Treatment of infections in cancer patients: an update from the Neutropenia, Infection and Myelosuppression Study Group of the Multinational Association for Supportive Care in Cancer (MASCC)

Bernardo L. Rapoport[1,2,3,*], Tim Cooksley[4,5], Douglas B. Johnson[6], Ronald Anderson[1], Vickie R. Shannon[7]

[1]Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa. bernardo.rapoport@up.ac.za, ronald.anderson@up.ac.za

[2]The Medical Oncology Centre of Rosebank, 129 Oxford Road, Saxonwold 2196, Johannesburg, South Africa.

[3]The Multinational Association for Supportive Care in Cancer (MASCC), Chair of the Neutropenia, Infection and Myelosuppression Study Group.

[4]Manchester University Foundation Trust, Manchester, United Kingdom. The Christie, University of Manchester, Manchester, United Kingdom. cooks199@hotmail.com

[5]The Multinational Association for Supportive Care in Cancer (MASCC), Vice-Chair of the Neutropenia, Infection and Myelosuppression Study Group.

[6]Douglas B. Johnson, Department of Medicine, Vanderbilt University Medical Center and Vanderbilt Ingram Cancer Center, Nashville, Tennessee, United States of America. douglas.b.johnson@vumc.org

[7]Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, United States of America. vshannon@mdanderson.org

***Correspondence:** Bernardo L. Rapoport
Department of Immunology
Faculty of Health Sciences
University of Pretoria
PO Box 667
Pretoria 0001
South Africa
Telephone: +27-11-880-4169
Email: bernardo.rapoport@up.ac.za

Abstract

Introduction: Patients with hematological and advanced solid malignancies have acquired immune dysfunction, often exacerbated by treatment, posing a significant risk for development of infections. These are often difficult to diagnose and poorly responsive to anti-infective therapy. This review evaluates the utility of current clinical and treatment guidelines, as well as recent and emerging innovative approaches and therapies, in the setting of management of infections in cancer patients.

Areas Covered: These include causes of infection in cancer patients, management of patients with high-risk and low-risk febrile neutropenia, management of low-risk patients in an outpatient setting, the role of granulocyte colony-stimulating factor (G-CSF) in the prevention and treatment of neutropenia-related infections, management of lung infections in various clinical settings, and emerging challenges surrounding the risk of infection in cancer patients treated with novel treatments, including targeted therapies, and immunotherapies. The literature search was performed by accessing PubMed and other databases, focusing on published clinical trials of relevant anti-cancer agents and diseases. These primarily coveried the recent past, but also included several key studies published during the last decade and, somewhat earlier in a few cases.

Expert Review: Notwithstanding the promise of gene therapy/gene editing in hematological malignancies and some types of solid cancers, innovations introduced in clinical practice include more discerning clinical management such as the generalized use of biosimilar formulations G-CSF and the implementation of novel, innovative immunotherapies.

Keywords: Antibiotic and host-directed therapies; febrile neutropenia; granulocyte colony-stimulating factor; hematological malignancies; opportunistic infections; solid tumors.

1. Introduction

Cancer care has become increasingly specialized, and advances in therapy have resulted in many patients receiving care. Patients with cancer are at increased risk of infection, which is a rightly feared cause of significant morbidity and mortality. In this expert review, we consider the basic mechanisms of infection in cancer patients, the clinical workup and management of neutropenic fever, including those with low-risk febrile neutropenia (FN), who can be managed in an ambulatory outpatient setting. Other topics include the role of granulocyte-colony stimulating factor (G-CSF), pneumonia in cancer patients, fungal infections, infections in specific oncological clinical settings, as well as the emerging infection challenges in cancer patients treated with targeted therapies.

2. Basic Mechanisms of Infection in Cancer Patients

Immunosuppression in primary cancer may be persistent such as that associated with hematological malignancies, predisposing for serious, often life-threatening, microbial and viral infections, albeit often amenable to correction by successful bone marrow/hematopoietic stem cell transplantation. In the case of solid tumors, notwithstanding issues such as immunosenescence, co-morbidities, poor nutrition, smoking, and anatomical obstruction, it is usually only in the very advanced stages of these malignancies that serious, generalized immunosuppression develops. In this latter scenario, intense secondary cancer-related immunosuppression spreads systemically from the primary tumor site. Importantly, tumor-related immune dysfunction in the context of both hematological and solid malignancies is exacerbated by superimposition of the immunosuppressive effects of anti-neoplastic therapy.

This section of the review will briefly cover immunosuppression associated with several types of hematological malignancy, followed by a consideration of acquired immune dysfunction and predisposition to life-threatening infection in patients with advanced solid tumors.

2.1 Hematological malignancies

Notwithstanding the significant influence of aggressive therapeutic and corrective strategies, disease-associated immunosuppression also contributes to infection-related morbidity and mortality in patients with hematological malignancies. In the case of the acute leukemias, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL), immunosuppression results from rapid, uncontrolled proliferation of immature, progenitor cells. On the other hand, chronic leukemias, including chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), and hairy cell leukemia (HCL), usually have a more insidious clinical course, with the former most frequently characterized by neutrophilia that encompasses both functionally normal and mildly impaired cells. The most commonly occurring leukemia in adults, CLL, presents as a lymphocytic leukocytosis, while HCL, which results from disordered proliferation of mature B cells that have a propensity to invade the bone marrow, liver and spleen, often presents as a pancytopenia and less commonly as a leukocytosis.

2.1.1 Acute myeloid leukemia

This is a complex, heterogeneous disease consisting of eight subtypes, each with a distinct genetic abnormality. The most common subtype is myeloid leukemia, which has a high prevalence of neutropenia and functionally impaired neutrophils, these being the primary risk factors for development of severe, cancer-related infection in this patient population [1, 2]. These patients, particularly those with severe baseline neutropenia, are at very high risk for the development of life-threatening infection due to chemotherapy-related exacerbation of neutropenia [3].

Although neutropenia represents the most prominent cause of immunosuppression and susceptibility for development of infection in AML, T lymphocyte dysfunction in the bone marrow microenvironment [4] also extends systemically, resulting in dysfunction of $CD8^+$ cytotoxic T cells in particular, that may be associated with a poor clinical outcome [5, 6]. The situation with respect to B cell function in AML is less clear with one study having reported impaired humoral immunity that persists for longer than one year following intensive cytotoxic chemotherapy [7]. On the other hand, another more recent study described abnormalities of T lymphocyte and natural killer cell function in AML, while B cell function was unaffected [8].

2.1.2 Acute lymphoblastic leukemia

This condition is predominantly a disease of childhood, accounting for 80% of cases overall, the majority of these (approximately 80%) being B cell-ALL of bone marrow origin, with T cell–ALL representing the balance [9]. Like AML, B cell-ALL is associated with an increased susceptibility to infection largely due to bone marrow derangements that result in substantially increased numbers of immature circulating leukocytes and a high prevalence of thrombocytopenia. In this latter context, it is now well recognized that platelets are prominently involved in systemic, anti-infective host defense [10]. Pre-therapy levels of circulating immunoglobulins (Igs), on the other hand, are generally normal in children with B cell-ALL [11].

Interestingly, children who develop B cell-ALL already manifest irregular immune function at birth that is characterized by an unusual systemic cytokine profile associated with increased levels of the cytokines, interleukin (IL)-6, IL-17, and IL-18 [12], seemingly indicative of early immunosuppression [12]. During acute disease, expansion of immunosuppressive regulatory T cells (Tregs) and granulocyte-derived myeloid suppressor cells (MDSCs) is evident in both the bone marrow and circulation of children with B cell-ALL [13] and precursor B cell-ALL [14], respectively. Although associated with tumor cell immune evasion and poor prognosis, the presence of elevated numbers of these different types of suppressor cells in the circulation may also negate anti-infective host defenses.

