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Review

Healthcare-associated infections in patients who are immunosuppressed due to chemotherapy treatment: a narrative review

Rosimeire da Silva[1], Tiago Casella[1,2]

[1] *São José do Rio Preto Medical School, São Paulo, Brazil*
[2] *Hospital de Base de São José do Rio Preto, São Paulo, Brazil*

Abstract

Introduction: Chemotherapy is one of the best methods to cure oncologic patients. However, it leads to adverse effects that contribute to the establishment of infections. Up-to-date knowledge is needed to offer the best care to patients.

Methodology: This is a narrative review based on searching articles in five databases (PubMed, LILACS, Research Gate, Google Scholar, and SciELO) using "cancer treatments", "chemotherapy", "febrile neutropenia", "cancer opportunistic infections", "chemotherapy AND febrile neutropenia", "cancer AND hospital infections", and "immunosuppression AND cancer patients" as keywords. No filter was applied, however, articles published in the last five years were preferentially selected to compose this article.

Results: Almost all microorganisms can cause infection in cancer patients, including colonizing and normal microbiota. However, *Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp., Staphylococcus* spp., and *Streptococcus* spp. are the most reported agents. Viruses may be underrepresented because molecular techniques are needed to identify them. Bloodstream and associated infections are among the highest occurrences because of the devices that are constantly introduced. Antibiotic administration selects for resistant microorganisms, which leads to delay or even failure in the treatment. Protocols for efficient infection prevention and control measures must involve staff from the kitchen, janitors, nurses, and physicians, in addition to patients and relatives.

Conclusions: Bloodstream infections caused by the bacteria and which have the most resistance to several antimicrobials are the main concern for oncologic patients. Preventive and educative actions must be taken by a multidisciplinary team in order to achieve the best care for the vulnerable patients.

Key words: Cancer; chemotherapy; neutropenia; opportunistic infection.

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Introduction

Cancer, as defined by the World Health Organization (WHO), is the disordered and uncontrolled proliferation of cells [1]. These cells multiply rapidly, grouping and forming tumour, which invade tissues and organs that are close to or distant from the origin (metastases). Cancer may emerge anywhere on the body and can present different degrees of tumour aggressiveness [2]. Official data from the WHO revealed 18 million new cases of cancer diagnosed in 2018 (the most frequent were lung, breast, and prostate cancers) [3]. In relation to mortality rates, cancer is currently the second highest cause of death worldwide (8.97 million deaths), but will probably become the first cause by 2060 (18.63 million deaths estimated), which unquestionably defines cancer as an urgent public health problem [3].

There are four main strategies for cancer treatment: surgery, radiotherapy, chemotherapy, and bone marrow transplantation. Chemotherapy is defined as the use of chemical substances capable of destroying, inhibiting, or neutralizing the growth of tumour cells, and can be used separately or in combination with other drugs [4]. This method consists of the application of drugs which reach the cells at different stages of the cell cycle and reduce the uncontrolled growth of altered cells [5]. Some studies indicate that the application of chemotherapy combinations in high doses has resulted in a high cure rate and improved survival curves among cancer patients. However, these patients were also more likely to have late complications due to high levels of exposure to drug toxicity [4,5].

Despite being a very effective therapeutic strategy, the performance of chemotherapeutic agents is not always successful. They also affect the healthy cells due to their low specificity [6]. Thus chemotherapeutic agents do not act exclusively on tumour cells and are known as one of the most toxic pharmacological groups

[4,6]. Normal cells and tissues that are constantly renewed, as in the case of bone marrow, hair, and digestive mucosa, are affected by their action [7]. The treatment causes different levels of toxicity, such as structural injuries and changes in normal physiology and biochemistry of tissues; some of these are irreversible and can even become a limiting factor to the treatment itself [4,7].

In this context, two main aspects related to chemotherapy must be considered: the side effects of toxicity, and the positive and negative impacts on the individual's quality of life, physically and psychologically. The main adverse effects of chemotherapy are related to haematological changes that include leucopoenia, anaemia, thrombocytopenia and febrile neutropenia (FN), which may contribute to infectious events [6,7].

Post-chemotherapy patients are more susceptible to infections since cancer treatment affects the production of neutrophils, and predisposes to bacterial, viral and/or fungal infections, which inhibit or delay inflammatory responses. In addition, the treatment constantly exposes the patients to invasive artefacts such as central and peripheral venous catheter, urinary catheter, drains, and others, which increases the risk of microbial invasion [8]. In this context, hospitals may represent higher risks to patients undergoing chemotherapy because of the potential exposure to multidrug-resistant (MDR) microorganisms.

