole more rapidly than adults.

patient, and cohorting—that is, if feasible, patients should be placed in single rooms; otherwise, placement together with other patients colonized by the same pathogen is recommended. In addition, it is of utmost importance to notify promptly and completely all the units or other hospitals involved in patient's care about all the isolated pathogens.

Antimicrobial stewardship should include the following 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; microbiology laboratory; infectious diseases consultation service, including infection control unit; and hospital pharmacy.

Duration of Antibacterial Treatment

Duration of empirical antibiotic therapy in neutropenic patients has not been extensively evaluated in randomized clinical trials. By

tradition, empirical antibiotics are continued until neutrophil recovery, to avoid infection relapse and mortality. However, 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.[106,107] Other observational studies performed in high-risk patients with prolonged neutropenia confirmed that discontinuation of antibiotics was associated with relapse of fever in few patients but without an increase in mortality, providing the antibacterial treatment was restarted immediately.[108,109] Therefore, in neutropenic patients with fever of unknown origin, empirical antibiotics could be discontinued after greater than or equal to 3 days in patients who are hemodynamically stable since presentation and afebrile for greater than or equal to 2 days, irrespective of the neutrophil count.[99a] Close clinical observation as inpatients is recommended because antibiotics should be promptly restarted in case of fever recurrence. There are also some ongoing randomized clinical trials, both in patients with hematologic malignancies and solid tumors, which address this issue.

In case of microbiologically or clinically documented infection, antibiotic treatment of usually 10 to 14 days is recommended, and all signs and symptoms of infection should be resolved before antibiotic discontinuation. Also in such cases, and with the same precautions, antibiotic therapy could be stopped before neutrophil recovery, provided a full cycle of treatment was completed.

Antibacterial Treatment Modification

Frequent therapeutic changes are common in cancer patients with persistent fever and neutropenia. Microbiologically documented infections should be treated with antibiotics according to the susceptibility testing results, even if patient's clinical conditions improved spontaneously. Antibiotic treatment should be also modified if failure is suspected, for instance, deterioration of clinical conditions, persistence of positive cultures, relapsing symptoms of the initial infection, or signs or symptoms of infections in new sites.

More controversial is what to do when the patient remains febrile in the absence of evident signs of clinical deterioration but also in the absence of any microbiologic or clinical documentation of infection (unexplained fever or fever of unknown origin) or in case of documented infections caused by pathogens that are susceptible in vitro to the initial empirical regimen. In general, good clinical practice in infectious diseases suggests that persistence of fever does not necessarily mean failure of a given antibiotic regimen, especially if the patient is otherwise clinically stable. A neutropenic patient with bacteremia might require 2 to 7 days to defervescence, even if the isolated pathogen is susceptible to the allocated antibiotic regimen. Therefore, it is likely that in patients with fever but who are otherwise in good clinical condition, the best clinical option should be watchful waiting because there is no evidence that fever is a suitable criterion for escalation of antibiotic therapy in the absence of clinical or microbiologic data.

Empirical and Preemptive Antifungal Therapy

The empirical antifungal therapy consists of administering an antifungal drug in a persistently febrile and neutropenic cancer patient after a variable period of empirical antibacterial therapy (usually 4 to 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.[110-110c] These studies were not double blind or placebo controlled and did not conclude that there was an unequivocal advantage of the empirical antifungal approach. In both 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 point, almost all other studies used a composite end point, which 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 the control, and differences were only based on lower toxicity. Of interest, a meta-analysis of the six trials where 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.[110] 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, 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 [BAL] fluid, cytologic detection of fungal hyphae, or positive culture of sputum or BAL fluid), and imaging data (e.g., chest computed tomography [CT] 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 they were afebrile.[111] In the first randomized, noninferiority trial, which 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.[112] Other studies compared the two strategies, with results that were consistently in favor of the diagnostic-driven approach.[113]

There are some pitfalls in using the diagnostic-driven approach. The first is the need for a well-equipped radiology department with skillful radiologists who are willing to collaborate. The second is that many clinical centers worldwide cannot afford the quite expensive antigen-detection assays. The third is that, even if the test is available, the turnaround time is crucial 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 and therefore lowering its reliability. It remains controversial whether this effect is merely the result of the activity of the antimold drug (which by preventing aspergillosis cases obviously prevents galactomannan spreading to the bloodstream and therefore being detected) or if there is a real effect on the test performance.