T cell-ALL is also an early lymphoid malignancy characterized by infiltration of, and proliferation within the bone marrow, of immature T lymphoblasts, resulting in hyper-leukocytosis, neutropenia and thrombocytopenia, predisposing for development of frequent, severe and prolonged infection. In adults, about 20% of cases are of T cell-ALL origin.

2.1.3 Chronic myeloid leukemia

Uncontrolled proliferation of cells of the myeloid lineage is the cause of CML. This uncommon malignancy that mostly affects older males, results in a significant leukocytosis comprising granulocytes at all stages of maturity, with varying phagocytic and antimicrobial

competencies [15]. Although patients are frequently asymptomatic, especially in early-stage disease, some may nevertheless experience undue susceptibility to development of bacterial infection. In patients with chronic myelomonocytic leukaemia, which is an uncommon, aggressive myeloid neoplasm of older adults associated with a persistent monocytosis that may necessitate splenectomy, the median time from diagnosis to splenectomy is about six months, with a median post-splenectomy survival of 25 months [16].

2.1.4 Chronic lymphocytic leukemia

This is a B cell chronic leukemia that usually, but not always, progresses slowly and is the most common leukemia affecting older adults in Western countries. It may also be considered a type of non-Hodgkin's lymphoma that results from clonal proliferation in the bone marrow, secondary lymphoid organs and blood of mature B cells that have varying levels of CD5 expression [17]. It has been reported that these CLL-B cells appear programmed to differentiate into IgM-secreting plasma cells with limited capacity for isotype switching [17, 18]. This defect in B cell function may result, at least in part, from attenuation of T cell help due to immunosenescence and over-expression of inhibitory immune checkpoint molecules [19, 20]. These abnormalities result in a high incidence of hypogammaglobulinemia and impaired responses to immunization, often necessitating Ig replacement therapy due to recurrent, often severe, infection with common bacterial pathogens, especially encapsulated bacteria [21]. In addition to hypogammaglobulinemia and T cell subset deficiency, defects in complement activity and neutrophil/monocyte function also occur in CLL patients [22]. Other hematological malignancies associated with hypogammaglobulinemia and increased frequency of often severe infection, include multiple myeloma and malignant lymphoma/non-Hodgkin's and Hodgkin's lymphoma.

Hairy cell leukemia is an uncommon malignancy, predominantly affecting older males, resembling CLL because it is associated with proliferation of mature, monoclonal B cells found predominantly in the bone marrow, blood and spleen [23]. Important frequent presenting features with respect to immune dysfunction include neutropenia, monocytopenia, and thrombocytopenia that may predispose for repeated infections [23].

2.2 Immunosuppression and infection in advanced solid malignancies

Untreated early-stage solid malignancies are not usually associated with increased predisposition for the development of infection. However, in advanced disease, tumor progression is accompanied by transition from localized inflammation and immunosuppression in the tumor microenvironment to a phase of more widespread, systemic immune dysfunction. This has been described in various types of cancer, including colorectal carcinoma [24] and non-small cell lung cancer [25]. Increased numbers of MDSCs, Tregs and immunosuppressive cytokines, such as IL-10 and IL-6, as well as the acute phase reactant, C-reactive protein (CRP), characterize systemic immunosuppression [25]. Compounded by other major contributory factors, particularly chemotherapy, as well as radiation, obstruction-mediated disruption of mechanical barriers, co-existent diabetes mellitus [26], malnourishment and immunosenescence, tumor-induced peripheral immunosuppression may underpin the almost 10-fold increase in sepsis mortality recorded in patients with advanced cancer relative to that of cancer-free sepsis patients [27, 28].

In addition, patients with lung cancer in whom both age and tumor stage represent significant risk factors for infection, pneumonia has been reported to occur in 50–70% of patients due to the combined effects of cancer-related immunosuppression and derangements of lung architecture that cause pulmonary obstruction [29, 30]. This, in turn, leads to impaired airway clearance and microbial airway colonization, predisposing for development of pneumonia and aspiration [30]. Other types of malignancy that may cause airway obstruction include lymphomas and tumors of the head and neck, thyroid, larynx, and esophagus [30]. Lung cancer is also a recognized risk factor for developing pulmonary tuberculosis [31].

In addition, intra-abdominal tumors with obstruction of the genitourinary or hepato-biliary tracts may be complicated by severe urinary tract infections or cholangitis [32, 33]. In patients with colon cancer, invasion of the colonic mucosal invasion by cancer may also predispose to local abscess formation primarily by enteric flora [34]. Locally advanced breast cancer is associated with a greater risk of *Staphylococcus aureus* abscess formation [35].

The immunological abnormalities associated with these various types of malignancy are summarized in Table 1.

Hematological malignancies	Immunologic abnormality
Acute myeloid leukemia	Neutropenia; T lymphocyte and natural killer dysfunction
B cell acute lymphoblastic leukemia	Immaturity of circulating leukocytes; thrombocytopenia; increased numbers of circulating Tregs and MDSCs
T cell acute lymphoblastic leukemia	Neutropenia; thrombocytopenia
Chronic lymphocytic leukemia, multiple myeloma	Hypogammaglobulinemia; defective complement activation
Hairy cell leukemia	Neutropenia; monocytopenia; thrombocytopenia
Solid malignancies	**Immunologic abnormality**
Colorectal cancer	Generalized immune dysfunction resulting from chronic systemic inflammation
Non-small cell lung cancer	Generalized immune dysfunction resulting from chronic systemic inflammation
Malignancies of the, head and neck, thyroid, larynx and esophagus	Impaired pulmonary host defense due to airway obstruction
Intra-abdominal malignancies	Localized immune dysfunction due to obstruction of the genito-urinary and hepato-biliary tracts

Table 1. Acquired immune dysfunction associated with certain types of hematological and solid malignancies

3. Neutropenic sepsis

Neutropenic sepsis is a potentially fatal complication of systemic anti-cancer treatment (SACT). Neutropenic sepsis is defined as a temperature > 38^{o}C and a neutrophil count <0.5 x 10^{9}/L [36].

3.1 Clinical workup

Comprehensive history and examination remain the fundamental cornerstone in the workup of suspected neutropenic sepsis [36-38]. The history element, in particular, needs to elicit any symptoms suggestive of a focal site for infection, establishing any recent infective contacts, clarifying the chemotherapy regimen and confirmation of antimicrobial and G-CSF prophylaxis.

Initial biochemical investigations for patients presenting with suspected neutropenic sepsis include complete blood count, urea and electrolytes, liver function tests (including serum albumin), coagulation screen, CRP, lactate, and performance of blood cultures. At least 2 sets of blood cultures should be performed from separate venepuncture sites [39, 40]. If the patient has a central line, paired blood cultures should be obtained from each lumen of the line and peripherally.

Further cultures should be guided by the clinical history and examination [36]. Sputum cultures should be obtained in those who are expectorating. A chest X-ray should be performed in all patients with respiratory symptoms and there should be a low threshold for performing this investigation in all patients, especially in those with a previous history of respiratory infections. Assessment for upper respiratory viral pathogens, including SARS-CoV-2, may be useful in determining the etiology of the fever. Stool cultures should be sent in the case of patients with diarrhoea and include analysis for *Clostridium difficile* toxin and common viral pathogens. Urine culture should be obtained in those with urinary symptoms or a positive urinalysis. Cerebro-spinal fluid (CSF) should be analyzed in those with symptoms suggestive of central nervous system infection, ensuring that any coagulopathy or thrombocytopenia are appropriately corrected prior to performing lumbar puncture. Obtaining cultures should not delay the initiation of antibiotic therapy.