When comorbidities and pathogens combine in immunosuppressed patients, there is a higher risk of developing serious infections, which can lead to high mortality rates in patients undergoing chemotherapeutic treatment [9,10]. Although successful treatments for infections in hospitals are present, hospitalization should be avoided as much as possible. People infected with nosocomial pathogens usually have longer hospital stay and require other types of medications, which may be less effective, more toxic and more expensive [11–13].

Methodology

Considering the current and prospective scenario of cancer around the world, the high risks related to immunosuppressed patients, and the progressive rates of hospitalization during or after chemotherapeutic treatment, our objective was to compile the recently published studies in the topic. For this reason, we did not perform a systematic review of the literature to address a specific issue. Instead, we bring a brief narrative review intended to amend and fill some gaps, providing up-to-date knowledge and continued education to scientists and other professionals about infections in patients undergoing chemotherapy. We searched for articles available in five repository databases (PubMed, LILACS, Research Gate, Google Scholar, and SciELO) using the following terms: "cancer treatments", "chemotherapy", "febrile neutropenia", "cancer opportunistic infections", "chemotherapy AND febrile neutropenia", "cancer AND hospital infections", and "immunosuppression AND cancer patients".

All types of documents were considered to compose the descriptive review: full texts, clinical or randomized trials, meta-analysis, reviews, systematic reviews, government agency newsletters, and books. Year of publication in specific timespan was not considered, but scientific articles published in the last five years were preferably selected because of noteworthiness. No filter was applied regarding age, gender, ethnicity, or any other distinctiveness for individuals in selected studies since no specific group of patients or population were targeted. The bibliographic search was conducted from January to July 2021, and the studies found were used to support this whole manuscript.

Results and discussion

Immunosuppression and opportunistic infections

Chemotherapeutic treatment may lead to consequences and side effects, including immunosuppression, in which the immune system that is constantly exposed to cytotoxic drugs is altered and weakened, impairing the body's protective functions. The most frequent cause of complication and death related to chemotherapy is the acquisition of opportunistic infections, which seriously affects the patients' health [8].

Individuals under chemotherapy are more susceptible to infections because the therapy directly affects the production of neutrophils [9]. Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 cells/mm^3 [14]. This cell reduction predisposes the organism to the invasion and proliferation of pathogens by inhibiting or hindering cascades of inflammatory responses [9]. Neutropenia may result in fever, causing the condition called FN, a serious side effect of many chemotherapeutic treatments [15,16].

Several agents such as bacteria, fungi and virus can cause infections in immunosuppressed patients [16]. The bacteria mainly isolated from nosocomial infections during or after chemotherapy treatment are *Escherichia coli, Klebsiella* spp., *Pseudomonas aeruginosa*, and *Staphylococcus aureus* [8,9,17,18]. The most important fungi species associated with

infections in cancer patients are *Candida* spp. and *Aspergillus* spp., which are among the most dangerous and fatal fungi [19–21]. Viral infections are also frequently associated with patients undergoing chemotherapy treatment, especially herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV) and respiratory viruses such as influenza, respiratory syncytial virus, and others [19,22]. In this perspective, the most common spots for nosocomial infections in patients under chemotherapy are bloodstream, skin, oral cavity, gastrointestinal tract, respiratory tract, post-surgical sites, and urinary tract [8,19,22–24].

Bloodstream infections (BSI) occur when pathogens reach the blood vessels and is a very common complication responsible for high levels of mortality in cancer patients [22,25]. The microorganisms most commonly reported are bacteria and may account for over 90% of all BSI [22]. Some studies have reported changes in the microbiological profile and epidemiology of BSI. In the past, the incidence of Gram-positive bacteria was higher than the Gram-negative, and recent studies have shown the opposite pattern [17,24,26–28]. In this context, the bacterial species most frequently found in blood cultures have been *E. coli*, *Klebsiella* spp. and *P. aeruginosa* (Table 1).

It seems that there is no infectious predisposition related to gender (male or female) and BSI in cancer patients. However, Gudiol, Aguado and Carratalà highlight some specific factors that can influence in the final outcome of patients with cancer and BSI, such as: underlying disease, age, presence of other comorbidities, severity of the disease, and source of the infection [25]. The infection sites with increased risk for cancer patients are correlated with a major susceptibility of bloodstream contamination, for example: use of venous catheters, urinary catheters, dialysis, and the need for care in an intensive care unit and ventilator support [11,27–29]. Thus, the origin of BSI can be unknown, associated with other infection sites and cancers (respiratory tract, gastrointestinal tract, hepatobiliary origin, genitourinary tract, skin and soft tissue, and other sites) or catheter-related [24].

Table 1. Bibliographic data related to the main infection types acquired by chemotherapy patients. Percentage of occurrence of each type of infection acquired/developed by patients under chemotherapy, the main microorganisms that caused the infections, the main types of associated cancer, the signs and symptoms developed during the course of infection, the main methods used for diagnosis, and the antibiotics for which the microorganisms presented resistance. The references cited for each site of infection are also listed.