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. Figure 310-3 summarizes the possible approaches to a patient with persistent febrile neutropenia. Table 310-8 reports drugs indicated for empirical or targeted antifungal therapy. Drugs approved for empirical therapy include liposomal amphotericin B, caspofungin,

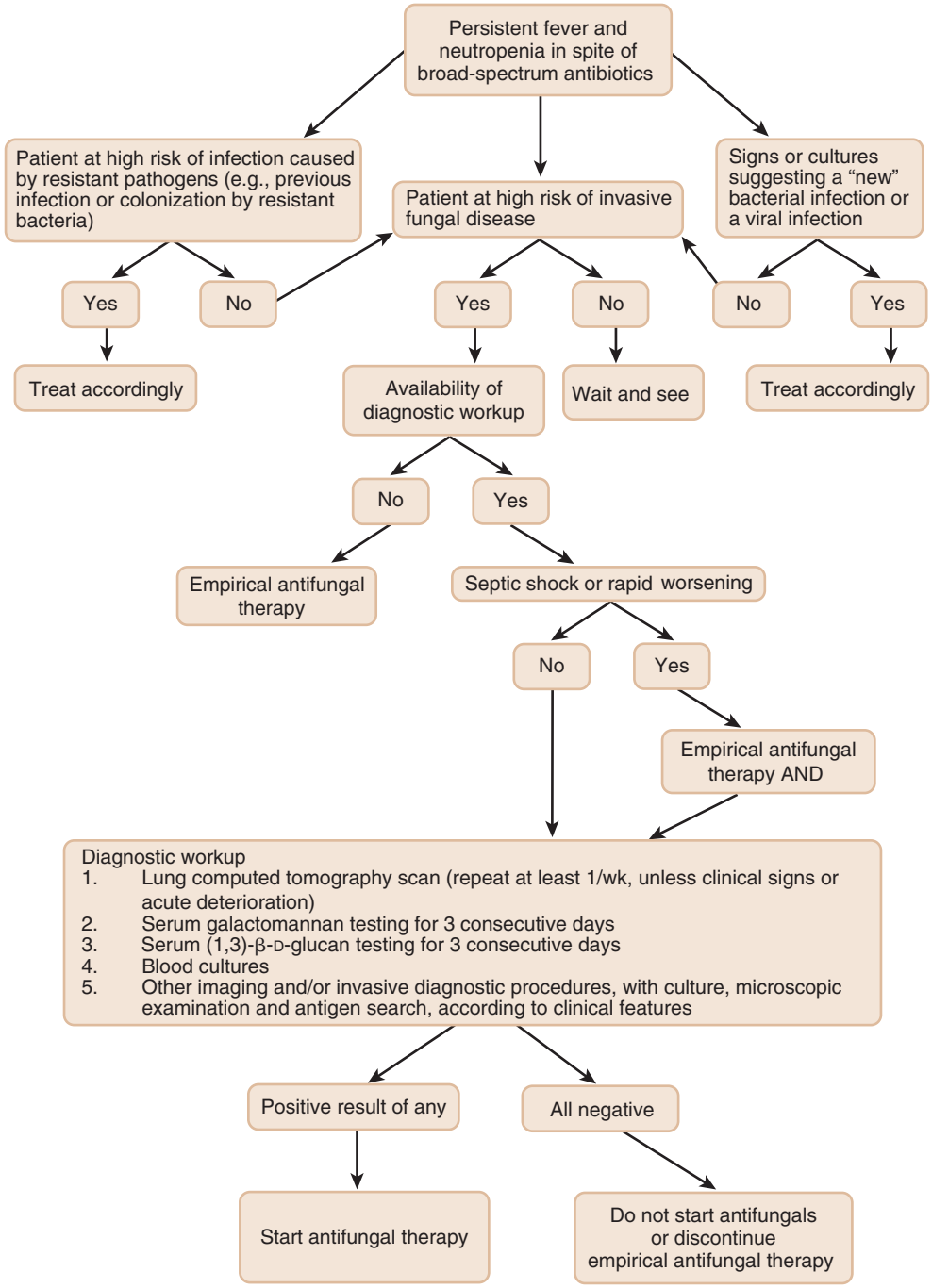

FIGURE 310-3 **Management of persistently febrile neutropenic patient.**

and itraconazole, whereas there is no drug approved specifically for preemptive treatment. 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 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; (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 case, shifting to another family (caspofungin for *Candida* and lipid amphotericin B for *Aspergillus*) seems the only possible option.