3.2 Management of emergencies and high-risk patients

Most patients with suspected neutropenic sepsis present to an Emergency Department (ED) and should be treated as an acute medical emergency [41]. Empirical antibiotic therapy should be administered immediately [36-39, 42]. Protocols and innovations should be considered to improve the time to delivery of first dose intravenous antibiotics in septic patients post-chemotherapy [43-45.] The aim of empirical antimicrobial therapy is to provide broad spectrum cover guided by local patterns of frequency and resistance of causative organisms [36].

Beta-lactam monotherapy is generally preferable as meta-analyses have demonstrated combination therapy with a beta-lactam and an aminoglycoside do not improve survival, but are associated with higher levels of morbidity and adverse events [46]. Vancomycin is not recommended as part of the standard initial empirical antimicrobial regimens, but may

be indicated in patients requiring increased gram-positive cover, such as those with clinical evidence of line infection, soft tissue infection or severe mucositis [39]. Local antimicrobial policies should be followed.

Alongside empirical antimicrobial therapy, patients with neutropenic sepsis require the same standard sepsis management as those with non-neutropenic sepsis, with early interventions, and aggressive resuscitation [46-49]. Source control should be achieved as soon as possible with early removal of any intravascular device if suspected to be driving high-risk neutropenic sepsis [37].
The use of steroids in patients with septic shock remains controversial with contradictory results from large randomized controlled trials [50, 51]. Corticosteroids may reduce the risk of death to a small extent at the expense of increasing neuromuscular weakness. In patients with neutropenic sepsis, a significant proportion of whom are likely to have had steroid therapy and potentially a degree of adrenal dependence, the balance may favor a trial of physiological steroids.

Granulocyte colony-stimulating factors (G-CSF), such as filgrastim, are not recommended as standard adjuncts to therapy in patients presenting with neutropenic sepsis [36, 39]. Although shown to reduce the duration of neutropenia and fever, they have not been associated with improved mortality outcomes [52]. Furthermore, G-CSF treatment is associated with a risk of acute lung injury [53].

Early decisions regarding ceilings of care, appropriateness of intensive care unit (ICU) admission for organ support, and resuscitation decisions are important in those presenting with high-risk neutropenic sepsis. Outcomes of septic patients with cancer admitted to ICU have significantly improved over the last two decades [54, 55]. Neutropenia and the type of malignancy in critically ill septic patients with cancer are not associated with poorer short-term outcomes [54, 56, 57].

An important consideration in patients presenting with severe neutropenic sepsis in the first cycle of treatment with a fluoropyrimidine, such as fluorouracil (5-FU) and capecitabine, is DPD (dihydropyrimidine dehydrogenase) deficiency [58]. This is an autosomal recessive metabolic disorder in which there is a significant reduction in the metabolism of uracil and thymine that can result in life-threatening toxicity often associated

severe with neutropenia. Alongside standard emergency neutropenic sepsis management, early administration of uridine triacetate has been shown to improve outcome [58]. These patients usually require critical care admission.

Neutropenic patients not responding to standard antibiotic treatment may require antifungal treatment. Empiric antifungal therapy is recommended in high-risk patients with FN who have persistent fever after 4–7 days of broad-spectrum anti-bacterials and no identified infection source. A network meta-analysis of 17 randomized clinical trials showed amphotericin B lipid complex, conventional amphotericin B, liposomal amphotericin B, itraconazole, and voriconazole had a significantly lower rate of fungal infection-related mortality than no antifungal treatment. The meta-analysis showed that caspofungin appears to be the most effective agent for all-cause mortality and fungal infection-related mortality, whereas micafungin tended to be superior for treatment response. However, more studies are needed to determine the best antifungal agent for empiric treatment [59].

It is essential to point out that multidrug-resistant pathogens are emerging, and there is a lack of novel anti-infective agents under development; therefore, judicious use of antimicrobials based on the principles of antibiotic stewardship is critical. Patients with high-risk FN should be treated with empiric antibiotic treatment. Several clinical studies support the assumption that the primary antibiotic regimen might be safely discontinued before recovery of neutrophil counts if the patient remains afebrile for several days and all infection-related symptoms have been settled [60].

3.3 Low-risk febrile neutropenia

Patients with febrile FN are a heterogeneous group with only a minority of treated patients developing significant medical complications. Outpatient management of patients with low-risk FN is a safe and effective strategy [61-65]. The Multinational Association of Supportive Care in Cancer (MASCC) has pioneered work in this field and has developed a risk-assessment model that includes seven independent prognostic variables, each with an assigned integer value (see Table 2) [64]. A MASCC risk index equal to or greater than 21 identifies low-risk patients with a positive predictive value of 91% (specificity 68% and sensitivity 71%) of developing serious complications [61]. Patients with a MASCC risk

index greater than 21 should be considered candidates for FN outpatient antibiotic therapy [61-64]. The MASCC risk index has been prospectively validated in several settings, and its use is broadly recommended as a simple and easy strategy to apply as a triaging tool. The CISNE (Clinical Index of Stable Febrile Neutropenia) index was developed as an alternative risk stratification score and is designed to validate a clinician's opinion that solid tumor patients with FN are suitable for outpatient management [66,67].

Characteristic	Score
Burden of illness (febrile neutropenia) **1.** No or mild symptoms **2.** Moderate symptoms **3.** Severe symptoms of moribund	 5 3 0
No hypotension (Systolic blood pressure >90mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age <60 years	2

Table 2. Multinational Association for Supportive Care in Cancer (MASCC) Risk Score.

Intravenous and oral antibiotic regimens have been shown to be equally effective in low-risk FN patients in randomized clinical trials [68, 69]. Fluoroquinolones have high oral bioavailability and a broad spectrum of activity against gram-negative pathogens with equivalence between oral moxifloxacin and combined oral amoxicillin/clavulanic acid and ciprofloxacin [69]. It is essential to consider local sensitivity and resistance patterns in determining the most appropriate regimen.

Emergency outpatient/ambulatory care benefits include admission avoidance, reducing pressure on often overcrowded and overstretched EDs, cost savings, reduced risk of nosocomial infections and improved patient experience and satisfaction [70-72]. Furthermore, late presentation of patients with FN remains a significant risk, sometimes driven by concerns of prolonged hospital admission. A greater awareness of, and access to, outpatient ambulatory pathways may help mitigate this situation [73,74]. Ambulatory emergency medicine is a model used internationally to reduce pressures on EDs. This well-described approach works by a variety of means including reducing attendances to an ED through alternative routes and length of stay, thereby increasing

patient flow through the acute system. The references describe this model in greater detail and a further description of the merits of ambulatory emergency medicine is beyond the scope of this review.

The number of patients required to deliver a sustainable ambulatory low-risk FN service appears relatively small [72, 75, 76]. An Australian ambulatory FN clinic treated 25 patients in its first year with an estimated cost saving of $AUD 71895 [77]. With the increasing demand for cancer therapies and challenges in delivering emergency oncology care, ambulatory management of presentations such as low-risk FN is a key strategy for ensuring safe and sustainable services [71,78].