Occurrence	**Bloodstream**	**Skin**	**Oral**	**Gastrointestinal**	**Urinary**	**Respiratory**	**Post-surgical**
	80-90%	**10-20%**	**15-25%**	**5-20%**	**1-3%**	**10-15%**	**8-14%**
Microorganisms	**Bacteria** *Aeromonas hydrophila* *Acinetobacter* spp. *Bacteroides* spp. *Citrobacter* spp. *Clostridium* spp. Coagulase-negative staphylococci *Corynebacterium* spp. *Enterobacter* spp. *Enterococcus* spp. *Escherichia coli* *Klebsiella* spp. *Listeria monocytogenes* *Morganella morganii* *Proteus* spp. *Pseudomonas aeruginosa* *Salmonella* spp. *Staphylococcus aureus* *Stenotrophomonas maltophilia* *Streptococcus* spp. Viridians group streptococci **Fungi** *Candida albicans* *Fusarium solanii* *Scedosporium* spp.	**Bacteria** *Bacillus* spp. *Micrococcus luteus* *Pseudomonas* spp. *Roseomonas mucosa* *Staphylococcus* spp. *Streptococcus* spp. **Fungi** *Candida* spp. *Aspergillus* spp. *Fusarium* spp. *Mucor* spp. *Trichosporon asahii* **Virus** Herpes simplex virus Herpes zoster virus	**Bacteria** Coagulase-negative staphylococci *Streptococci* spp. *Clostridiales* spp. *Escherichia coli* *Fusobacterium nucleatum* *Gemella* spp. *Granulicatella* *K. pneumonia* *Pseudomonas aeruginosa* *Treponema maltophilum* *Veillonella* spp. **Fungi** *Candida* spp. *Actinomyces* spp.	**Bacteria** *Clostridium* spp. *Bacteroides* spp. *Lactobacillus* spp. *Bifidobacterium* spp. Lactobacillaceae Enterbacteriaceae Bacteriodaceae Prevotellaceae	**Bacteria** *Escherichia coli* *Klebsiella* spp. *Pseudomonas aeruginosa* *Staphylococcus aureus* *Enterobacter* spp. *Enterococcus faecalis,* *Acinetobacter* spp. *Proteus mirabilis*	**Bacteria** *Pseudomonas aeruginosa* *Stenotrophomonas maltophilia* *Nocardia* spp. *Haemophilus influenzae* *Streptococcus pneumoniae* *Staphylococcus aureus* **Fungi** *Aspergillus* spp. *Fusarium* spp. *Mucor* spp. *Pneumocystis jurovecii* *Rhizopus* spp. **Virus** Influenza virus A and B Adenovirus Parainfluenza virus Cytomegalovirus Coronavirus Respiratory syncytial virus	**Bacteria** *Escherichia coli* Coagulase-negative staphylococci *Staphylococcus aureus* *Enterococcus faecalis* *Pseudomonas aeruginosa* *Streptococcus* spp. *Corynebacterium* spp. *Enterococcus* spp. *Citrobacter* spp. *Klebsiella* spp. *Enterobacter* spp. *Proteus mirabilis*

Table 1 (continued). Bibliographic data related to the main infection types acquired by chemotherapy patients. Percentage of occurrence of each type of infection acquired/developed by patients under chemotherapy, the main microorganisms that caused the infections, the main types of associated cancer, the signs and symptoms developed during the course of infection, the main methods used for diagnosis, and the antibiotics for which the microorganisms presented resistance. The references cited for each site of infection are also listed.