Management of a Neutropenic Patient with a Localized Infection

Catheter-Related Infection

The role of indwelling catheters in causing fever and infection in neutropenic patients is probably 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), 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 peripherally and catheter-drawn blood culture) that

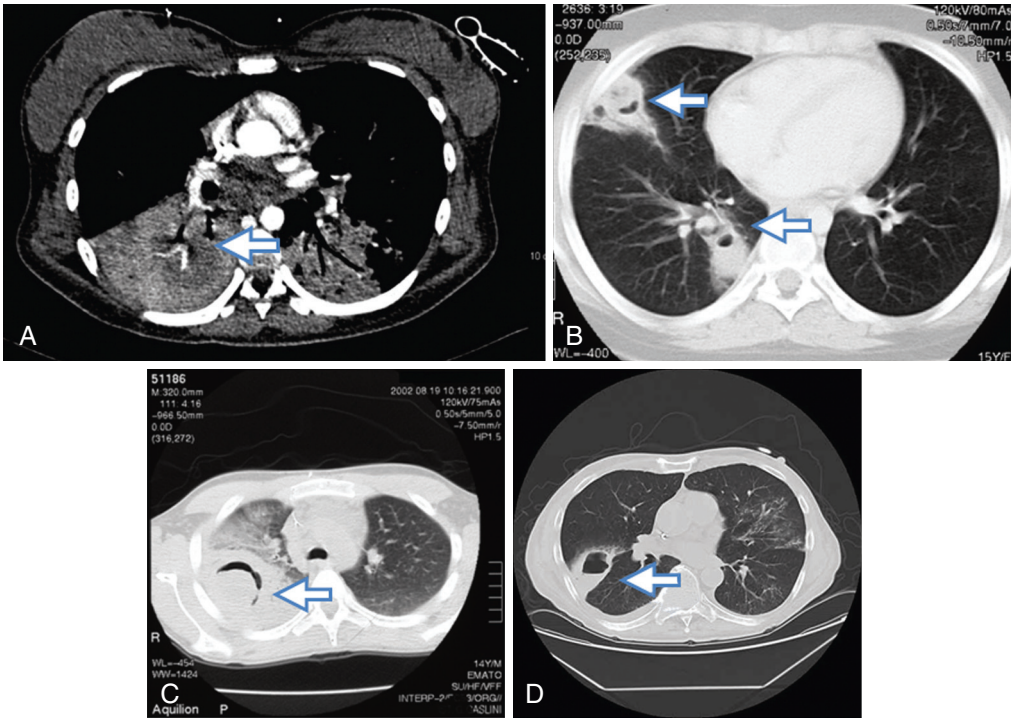

FIGURE 310-4 Pulmonary cavitary lesions resulting from different etiologies, in the presence and absence of neutropenia. A, Neutropenic patient with hemoptysis and pulmonary cavitation *(arrow)* in presence of *Klebsiella pneumoniae* bacteremia**. B,** Neutropenic patient with pulmonary cavitation *(arrows)* in 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.

could be used. When a catheter-related infection is proven or suspected, 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 MIC values for vancomycin 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 a 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.

Pneumonia

The choice of the 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 on epidemiologic and anamnestic data. For example, viridans streptococci have been associated with acute respiratory distress syndrome in neutropenic patients with severe oral mucositis. If this is a likely possibility, penicillin in combination with a glycopeptide appears to be the most logical choice. 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 obvious considerations if the risk of highly resistant pathogens is present. On the contrary, if pneumonia apparently occurs as a breakthrough infection in a patient already receiving broad-spectrum antibiotics, fungal etiology is more likely and antifungal therapy is logical, although a resistant bacterial pathogen, including *Legionella* or *M. pneumoniae*, is also a possibility. Interstitial pneumonia is relatively rare during neutropenia, but it does occur. In this case, CMV, influenza virus, *P. jirovecii*, and *M. pneumoniae* are the likely etiologies. The appropriate diagnostic measures should be implemented, and treatment should be tailored accordingly. In any case, it is important to remember that the observation of a cavitary lesion in a febrile and neutropenic patient with acute leukemia should raise the suspicion of a bacterial infection, especially in presence of positive blood cultures (e.g., *S. aureus* or gram-negative rods) (Fig. 310-4). 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.[114]

Abdominal Infections

Febrile neutropenic patients may present with GI 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 anti-anaerobic activity should be immediately implemented. In some cases (3% to 6%), especially in patients receiving aggressive treatment for acute leukemia, full-blown neutropenic enterocolitis may develop, with high fever, severe abdominal pain, and sometimes hemorrhagic diarrhea evolving into acute abdomen and septic shock. In centers with a high incidence of *C. difficile* infection, antibiotic treatment directed toward this pathogen should also be considered in the initial therapeutic approach (see Chapter 245). Surgical intervention is usually not indicated but may be recommended in the setting of obstruction, perforation, persistent GI 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.[115]

Use of Colony-Stimulating Factors

Many case reports have suggested the effectiveness of growth factors in the treatment of severe, life-threatening bacterial or fungal infec-

tions. However, a meta-analysis published in 2002 suggested the lack of efficacy of systematic, widespread use of G-CSF for therapy of febrile neutropenia.[116] In any case, the use of G-CSF (e.g., filgrastim 300 µg daily in adults and 5 µg/kg/day in children) 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.

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