4. Therapeutic Usage of G-CSF

Patients developing grade 3 and 4 neutropenia or FN during chemotherapy treatments commonly require dose reductions and/or dose delays to their chemotherapy program, resulting in reduced relative dose intensity (RDI). Treatment outcomes may be compromised, mostly when treatment intent is either curative or to prolong survival. Prophylactic use of G-CSF is a therapeutic strategy for maintaining the RDI during treatment, decreasing the incidence of severe neutropenia and FN, and improving treatment outcomes and quality of life. Granulocyte colony-stimulating factor may be utilized to raise the circulating neutrophil count in patients facing severe and prolonged neutropenic episodes after chemotherapy treatment. Additionally, G-CSF is used in patients requiring mobilization of peripheral blood stem cells for harvesting. Colony-stimulating factors should be administered after autologous stem cell transplant (SCT) to reduce severe neutropenia duration and may be administered after allogeneic SCT to reduce severe neutropenia duration. Evidence-based guidelines have been developed by ASCO, NCCN, and ESMO defining the appropriate use of G-CSF in cancer oncology patients [36, 79, 80]. The main indications for the usage of G-CSF are summarized in the sections below.

4.1 Indications for the Usage of G-CSF

4.1.1 Primary Prophylaxis

Primary prophylaxis is defined as the usage of G-CSF in the first cycle and subsequent cycles. Most G-CSF guidelines recommend that primary prophylaxis for patients receiving chemotherapy regimens with an overall risk of FN is greater than 20%. Patients receiving myelotoxic chemotherapy with curative or radical intent (including adjuvant/neoadjuvant settings) are included in this category. Additionally, primary prophylaxis should be considered for patients receiving myelotoxic chemotherapy with a documented incidence rate of FN of 10 – 20% and has one or more of the significant risk factors for the development of neutropenic sepsis as summarized in Table 3 [80].

Risk factors associated with development of FN with an overall risk of 10-20%
Patient age > 65 years
Poor performance status
Previous episodes of febrile neutropenia
Extensive prior treatment including large radiation ports
Cytopenias due to bone marrow infiltration
Poor nutritional status
The presence of open wounds or active infections
Advanced cancer
Serious co-morbidities

Table 3. Risk factors associated with development of FN with an overall risk of 10-20%.

Primary prophylaxis is supported by the fact that approximately half of the neutropenic episodes occur in the first chemotherapy cycle [81].

4.1.2 Secondary Prophylaxis

Secondary prophylaxis is defined as the usage of G-CSF in subsequent cycles after initial episodes of severe neutropenia and/or FN. This strategy may be considered if dose reduction or treatment delay is associated with a decrease in disease-free or overall survival. Examples of such malignancies in this category include adjuvant breast cancer, non-Hodgkin's lymphoma, Hodgkin's disease, testicular cancer, and other germ cell tumors, as well as patients undergoing neoadjuvant chemotherapy with curative intention. For patients undergoing chemotherapy with palliative intent, dose modifications are considered a reasonable alternative.

5. Opportunistic bacterial, viral, and fungal infections of the lung in cancer patients

Lower respiratory tract infections (LRTIs) are a substantial health burden, accounting for 20 million hospitalizations and 4 million deaths worldwide [82]. Over the past decades, an expanding list of host and community factors such as aging populations, aggressive childhood vaccination programs, the expansion of solid organ and hematologic transplants, novel chemotherapies, and immune-modulating interventions, as well as the

emergence of multidrug-resistant organisms, have significantly altered the landscape of LRTIs. These factors influence both the burden of severe pneumonias and the appearance of unusual bacterial, fungal, viral, and parasitic organisms involved in pneumonia pathogenesis. This section of the review offers a broad overview of host factors, predominantly in the immunocompromised, but also non-immunocompromised patient, that contribute to pneumonia susceptibility. Evolving diagnostic platforms for pneumonia and updated guidelines informing its management are also discussed. We will focus on types of pneumonias acquired outside of the hospital, or community-acquired pneumonias (CAP). Hospital-acquired and ventilator-associated pneumonias are beyond the scope of this discussion.

5.1 Pneumonia: definitions, epidemiology, and classification

Although the term LTRI can be applied to types of lung infections other than pneumonia, such as lung abscesses, bronchitis, or bronchiolitis, for the purpose of this discussion, LRTI is used interchangeably with pneumonia. The newest classification schemes divide pneumonia into two significant categories: CAP and hospital-acquired pneumonia (HAP). Inpatients with pneumonia are further classified according to those with CAP at the time of admission and those who develop pneumonia 48 hours or more after hospitalization (HAP) or after placement on a ventilator (VAP) [83,84]. These designations foretell unique organism exposures and thus inform guidelines for diagnostic tests, empiric treatment regimens, and goals for infection prevention. The 2019 American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guidelines (Table 4) abandoned the category of health-care-associated pneumonia (HCAP), based on ideological concerns that HCAP designations missed the intended goal of identifying patients at high risk for drug-resistant pathogens, [e.g., methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa*] that are not covered by standard empiric therapy for CAP. Instead, the global application of HCAP has led to potential harm due to a significant overuse of anti-MRSA and anti-pseudomonal antimicrobial therapies [85]. Depending on the clinical context, HCAP is now regarded as a form of CAP or HAP.

Patient Category	Primary antimicrobial recommendations	Alternative
Outpatient, immunocompetent, no co-morbidities, healthy	Macrolide monotherapy, conditionally recommended depending on resistance levels	Doxycycline
Outpatient, recent antimicrobial therapy, underlying co-morbidities	Fluroquinolone	β -lactam/macrolide or β -lactam/doxycycline
Hospitalized, not requiring ICU care	β-Lactam/macrolide combination or fluroquinolone monotherapy	β -lactam plus doxycycline
Hospitalized, in ICU	β-Lactam/macrolide or β-Lactam/fluoroquinolone combination Evidence in favor of β-lactam/macrolide combination	Suspect MRSA: add linezolid or vancomycin Suspect *Pseudomonas aeruginosa*: modify regimen to include β-lactam and quinolone

Table 4. IDSA and ATS 2019 antimicrobial guidelines for management of CAP.

IDSA = Infectious Disease Society of America
ATS = American Thoracic Society
MRSA = Methicillin-resistant *Staphylococcus aureus*

Community-acquired pneumonia is a major cause of morbidity and mortality, accounting for nearly 4.5 million outpatient emergency room visits and 1.5 million hospitalizations in the United States annually. Despite advances in antimicrobial therapies, CAP remains the most common infectious cause of death in the United States [86]. Nearly 1/3 of leukemia patients receiving chemotherapy and up to 80% of HSCT recipients experience at least one episode of pneumonia over the course of cancer therapy [87-91]. Attributable mortality is unacceptably high, with case fatality rates for pneumonia reaching 80% among leukemia patients and 90% among HSCT recipients [92-94].

5.2 Lung immune defense mechanisms and their role in pneumonia development

Despite daily exposure to an extensive array of ubiquitous microbes, LRTIs under normal circumstances are rare [95-97]. Lung infection is mitigated by the coordinated actions of robust constitutive (innate) and recruited (adaptive) immune defense mechanisms. Mucous-producing goblet cells and ciliated epithelium lining the conducting airways are major components of the mucociliary escalator, which trap and expel microbes towards the glottis. This system works in concert with avidly phagocytic alveolar macrophages and

secreted antimicrobial products in surface lining fluids to prevent clinically relevant microbial replication within the distal airways and alveoli. In addition, the recruitment of inflammatory cells, including neutrophils, natural killer cells, dendritic cells, cytotoxic T cells, and monocytes, aid in antimicrobial lung defense and pneumonia control. A measured immune reaction commensurate with microbial replication within the alveoli, is a critical determinant of pneumonia severity. Dysregulated inflammatory responses tilt the balance of immunity toward uncontrolled lung injury and more severe pneumonia [98].