Occurrence	Bloodstream	Skin	Oral	Gastrointestinal	Urinary	Respiratory	Post-surgical
	80-90%	**10-20%**	**15-25%**	**5-20%**	**1-3%**	**10-15%**	**8-14%**
Type of cancer most associated	Breast Gastrointestinal Genitourinary Gynecologic Head and neck Hematologic malignances Hepatobiliary Lung Respiratory tract Sarcoma Skin	Breast Gastrointestinal Nasopharyngeal carcinoma Ovarian Lung Liver	Breast Gastrointestinal Head and neck Oral	Breast Colorectal Gastric Hepatocellular carcinoma Melanoma Pancreatic	Cervix carcinoma Gynecologic Prostatic	Lung	Breast Lung Head and neck Brain Ovarian Hematologic malignances
Signs and symptoms	Chills, mental confusion and delirium, fever (> 38 ºC) or hypothermia (< 36 ºC), hypotension (systolic blood pressure < 90; mean blood pressure < 65 or 40 mmHg baseline blood pressure drop), tachycardia (> 90 bpm), cutaneous rash, bruising, and bleeding	Skin lesions, papules, nodules, ulcers, vesicles, hemorrhagic or crusted lesions, ecthyma gangrenosum, necrotizing fasciitis, fever (> 38 ºC), chills, rigor, hypotension, mechanical phlebitis	Dry mouth, burning, lesions, bad breath, gingiva pain, hypersalivation, gingival bleeding, feeding difficulties, mucosal ulceration	Nausea, fever, vomiting, bloating, abdominal discomfort, cramps or pain (diffuse as the infection progresses), constipation, diarrhea, severe retrosternal pain, and dysphagia	Dysuria, pyuria, urethral obstruction	Sinusitis, otitis, fever, cough, dyspnea, chest pain, sputum, radiologic infiltrates, rhinorrhea, nasal congestion	Lymphedema, fever (> 38 ºC), surgical site bleeding or inflammation sites
Diagnostic methods employed	Microorganism identification in blood cultures or evident clinical signs and symptoms	Microorganism identification in skin cultures, evident clinical signs and symptoms, skin biopsy	Microorganism identification lesion culture, panoramic, interproximal and periapical radiographs, inspection of the oral mucosa, sialometry	Microbiological culture, RT-PCR, analysis of fecal microbiota, ultrasonography, computed tomography scanning or magnetic resonance	Urine or tissue culture or evident clinical signs and symptoms	Molecular diagnostic assay, antigen detection, microscopy, cell culture-based assay, nasopharyngeal swabs, pleural fluid culture, radiographic findings, lung biopsy	Tissue culture or evident clinical signs and symptoms
Associated antimicrobial resistance	Ampicillin-resistant vancomycin-susceptible *E. faecium* ESBL-producing Enterobacteriaceae AmpC-producing Enterobacteriaceae MDR-*Pseudomonas aeruginosa* Vancomycin-resistant *Enterococcus* spp.	Vancomycin-resistant *Enterococcus* spp. MRSA Chlorhexidine-resistant *Micrococcus* Chlorhexidine-resistant gram-negative bacilli Chlorhexidine-resistant staphylococci Echinocandins-resistant *Trichosporon* spp. Flucytosine-resistant *Trichosporon* spp.	ND†	MDR-Enterobacteriaceae specially *E. coli*, *Salmonella* spp., *K. pneumoniae*, and *A. baumannii* MRSA Vancomycin-resistant *Enterococcus* spp.	Amoxyclave-resistant Gram-negative bacteria[1] Amoxyclave-resistant Gram-positive bacteria[2] Ampicillin-resistant Gram-negative bacteria[1] Ceftazidime-resistant Gram-negative bacteria[1] Ceftazolin-resistant Gram-negative bacteria[1] Cefuroxime-resistant Gram-negative bacteria[1] Ciprofloxacin-resistant Gram-negative bacteria[1] Cloxacillin-resistant Gram-positive bacteria[2] Tetracycline-resistant Gram-positive bacteria[2]	MRSA	Carapenem-resistant *P. aeruginosa* Ciprofloxacin-resistant *P. aeruginosa* ESBL-producing *E. coli* ESBL-producing *K. pneumoniae* Fluoroquinolone-resistant *Enterobacteriaceae* MDR *A. baumannii* MRSA Vancomycin-resistant *E. faecium* Vancomycin-resistant *S. aureus*
References	[17,22,25-27]	[30,32-35]	[22,37,38]	[22,39-42]	[19,22,52]	[22,43-48]	[50,51]

ND: data not found. ESBL: Extended-spectrum Beta-lactamase; MDR: multidrug-resistant; MRSA: Methicillin-resistant Staphylococcus aureus; RT-PCR: Real-time quantitative Polymerase Chain Reaction. [1]Gram-negative bacteria considered: *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Enterobacter* spp; [2]Gram-positive bacteria considered: *Staphylococcus aureus*.

During chemotherapy treatment, various catheter types are commonly used because they protect peripheral veins, decrease patient anxiety associated with repeated venipunctures, and allow effective bloodstream access, drugs application (chemotherapy medication, antibiotics, and others), blood samples collection, transfusions, parenteral nutrition and other interventions [12,22,30,31]. Thus, patients often carry short-term or long-term central venous catheters (CVC). On the one hand, if catheters facilitate the performance of invasive procedures, they can also be considered as an access point for infectious agents, with a considerable predominance of microorganisms that cause skin infections, especially in regard to those devices inserted for prolonged periods [19,22,30,32].

Microbes found on skin microbiota, such as bacteria (*Bacillus* spp., *Micrococcus luteus*, *Pseudomonas* spp., *Roseomonas mucosa*, *Staphylococcus* spp., *Streptococcus* spp.), fungi (*Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Mucor* spp. and *Trichosporon asahii*) or viruses (herpes simplex and herpes zoster) are usually related to skin infections, and only 5-10% of those are characterized as polymicrobial infections [19,22,33]. In order to prevent possible infectious proliferations, some catheters are impregnated with antimicrobial or antibiotic substances [22,34,35]. Previous studies do not correlate gender or age with the occurrence of skin infections in cancer patients, but to the introduction of some device or to surgical site infections.