Cancer and its treatment, as well as other immunosuppressive states, instigate profound derangements in both innate and adaptive immunity, resulting in a spectrum of functional and anatomic immune defects, including leukocyte depletion, dysregulated inflammation, graft-versus-host disease (GVHD), and impairments in chemotaxis, pathogen recognition, and neutrophil phagocytosis. These derangements act as major substrates for opportunistic infections that substantially increase pneumonia risk. Impaired and/or overwhelmed lung immune defense activities are also thought to play a pivotal role in the development of pneumonia in the immunocompetent host. Other risk factors for pneumonia include older age, impaired airway protection associated with drug or alcohol abuse, seizures, stroke, or anesthesia, chronic co-morbidities (bronchiectasis, asthma, COPD, stroke, malnutrition, congestive heart failure), tobacco use, substance (opioid) abuse and poor or overcrowded housing conditions (prisons, homeless shelters). Additionally, primary viral upper respiratory tract infections may predispose to secondary bacterial pneumonias. Multiple risk factors may coexist, which compound the problem [99, 100].

Seasonal variations in CAP and HAP incidence are expected, with an increased frequency of viral pneumonias occurring during the winter months [101]. Worldwide, *S. pneumoniae* is the most commonly identified bacterial cause of CAP; however, microbiologic etiologies are influenced by geographic region and the efficacy of integrity of the host immune defense mechanisms. Pneumonia among immunocompromised patients is commonly designated as HAP due to frequent healthcare interactions in this patient population. *S. pneumoniae, S. aureus,* and *H. influenzae* are prominent causes of pneumonia in this patient group. Neutropenic patients are at increased risk for pneumonia in the community and hospital settings, and their frequent hospital exposures predispose them to recalcitrant

infections caused by multidrug-resistant organisms. The major infection risk categories and associated microbes for pneumonia are listed in Table 5 and discussed below.

Defect / disorder	Bacterial	Viral	Fungal	Parasitic
Leukocyte dysfunction Neutropenia	*Streptococcus pneumoniae,* *Staphylococcus aureus* *Pseudomonas spp.* nontypeable *Haemophilus influenzae* *Klebsiella pneumoniae* *Escherichia coli, Serratia marcescens* *Proteus* spp, *Acinetobacter baumannii*-complex Other gram-negative enterobacteriaciae *Nocardia* *Legionella* spp *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Stenotrophomonas maltophilia* *Alcaligens spp.* *Burkholderia spp.*	CMV Influenza PIV hMPV Adenoviruses, RSV VZV HHV-6	*Aspergillus* spp Non-*Aspergillus* molds (*Scedoscprorium spp, Fusarium spp, Pseudallescheria boydii*) *Mucorales* spp Dermaticeous molds *Pneumocystis jirovecii* *Histoplasma capsulatum* *Coccidiodes immitis* *Cryptococcus spp* *Blastomycetes derrmatitidis*	Toxoplasma
Cellular and humoral defects	*Streptococcus pneumoniae* *Mycobacterium tuberculosis* Atypical mycobacterial infections	CMV HIV RSV Influenza virus, PIV HRV HEV CoV		*Strongyloides* *Toxoplasma spp* *Trypanosoma cruzi*
Glucocorticoids	*Nocardia* spp		*Aspergillus* spp *Pneumocystic jirovecii*	*Strongyloides* *Toxoplasma* *Trypanosoma cruzi*

Table 5. Infectious etiologies of CAP and associated immune defects/disorders.

5.3 Infective lung pathogens in cancer patients

The most common bacterial isolate of CAP in patients with neutropenia and fever, regardless of cancer history, is *S. pneumoniae* [102]. Other common causes include *S. aureus*, *Pseudomonas spp*., and non-typeable *H. influenzae*. *Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Proteus* spp, *Acinetobacter baumannii*-complex, while other gram-negative enterobacteriaciae spp. represent additional bacterial causes. Atypical bacteria, including *Legionella pneumophila*, *Nocardia spp*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae,* are less common, but potentially lethal etiologies of CAP in neutropenic populations. Sporadic outbreaks of *L. pneumophila* in the post-transplant setting have been reported with no correlation with the type of transplant or engraftment status [103]. *Extended-spectrum* beta-lactamase-producing Enterobacteriaceae and infections caused by non-fermenting gram-negative bacilli (*Stenotrophomonas maltophilia, Alcaligenes spp., Burkholderia spp*) are increasingly identified in both CAP and HAP settings [104]. The emergence of pneumonias caused by drug-resistant pathogens, such as *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA) in the neutropenic setting, carries an ominous prognosis, with disproportionately higher mortality rates than those caused by antimicrobial-sensitive bacterial organisms.

Both the duration (>1 week) and severity (<100 cells/μl) of neutropenia influence the risk of fungal pneumonia [105,106]. Hence, infections caused by gram-negative bacterial pathogens predominate during the early (less than seven days) neutropenic period, while fungal infections caused by *Aspergillus, Zygomycetes,* and *Fusarium spp* are common as neutropenia persists beyond 1 – 2 weeks. The spectrum of pulmonary fungal infections in neutropenic patients includes members of the invasive *Aspergillus* spp, the non-*Aspergillus* molds (*Scedosporium* spp*, Fusarium* spp, *Pseudallescheria boydii), Mucorales spp* and the dermatiaceous molds [107]. *Aspergillus spp,* particularly *A. fumigatus,* is the most frequently identified fungal organism in neutropenic patients. *A. niger, A. flavus*, and amphotericin- and azole-resistant mold infections have also emerged as important pathogens in this setting [108-110]. Mixed infections with fungal species and respiratory viruses, cytomegalovirus (CMV), and/or gram-negative bacilli are also common. Recent declines in pneumonias caused by endemic fungi, including *Histoplasma capsulatum*, *Coccidioides immitis,* and *Blastomycetes dermatitidis,* have been attributed to the use of fluconazole prophylaxis in hematologic malignancies and following HSCT as the standard

of care. Rates of *Pneumocystis jirovecii* pneumonia (PCP) have declined significantly with the use of trimethoprim-sulfamethoxazole prophylaxis during the neutropenic period after HSCT [111,112].

The main indications of PCP prophylaxis include acute lymphocytic leukemia, allogeneic HSCT, treatment with alemtuzumab, fludarabine/cyclophosphamide/rituximab treatment for chronic lymphocytic leukemia, more than four weeks of treatment with corticosteroids, well-defined primary immune deficiencies in children, lymphoma treated with R-CHOP14 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), treatment with nucleoside analogs (fludarabine, cladribine, mycophenolate mofetil), and radiotherapy for brain tumors or brain metastasis receiving treatment with high-dose steroids. Trimethoprim/sulfamethoxazole is the preferred agent for the primary prophylaxis of PCP infections in adults. Second-line agents include dapsone, atovaquone, and pentamidine aerosols [113].
Experience at the world's largest cancer hospital indicates that *Candida spp* are rare causes of CAP or HAP, even in severely immunocompromised patients [114,115].

Aggressive cytomegalovirus (CMV) prophylaxis and pre-emptive measures have resulted in substantial reductions in CMV incidence following HSCT. Recipients of allogeneic transplants and seropositive recipients of seronegative hematopoietic stem cells are at the greatest risk for CMV pneumonitis [116]. Lung injury correlates with the intensity of T lymphocyte-depleting therapies and emerges as a delayed immune response to CMV antigens. Thus, in the absence of antiviral prophylaxis, CMV pneumonitis occurs after immune reconstitution, typically 1-3 months after HSCT. Pulmonary shedding of CMV is common, and thus, detection of CMV in bronchoalveolar lavage fluid does not reliably predict infection. Other primary viral etiologies of CAP that are frequently encountered in neutropenic patients include influenza, parainfluenza, human metapneumovirus (hMPV), and adenoviruses. Respiratory syncytial virus (RSV) varicella-zoster virus (VZV) and human herpes virus 6 (HHV-6) are less common, but potentially lethal etiologies [104].