Chemotherapy-related oral infections, which account for 15-25% of the total infections in neutropenic patients contribute significantly to mortality [22,36]. Susceptible areas include teeth, gingivae, salivary glands, and mucosa membranes of mouth and pharynx, which may develop mucositis, xerostomia, osteoradionecrosis, candidiasis, HSV infection, and others [37]. Common oral opportunistic microorganisms include *Actinomyces* spp., *Candida* spp., coagulase-negative staphylococci, *Streptococcus* spp., *Clostridium* spp., *E. coli*, *Fusobacterium nucleatum*, *Gemella* spp., *Granulicatella* spp., *Klebsiella pneumoniae*, *P. aeruginosa*, *Treponema maltophilum*, and *Veillonella* spp. [22,37,38]. Therefore, cancer patients should be advised to consult the dentist before chemotherapy begins, and any traumatic dental management during cancer treatment should be avoided or postponed. Gender, age, or ethnicity seem to not be associated to the oral infections in cancer patients mentioned above.

The gastrointestinal tract is the largest reservoir of microorganisms in the human body [22,39,40]. Although the intestinal microbiota is unique for each person and closely related to the environment and individual exposures, most bacteria belong to the *Bacteroides* and *Clostridium* genera, with the major commensal species being *Bifidobacterium* spp. and *Lactobacillus* spp. [41]. In general, the microbiota of the small intestine is mainly composed of genera from the Enterobacteriaceae and/or Lactobacillaceae bacterial families, while the colon has Bacteriodaceae and Prevotellaceae as the predominant microbes [41].

Recent reports have indicated that the intestinal microbiota is able to modulate the patient's response to chemotherapy treatment [22,39,40,42]. So, it is important to point out that chemotherapeutic drugs are metabolized in the intestines to a large extent, and these same medications, and anticancer treatment as a whole, may directly affect the gut microbiota [42]. Chemotherapeutic medication can damage the mucosal gut epithelium, causing gastrointestinal toxicity (which occurs in up to 80% of all patients), bacterial translocation (that may lead to systemic infection, making the patient more susceptible to diseases), major exposure to potential pathogens, abnormal exposure to treatment medications, and hyper-inflammation [40–42].

Respiratory and lung infections account for 10-15% of the infection sites in FN patients and can be caused by bacteria (*Haemophilus influenzae*, *Nocardia* spp., *P. aeruginosa*, *S. aureus*, *Stenotrophomonas maltophilia*, and *Streptococcus pneumoniae*), viruses (influenza virus A and B, adenovirus, parainfluenza virus, cytomegalovirus, coronavirus and respiratory syncytial virus) and/or fungi (*Aspergillus* spp., *Fusarium* spp., *Mucor* spp., *Pneumocystis jurovecii*, and *Rhizopus* spp.) [22,43,44]. In this context, it is possible to highlight that most respiratory infections are caused by bacteria and/or viruses, with the possibility of viral-bacterial co-infection [43–45].

Pneumonia is a severe infectious complication for neutropenic patients and studies have demonstrated that the mortality in viral pneumonia (mainly caused by rhinovirus, influenza and parainfluenza viruses) increased up to 25% in immunocompromised patients [45]. Although respiratory or lung infections in cancer patients are not associated with gender, recent studies have reported an increased risk of lung infections among children younger than 2 years [44] and the elderly (over 65 years old) with cancer [43,45]. This brings attention to a risk group of patients already immunosuppressed because of age in addition to the cancer itself. Recently, a new coronavirus type was discovered and named as severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2). This virus has disseminated worldwide due to its high transmissibility [46]. This virus causes a series of symptoms and aggravation and patients with respiratory infections or lung cancer are included in the risk group with higher mortality rate in comparison to general population [46–48]. In order to reduce respiratory infections in general, health-care units have used broad-spectrum antibiotics (because the microorganism that causes the infection is often unknown) and vaccination has been highly recommended [44,45,49].

The need for any type of surgery must be well evaluated in the case of immunosuppressed patients due to the high exposure and high invasiveness of this medical procedure. The occurrence of surgical infections in patients with cancer has been reported between 8% and 14% [50,51]. The infectious agents most associated with surgical sites in these patients are bacteria, specifically *Enterococcus faecalis*, *E. coli*, *P. aeruginosa*, and *S. aureus* [50,51]. Gram-negative bacteria were showed to be more prevalent than Gram-positive regardless of the type of surgery [50]. Furthermore, it has been shown that some microorganisms have higher prevalence in specific surgical sites; for instance, *E. coli* was the most frequent bacteria in gastrointestinal, gynecological, urological, and head and neck surgeries. In addition, *S. aureus* was the second most common bacteria associated with surgeries, but it is mostly associated with breast and thoracic surgical procedures [50]. The performance of surgery is considered as an important risk factor for cancer patients and postoperative nosocomial infections appears to be more severe in cases with advanced age, male gender, comorbidities, distant metastasis, rural or low-volume hospitals [25,51].

Neutropenic patients are rarely affected by urinary tract infections – UTI (1-3%), and when it occurs the symptoms are minimal, with frequent absence of dysuria and pyuria [22]. As the symptoms are often rare, urinalysis and urine cultures should be performed routinely in order to detect possible microorganisms and start early treatment [19,22]. Eventually, it is necessary to insert urinary catheters during cancer treatment in case of obstruction or urinary incontinence [19]. The predominant microorganisms in catheter-associated UTI reported in literature are the same as are commonly reported in regular patients with UTI: *Acinetobacter* spp., *Enterobacter* spp., *E. faecalis*, *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa*, and *S. aureus* [52].

Maharjan *et al*. verified prevalence of catheter associated UTI in women, with predominance of *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *Enterobacter* spp., *E. faecalis*, *Acinetobacter* spp., and *P. mirabilis*, probably due to the anal proximity with urogenital organs and shorter urethra [52]. However, there is no predisposition related to age and occurrence of such infection in cancer patients. There are few published studies regarding UTI in patients undergoing chemotherapy, probably due to its low occurrence or low culture screening [22].

Sepsis is a set of serious manifestations throughout the body caused by an infection. Studies have shown that sepsis caused by bacteria occurs in 30% of neutropenic patients, and the incidence of Gram-positive and Gram-negative bacteria can vary between locations [53]. Overall, infections caused by Gram-negative bacteria are more prevalent and have a worse prognosis (18% mortality rate) when compared to those caused by Gram-positive bacteria (5% mortality rate) [53]. The microorganisms most commonly diagnosed in patients with neutropenic sepsis have been *Acinetobacter* spp., *Citrobacter* spp., *Clostridium difficile*, coagulase-negative staphylococci, *Enterobacter* spp., *Enterococcus* spp., *E. coli*, *Klebsiella* spp., *P. aeruginosa*, *S. aureus*, *S. maltophilia*, *S. pneumoniae*, *Streptococcus pyogenes*, the viridans group streptococci, some anaerobes, *Aspergillus* spp., *Candida* spp., and *Mycobacterium* spp. [53]. The diagnosis of sepsis is primarily clinical, combined with culture results that demonstrate infection in any site on the body and the blood [53]. Treatment is carried out with intensive administration of fluids, antibiotics, and surgical excision of infected or necrotic tissues along with pus drainage if required [31,54]. These interventions are usually applied together with supportive care methods, such as blood pressure monitoring, dialysis (if kidneys are affected), oxygen therapy, and others [53].

Antibiotic resistance and infection prevention

Antibiotics are considered as an effective method to treat infections in chemotherapy patients if the microorganisms are sensitive to this action. However, when the pathogen is resistant, the drug has low or even no effect on it, and the treatment strategy should be altered [12,16,31]. Although mitigation of infectious microorganisms is essential, continuous and progressive antibiotic administration can select for the antimicrobial resistant strains [19,55]. Therefore, the oncologist responsible for the treatment of patients with an infectious event should only choose the antimicrobial after a detailed investigation with laboratory (biochemical exams from blood),

microbiological (blood, skin, and/or urine cultures, nasopharyngeal swabs, etc.) and imaging tests (radiographs, ultrasonography, computed tomography scanning or magnetic resonance) [12,56].

Methicillin-resistant *S. aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS) and vancomycin-resistant enterococci (VRE) are the most important antimicrobial-resistant Gram-positive bacteria [57]. However, an increase in the frequency of infections caused by Gram-negative bacteria, along with the increase of the MDR ones, have been detected in the past decade [17,24,26–28,57,58]. Some studies have attributed such increase to the fluoroquinolone prophylaxis as well as to the rising of the carbapenem-resistant *A. baumannii* isolates, the MDR *P. aeruginosa* resistant to fluoroquinolones (such as ciprofloxacin, levofloxacin, moxifloxacin) and β-lactams (e.g. piperacillin/tazobactam, ceftazidime, carbapenems), and the extended-spectrum β-lactamase (ESBL)-producing Enterobacterales (resistant to all β-lactams except carbapenems) [24,57,59].

Hematologic malignancy, neutropenia, contact with the health care environment, hospitalization, use of devices, admission to an intensive care unit (ICU) in the past three months, recent colonization by an MDR microorganism, and changes in the microbiota due to use of antimicrobials are considered risk factors associated with the transmission of MDR microorganisms [60,61]. Multicentre studies have reported high rates of bacteremia in cancer patients caused by MDR bacteria, especially the ESBL-producers and the carbapenem-resistant ones [61–65].