5.4 Impaired cellular and humoral immunity

Cancer and its therapy frequently induce functional and absolute lymphopenia. Most induction chemotherapy regimens exert their effects through the depletion of lymphocytes [117]. Lymphocyte depleting agents, including anti-thymocyte agents, calcineurin inhibitors, monoclonal antibodies (alemtuzumab, rituximab), rapamycin (mTOR) inhibitors (sirolimus, everolimus) are notorious causes of lymphopenia. Conventional radiation therapy and treatment of GVHD following allogeneic HSCT are other known causes of lymphopenia [118,119]. Immune reconstitution may take a year or longer after HSCT, and other lymphocyte-depleting therapies have been completed [120,121]. Impaired lymphocyte function has been reported following viral illnesses caused by influenza and RSV in previously healthy individuals [122]. Severe lymphopenia, defined as absolute lymphocyte count <200 cells/mL, is identified as an independent risk factor for severe pneumonias caused by a variety of viral pathogens, including CMV, respiratory syncytial virus (RSV), influenza virus, parainfluenza virus (PIV), human rhinovirus (HRV), human enterovirus (HEV), and coronavirus (CoV), particularly among patients with hematologic malignancies and recipients of HSCT [123-127]. Community-acquired pneumonia associated with hMPV was first reported in 2001 and is now recognized as a leading cause of upper and lower respiratory tract infections, particularly in children, elderly adults, and immunocompromised hosts. Although most patients present with mild disease, fatal cases of hMPV pneumonia have been reported [128,129]. Like many of the other viruses, lymphopenia appears to be the most important risk factor for progression to lower respiratory tract disease progression.

Viral pneumonia may emerge as single isolates or coexist with bacterial (*Legionella, Nocardia spp*), fungal (*Aspergillus* spp, *P. jirovecii*, *Cryptococcus spp*), and parasitic (e.g., *Strongyloides* and *Toxoplasma spp,* and *Trypanosoma cruzi*) organisms [130-132]. The primary bacterial infections encountered in patients with impaired humoral immunity include *S. pneumoniae* and *H. influenzae* [133]. *Mycobacterium tuberculosis* (MTB) and atypical mycobacterial infections are rare causes of lymphopenic pneumonia in cancer patients. Most cases of MTB infection in this setting represent reactivation of latent infection and have been primarily reported among immigrants undergoing cancer therapy in non-endemic countries [134].

6. Glucocorticoids and Immunomodulating therapies

Many of the anti-inflammatory and immunosuppressive actions of glucocorticoids are mediated by the interference of key inflammatory signaling responses, such as depression of phagocytic function of alveolar macrophages and neutrophils, suppression of dendritic cell maturation and function, and restricted migration of inflammatory cells into areas of infection. These anti-inflammatory effects play a pivotal role in the development of pneumonia, particularly that caused by bacterial and fungal infections (including those due to *P. jirovecii*, *Nocardia* spp, and *Aspergillus* spp), as well as lung infections caused by certain herpes virus infections (e.g., CMV, varicella zoster virus) [128,135,136].

Immunomodulating therapies, including immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T-cells (CAR-T), cause profound adverse systemic inflammatory responses, which are discussed subsequently. It is important to note that differentiating non-infectious pneumonitis following ICI therapy from infectious pneumonia can be quite challenging, as clinical and radiographic features of both diseases overlap [137,138].

7. Clinical presentation and diagnostic evaluation of pneumonia in cancer patients

Common clinical features of CAP include fever, productive cough, dyspnea, tachypnea, and pleuritic chest pain. Leukocytosis, bronchial breath sounds, tactile fremitus, dullness to percussion, and egophony on lung examination are supportive findings; however, they are only present in approximately 1/3 of patients. Leukocytosis (typically between 15,000 and 30,000 per mm^3) with a leftward shift is a common finding, particularly in pneumonias of bacterial origin. Leukopenia may also be seen and portends a poor prognosis. Mucopurulent sputum is a prominent feature of bacterial pneumonias, while symptoms of coryza, symptoms and myalgias more often signal pneumonias of viral origin [139]. Lung nodules or mass-like lesions with associated adenopathy, and abnormalities of the skin, central nervous system, or bone are important clues to fungal pneumonia. However, no clear constellation of signs and symptoms is reliably predictive of any specific type of pneumonia [39]. Furthermore, impaired immune responses in the cancer setting may diminish the clinical and radiographic hallmarks of pneumonia. Thus, fever, leukocytosis,

and productive cough and the characteristic radiographic findings of lobar infiltrates may be minimal or absent. Competing diagnoses that mimic pneumonia, including diffuse alveolar hemorrhage, radiation pneumonitis, drug toxicity, hydrostatic pulmonary edema, and cancer progression, are frequent challenges for the neutropenic cancer patient and should be excluded with appropriate testing.

Despite all diagnostic efforts, the specific microbiologic etiology of lung infiltrates remains uncertain in 60-70%% of immunocompromised patients [140]. Inpatients and outpatients should be started on empiric antimicrobial therapy while undergoing workup for specific pathogens and competing causes. Among patients with CAP managed in the outpatient setting, a minimal workup consisting of clinical examination and a chest radiograph is reasonable. Sputum gram stain and cultures are not thought to improve treatment outcomes for mild outpatient CAP and are therefore not recommended [141]. For hospitalized patients with severe CAP, expanded testing to include sputum culture (either expectorated or endotracheal aspirate) and *L. pneumophila* and pneumococcus urinary antigen tests are recommended. Pretreatment basic blood work (complete blood count, metabolic panel) and blood, and urine cultures are also recommended in the hospitalized setting [39,141]. Peri-bronchial infiltrates, tree-in-bud patterns, pulmonary nodules with or without cavitation, and ground glass opacities are non-specific, but common chest imaging findings. Chest computed tomography (CT) is preferred as an early diagnostic test in patients with severe pneumonias and in febrile neutropenic patients with subtle or unusual clinical presentations and/or atypical infiltrates on conventional imaging. Uncomplicated cancer patients with CAP should be managed in the same way as those patients without cancer.

Fiberoptic bronchoscopy with bronchoalveolar lavage is generally reserved for patients with moderate or severe pneumonia, atypical presentations, and for patients with unusual, persistent, or worsening infiltrates despite antimicrobial therapy. When indicated, bronchoscopic sampling of the lower respiratory tract should be performed early, preferably before initiation of antimicrobial therapy, to offer the highest diagnostic yield [142,143]. Rates of serious complications have been correlated with a latency of initial antimicrobial dose of greater than 122 minutes [143]. Thus, antimicrobial therapy should not be delayed beyond 2 hours while awaiting bronchoscopy as the potential gains in test performance in the absence of antibiotics are modest at best and do not outweigh the risk

of potential harm associated with therapy delay [144]. Cytopathologic assessments of lung tissue may only be of incremental diagnostic value. Moreover, profound thrombocytopenia is a common problem in leukemic patients and in the post-transplant setting, which precludes safe transbronchial or surgical lung biopsies.

Biomarkers such as procalcitonin (PCT), B-natriuretic peptide (BNP), CRP, and serum lactate levels have been proposed to aid in pneumonia diagnosis, risk stratification, and management. Among these, PCT has shown the most promise. However, its use has been limited by, false negatives at the onset of bacterial infection due to delays in peak PCT levels and poor specificity, particularly in the setting of sepsis, shock, and multi-organ failure. . Furthermore, PCT thresholds that reliably discriminate viral from bacterial pneumonia have not been established. Thus, this test alone cannot be used to determine the need for antibiotics in patients with CAP [141,145-147].