A retrospective study conducted in Mexico City revealed that more than 20% of bacteria causing ventilator-acquired pneumonia in cancer patients were MDR [66]. Another retrospective study has shown that among the infections caused by MDR bacteria in cancer patients, the urinary tract infection was the most common type, followed by respiratory tract infection and BSI [64]. A study in Germany concluded that 8% of oncologic patients were colonized with MDR bacteria, especially the Enterobacterales resistant to $3^{rd}/4^{th}$-generation cephalosporins (such as ceftriaxone, cefotaxime, ceftazidime, cefepime), and that colonization was associated with a higher mortality rate in those patients [67]. A study conducted in Egypt has shown the presence of colistin- and carbapenem-resistant *K. pneumoniae* or *E. coli* isolated from cancer patients with no identification of the sites of infection [68]. Lastly, Jung *et al*. highlighted that MDR bacteria were commonly detected in patients with chemotherapy-induced neutropenic septic shock; 48% of these microorganisms are resistant to cefepime [24]. Therefore, in those instances, the authors recommended piperacillin/tazobactam or carbapenems as the probable more effective antibiotics. All the data presented show that oncologic patients are vulnerable to acquire hard-to-treat infections during chemotherapy, which demands more effective measures regarding infection prevention in such patients.

Even before cancer treatment begins, patients should be evaluated for possible active or latent infections that may emerge after administration of potentially immunosuppressive medications [58]. The initial and periodical clinical evaluations must take into account aspects such as: i) history of colonization or infectious diseases that may emerge in immunosuppression; ii) complete epidemiological history, including contact with other infected or immunosuppressed patients; iii) origin and travel to different areas, especially those areas with cases of endemic diseases; iv) history of drug reactions and antibiotic failure (especially due to MDR pathogens); v) treatment time (antineoplastic therapy for at least 6 weeks); vi) new symptoms in organs or systems; and vii) non-proven infections as cause of fever and possible comorbidities [57–59]. A multicentre study including hematologic patients with FN and no etiologic diagnosis reported that stopping empirical antimicrobials regardless of the neutrophil count decreased the number of days of exposure to that drug with no impact on mortality and other secondary outcomes [69], which supports that antimicrobial treatments in cancer patients must be performed with more criteria than other patients.

The WHO considers that about 40% of cancer deaths could be avoided while highlighting “infection prevention” as an essential component of all cancer care protocols [1]. Thus, there are some protective factors, whose objective is reducing chances of infectious disease events. The nosocomial infections have a negative impact on health services and their users due to consequences such as prolonged hospitalization period, high costs to patients and families, increased selection of antimicrobial resistant microorganisms, long-term disabilities, and death [11,13].

To better elucidate this issue, it has been demonstrated that BSI acquired in ICUs can lead patients to a longer hospital stay (extended by 12.69 days) and higher hospitalization costs (excess cost being US$ 7,669 per patient) [13]. Some reports have already concluded that infection control and prevention strategies are extremely important in reducing rates of nosocomial transmission of MDR bacteria in cancer

patients [60,70]. Therefore, it is undeniable that the establishment of strategies to prevent infections should be considered as of utmost priority for health-care institutions, in order to ensure patients' safety [55,71].

Infection control strategies are an essential part of the modern oncology care and comprise a multilevel approach, including patients, health-care workers, environment, and the community. The prevention actions are mainly based on simple hygiene procedures: washing hands, air quality, use of aprons, gloves, masks and eye protection, and prevention of device-related infections (for example, CVC and urinary catheters) [60,71].

It was estimated that out of all health-care associated infections developed in the ICUs, 40-60% are due to endogenous microorganisms, 20-40% due to the contaminated hands of healthcare professionals, 20-25% are due to antibiotic-driven changes, and 20% are potentially due to environmental contamination [72]. Thus, the risks for acquiring nosocomial infections are associated with the patients' own risk profile (> 65 years old, vulnerability, and disease severity), the risk of contamination associated with surfaces and indirect transmission of pathogens (potential exposure), and the risks related to the specificities of each microorganism itself and its antimicrobial resistance profile (persistence, MDR, and modes of transmission) [71,73].

The surfaces in hospitals present risk of infection because they can act as a reservoir of pathogens. In this circumstance, it is necessary to consider that beds and the entire hospital environment have dynamics related to the transit of patients and pathogens, in which patients leave microorganisms after and during their stay [72,73]. When the cleaning of beds and the circulation areas of the previous patient is not properly executed, new occupants have an average of 73% more chance of acquiring health-care associated infections [72].