The usual non-pathogenic colonizers of the upper airway may signify true disease in significantly immunosuppressed patients. Thus, treating clinicians are faced with the difficult task of discerning commensals from true pathogens. Molecular testing for specific pathogens using immunoassays and DNA-based diagnostic tools may facilitate diagnosis in these cases. The galactomannan (GM) immunoassay is widely used to detect galactomannan polysaccharide antigens within the cell wall of *Aspergillus spp.* The diagnosis of *Aspergillus* infection is supported by detection of an optical index (ratio of the test sample optical density relative to a provided control optical density) of 0.5 or greater in serum or bronchoalveolar lavage fluid [148]. False-positive results are caused by cross-reactivity with similar galatofuranose side chains found in *Fusarium spp*, *Penicillium* spp. and *Histoplasma capsulatum* [149-151]. Fungitell represents another immunoassay that detects the glucose polymer (1→3)-β-D-glucan (BDG). With the exceptions of *Zygomycetes* and *Cryptococcus spp*, BDG is ubiquitously found within the cell wall of most fungal species and is released into the blood and tissues during the course of invasive fungal infections. This assay has shown the highest diagnostic performance among patients with hematologic malignancies. However, due to low sensitivity, negative tests should be interpreted with caution and in the context of clinical, radiological, and microbiologic findings [152]. Polymerase chain (PCR) testing for various respiratory tract viruses, as well as *C. pneumoniae,* and *M. pneumoniae,* has been recently FDA-approved and should be considered in the appropriate clinical context. In addition, patients with

potential exposure to selected pathogens such as influenza virus, Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) and coronavirus-19 (SARS-COV-2), should undergo specialized testing.

8. Antimicrobial therapies in cancer patients with pneumonia

8.1 Antibacterial therapies

Initial antimicrobial considerations are virtually always empiric, as the causative pathogens are typically not known at presentation. Empiric antimicrobial choices should broadly cover the range of suspected pathogens described above and conditioned by known risk factors and immune status, pneumonia category (CAP, HAP, VAP) and severity, local antibiotic susceptibility profiles within the community, and recent antimicrobial history. Refinement of antimicrobial selections should occur as culture, and serologic data become available (Table 5).

Although regional variations exist, standard outpatient therapy for CAP should target the most common etiologies in the ambulatory setting, including *S. pneumoniae*, *H. influenzae,* and atypical pathogens such as *L. pneumophila, C. pneumoniae,* and *M. pneumoniae.* The 2019 American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guidelines advocate the use of a beta-lactam, macrolide or tetracycline monotherapy for outpatient treatment of patients with mild CAP without risk factors for MRSA or if local pneumococcal resistance is less than 25%. For outpatients with comorbidities (e.g., diabetes mellitus, alcoholism, malignancy, asplenia or chronic heart, lung, liver, or renal disease), or inpatients with CAP and no risk factors for MRSA or *P. aeruginosa*, beta-lactam/macrolide or beta-lactam/doxycycline combinations or monotherapy with a respiratory fluoroquinolone is recommended [141]. Expanded coverage for MRSA or *P. aeruginosa* is advocated if locally validated risk factors for either pathogen have been identified. In these cases, empiric treatment options include vancomycin for MRSA and piperacillin-tazobactam, ceftazidime, aztreonam, cefepime or other carbapenems such as meropenem or imipenem for *P. aeruginosa* [141]. Anti-influenza therapy should be added for patients with CAP who test positive for influenza. Initiation of antiviral treatment for Influenza within the first two days of symptom onset may confer improved outcomes, although benefits up to 4-5 days after symptoms begin may

offer residual benefit [153,154]. Early de-escalation of empiric therapy is reasonable among patients with a rapid response to antimicrobial therapy and in whom the offending pathogen has been identified. However, treatment durations for CAP should continue for a minimum of 5 days. The return of clinical stability should provide guidance (e.g., improvement and/or normalization of temperature, blood pressure, heart rate, respiratory rate, oxygen saturation blood pressure, and mentation). Longer treatment durations are recommended for CAP owing to unusual infections, such as *Burkholderia pseudomallei,* MTB or endemic fungi, or pneumonias complicated by meningitis, endocarditis, or other end-organ damage [141]. The 2019 IDSA/ATS guidelines do not advocate the empiric use of anaerobic coverage for patients with aspiration pneumonia, based on the limited etiologic role that anaerobic bacteria play in most cases. A mortality benefit with the addition of systemic steroids in the treatment of CAP has not been convincingly demonstrated in any large randomized trials, and, therefore, is not recommended [141].

8.2 Antifungal therapy

Amphotericin B remains the preferred drug in the empiric treatment of neutropenic fever, as well as severe and invasive fungal infections. The management of patients with FN with persistent fever has been addressed above. Amphotericin B offers reliable coverage for *Aspergillus* and *Cryptococcus spp., Zygomycetes*, and life-threatening infections caused by endemic mycoses (*Histoplasma, Coccidioides, Blastomyces, Sporothrix*). However, significant associated nephrotoxicity and infusion-related reactions and increasing resistance to *A. terreus and Fusarium spp,* has led to the expanded use of alternative antifungal therapies. These have included the newer triazoles, such as posaconazole, voriconazole, isavuconazole, and the echinocandins (caspofungin, micafungin, anidulafungin). Voriconazole and liposomal amphotericin B are preferred agents for invasive aspergillosis. Once clinical improvement is established, transition to oral voriconazole or itraconazole is recommended. Salvage therapy with posaconazole, caspofungin, or micafungin may be required for patients with recalcitrant invasive aspergillosis and in those patients intolerant to voriconazole. Triazole-echinocandin or amphotericin-triazole combinations have shown some benefit over antifungal monotherapy in neutropenic patients with refractory disease, although further investigations are needed. In this context, it is, however, noteworthy that the findings of the SECURE trial published in 2016 revealed that isavuconazole was found to be non-inferior to voriconazole for the first-

line therapy of suspected invasive fungal disease [155]. The authors concluded that “isavuconazole was well tolerated compared with voriconazole, with fewer drug-related adverse events”, supporting the therapeutic utility of isavuconazole as first-line treatment for invasive mould disease [155].

Surgical resection should be considered for patients with focal necrotizing pneumonias refractory to antifungal therapy, although intractable thrombocytopenia is often a limiting factor for surgical considerations [156,157].

8.3 Antiviral therapies

Appropriate management of acute viral pneumonias in the setting of immunocompromised cancer patients, including those who are pregnant, is a priority. However, this scenario is complicated by the absence of firm treatment recommendations. Accordingly, therapeutic strategies applicable to immunocompetent persons are generally followed. Nevertheless, determination of immune status is an essential first step in managing pneumonias caused by respiratory viruses other than influenza. The neuraminidase inhibitors, oseltamivir, inhaled zanamivir, and intravenous peramivir are FDA approved for the treatment of influenza, and are routinely prescribed for neutropenic and non-neutropenic patients with documented influenza infections [158,159]. Other antiviral treatment options in the non-immunocompromised setting are limited. Early administration of cidofovir in the management of adenoviral pneumonias in the immunocompetent host appeared promising in one study; however, randomized controlled studies are needed to allow firm conclusions [160]. Viral pneumonias during pregnancy, particularly those caused by herpes viruses, portend a poor prognosis. Thus, early administration of antiviral therapy, either alone or in combination with varicella zoster immune globulin, for management of varicella zoster pneumonia during pregnancy is recommended [161,162]. In the immunocompromised host with viral pneumonia, mortality rates may approach 80%, underscoring the need for early and aggressive therapy. Oral and aerosolized ribavirin and intravenous hyper-immunoglobulin are mainstays of treatment for RSV infection among immunocompromised patients with hematological malignancies and transplant recipients. Intravenous ribavirin has also shown efficacy among patients with life-threatening hMPV disease. Ganciclovir or foscarnet are recommended therapies for CMV and HHV-6 lower respiratory tract infections. Retrospective analyses and small case studies suggest that the addition of

CMV immunoglobulin to ganciclovir may offer an added benefit [163]. The utility of systemic corticosteroids in the management of viral pneumonias is highly debated with the weight of evidence varying with the type of viral illness. For example, high-dose steroids have been shown to worsen severe influenza pneumonia outcomes, while systemic steroid therapy may favorably impact mortality among patients with pneumonias not caused by influenza [164-166]. More robust data from randomized controlled trials are needed to confirm the efficacy of steroids in this setting.