Hand washing remains the most effective action against the spread of infectious agents. In 2006, the WHO defined the key moments for proper hand hygiene based on knowledge about cross-transmission of microorganisms among the patients, environment and health-care professionals [74]. The simple habit of washing hands with soap and water has the potential to remove almost all transient Gram-negative bacteria in 10 seconds, and is therefore the most efficient way of cleaning and removing microorganisms [1,60,71–73,75]. Introduction of the hand washing habit in hospital environments has proven to lead to reduction of infection rates, and patients reported that the health-care professionals encouraged and offered them the opportunity to wash their own hands more frequently [75].

The implementation of specific cleaning methods, protocols and practices is not enough in itself. It means that the theory needs to be strictly followed by the health workers, because hygiene and cleaning practices poorly performed in the hospital environment are unproductive and may increase the risk of proliferation of pathogens [73,76]. In this context, a guide with four daily basic steps has been proposed in order to preserve the patient safety. This guide is based on Look, Plan, Clean, and Dry the beds, which corresponds to a sequence of practices in order to pay attention to the environment where the patient is allocated, preparing and organizing the site to be cleaned, actually cleaning and disinfecting the beds, and finally keeping them dry [76].

In addition, it is known that many contaminations can come from poor food hygiene habits. There are some foodborne diseases caused by fungi or their sub-products, as mushrooms or mycotoxins. Some fungi that contaminate or spoil food are pathogens such as *Alternaria* spp., *Aspergillus* spp., *Candida* spp., *Fusarium* spp., and mucormycetes [77]. In general, it is important to properly wash fruits and vegetables, and avoid the consumption of undercooked meats, seafood, eggs or other food that can expose patients to infections, especially to oral infection [74,77]. Recently, a study focusing on outbreaks caused by *Salmonella enterica* serovar Infantis in a rehabilitation clinic in Germany showed that the probable route of the pathogen transmission occurred through cross-contamination in the kitchen [78]. The investigation revealed serious deficiencies in hygiene practices associated with the central kitchen, such as the use of antacids, food offered to patients some hours after cooking, maintaining the meal at inadequate temperatures, probable post-preparation contamination, manipulation and preparation of meals by contaminating employees (with or without symptoms), poor hand hygiene by health workers, and others. Another study focusing on a food hygiene training program for employees in a health-care institution revealed that after the educational intervention, the percentage of bacteria present on hands, work clothes, surfaces, equipment and kitchen utensils was significantly lower, contributing to the prevention of nosocomial infections [79]. Thus, food safety practices standardized by competent health agencies emphasize that safe handling and washing, as well as the correct cooking of food, all based on Hazard Analysis Critical Control Point plans, allow for better

safety of the patients' health, and consequently decrease the rates of infection or incidence of FN [71].

Environmental interventions include disinfection and sterilization of surfaces and equipment, air filtration, positive air pressure rooms, hand hygiene, and barrier protection from body fluids [80]. Patients should be advised to carefully monitor their own symptoms, including body temperature measurements, and seek emergency services in the presence of hyper- or hypothermia [6]. In addition, health care professionals should always be attentive and well informed about local epidemiology and the most common microorganisms found in their workplace. Furthermore, they must also be informed about innovative strategies to minimize exposure and risks of infections to patients in the course of chemotherapy treatment [72,76]. Therefore, the success in applying infection control and prevention strategies depends on correctly informing patients and health professionals about protective habits and risks of exposure to infectious pathogens [60,71]. The reduction of infection rate in post-chemotherapy cancer patients is a challenge and requires effort by the entire staff of a health-care institution in order to provide preventive care based on the best practices.

Conclusions

People undergoing chemotherapy for cancer treatment are among the most vulnerable patients to acquire or develop infections due to the immunosuppression. In general, age is commonly reported as a risk factor associated with nosocomial infections in cancer patients. On the other hand, gender represented a risk factor only for cases of urinary tract infections. Bloodstream constitute the most common site of infection, and bacteria such as *E. coli*, *Klebsiella* spp., *P. aeruginosa*, *Staphylococcus* spp., and *Streptococcus* spp. are the most frequently reported microorganisms responsible for infections in such patients. This scenario becomes more complicated since those bacteria are known to present antimicrobial resistance, making it difficult to achieve the patients' recovery. Accordingly, it is imperative for professionals that deal with those patients to improve the techniques employed in order to avoid such infections as much as possible. The application of effective prevention protocols in healthcare facilities is important to help avoid contamination. Preventive actions including adopting proper handwashing practices, and food and environmental hygiene are some of the main ways to protect patients. In addition, up-to-date information should always be available to all people of the multidisciplinary team.

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Corresponding author

Professor Tiago Casella, PhD
Departamento de Doenças Dermatológicas, Infecciosas e Parasitárias
Faculdade de Medicina de São José do Rio Preto
5416 Av Brigadeiro Faria Lima, Peru
Tel: +55 17 3201 5918
Fax: +55 17 3229 1777
Email: tiago_casella@yahoo.com.br

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