8.4 Host-directed therapies

Targeting the causative pathogen(s) with broad anti-infective therapies has been the primary focus in managing pneumonia with little emphasis on efforts to restore the failing immune responses that permit uncontrolled pathogen replication, or on attempts to curtail exaggerated immune activity and inflammatory responses at sites of pathology. Recently, host-directed therapies have emerged as potential adjunctive strategies against infection. Host-directed therapies have traditionally used granulocyte infusions and colony-stimulating factors to correct neutropenia; however, this approach has limited utility in patients with established infection. More novel approaches include the use of recombinant cytokines to manipulate existing leukocytes, manipulation of host cell factors that are required by a pathogen for replication, augmentation of the antimicrobial activities of phagocytes through the activation of cytokines, or modulation of inflammation by manipulating cytokine signaling pathways [167-170]. These novel strategies remain investigational, but offer promising therapeutic adjuncts to pneumonia management and a more personalized approach that is tailored to the specific needs of the patient.

9. Infections associated with targeted therapies

In recent years, the cancer field has moved beyond cytotoxic chemotherapy toward agents targeting oncogenes and other cancer cell signaling pathways and the immune system. These agents, while usually producing a lesser degree (or no) myelosuppression, are associated with distinct infectious considerations. A full review of every class of these agents is beyond the scope of this review the scope review, but general principles are listed below [171].

Immune checkpoint inhibitors, approved in >15 different cancers and growing, activate the anti-tumor T cell response by blocking programmed cell death-1/ligand-1 (PD-1/PD-L1). These agents do not appear to produce immunosuppression, and might even be hypothesized to have protective effects against some infections, as they are being tested with some success as therapeutics for severe chronic infections such as progressive multifocal leukoencephalopathy (PML) and mucormycosis [172,173]. One theoretical concern for ICIs is that they could exacerbate viral-induced inflammation to cause more pronounced autoimmune-like organ damage. A case of fulminant and fatal encephalitis following pembrolizumab was found to have low-positive Epstein Barr Virus (EBV) titers and T cells specific for, or with high homology to known EBV epitopes [174]. There have also been isolated case reports of tuberculosis reactivation, and possibly other latent infections such as varicella zoster virus in the setting of ICI use [175-177]. Therefore, a high index of suspicion should be entertained in presentations that are compatible with tuberculosis, although this appears to be a rare event. At this point, however, most links between immune-related toxicity from anti-PD-1/PD-L1 and infections are speculative.

A greater concern surrounding ICIs relates to treatment for immune-related toxicities [178-182]. The mainstay of therapy, high-dose corticosteroids, may produce risks for opportunistic infections. While the usual 4-6 week steroid taper is not associated with substantial infectious risks, many patients require more prolonged dosing or additional immunosuppressive agents. In these patients, a variety of opportunistic infections has been reported. One series of patients treated with combination anti-PD-1 and ipilimumab reported occasional cases of *P. jirovecii* pneumonia and invasive fungal infection in patients treated with corticosteroids +/- infliximab [177]. Thus, efforts to use steroid-sparing agents should be implemented in patients requiring prolonged immunosuppression (e.g. those >6 weeks). *P. jirovecii* prophylaxis should be used in patients with more prolonged tapers. Immune-mediated neutropenic sepsis is a rare presentation; such patients require standard neutropenic sepsis management initially, but may require high dose steroids and immunosuppression if neutropenia persists [183,184].

Oncogene or other targeted therapies target various cell signaling pathways, growth factors, or epigenetic proteins. Agents are variably myelosuppressive (Table 6), while others have other infectious considerations. Agents that treat T cell malignancies, such as alemtuzumab, directly deplete these cellular populations, and are beyond the scope of this

review. We will briefly review several classes of small molecule inhibitors and targeted monoclonal antibodies.

Therapeutic class	Examples	Mechanism of action	Infectious complication(s)	Other notes
Immune checkpoint inhibitors	Nivolumab, pembrolizumab, ipilimumab, atezolizumab	T cell activation by removing negative regulators	Possible reactivation of latent infections	Steroid-related complications arising from treatment of immune-related adverse events.
Anti-CD20	Rituximab, obinotuzumab, ofatumumab	B cell depletion	Susceptibility to encapsulated bacteria	May be ameliorated by intravenous immunoglobulin
Bruton's tyrosine kinase inhibitors	Ibrutinib, acalabrutinib	Impaired B cell signaling	Susceptibility to bacterial infections	
Anti-VEGF	Bevacizumab, axitinib, sunitinib	Blockade of blood vessel formation	Wound healing impaired	
Other tyrosine kinase inhibitors	Imatinib, erlotinib, crizotinib, dabrafenib	Blockade of various cancer cell signaling pathways	Diverse, ranging from myelosuppression (imatinib), superinfections from skin rash (erlotinib, trametinib)	
CAR-T cell therapy	Tisengenlecleucel, axicabtagene ciloleucel	T cells targeting cell surface molecules (e.g. CD20)	As with B cell depletion	Also may mask intercurrent infections following infusion due to CRS

Table 6. Therapeutic class of targeted and immune therapies and associations with infectious complications.

First, B cell-directed therapies used to treat B cell malignancies produce varying degrees of B cell depletion and/or dysfunction. Monoclonal antibodies to CD20, a B cell surface marker, including rituximab, ofatumumab, and obinotuzumab, are associated with depleted B cell numbers for at least 6-9 months. Although infectious complications appear slightly higher in rituximab + chemotherapy compared with chemotherapy alone, the rate of severe and opportunistic infections has been similar between rituximab and placebo in rheumatoid arthritis studies [185,186]. Hepatitis B may also be reactivated with rituximab; a black box warning was added in 2011 for this complication. Bruton's tyrosine kinase inhibitors, which block a key downstream signal from the B cell receptor, critical to maintaining B cell survival, include ibrutinib and acalabrutinib. High rates of infection (up to 70% in one study) have been reported with ibrutinib, rituximab, and bendamustine, but it is not clear that this

is higher than rituximab and bendamustine alone [187]. Opportunistic infections also occur with ibrutinib, but it also remains unclear whether other concurrent agents, or the immunosuppressive nature of CLL are the culprits [188]. Phosphatidylinositol 3-kinase-δ (PI3K-δ) inhibitors, also used in CLL for B cell signaling suppression, appear to be associated with higher rates of severe infection, including *P. jirovecii* and bacterial pneumonia [189].

Many tyrosine kinase inhibitors (TKIs), including those targeting BCR-ABL, HER2, BRAF, MEK, ALK, and EGFR, are also in widespread use. BCR-ABL inhibitors, which have revolutionized the treatment of CML and gastrointestinal stromal tumor (GIST), are associated with uncommon reactivation of hepatitis B and varicella zoster virus [190]. Imatinib is associated with grade 3 neutropenia in 15-20% of patients. Dasatinib may be the BCR-ABL protein tyrosine kinase inhibitor most associated with infectious complications [191]. Other kinase inhibitors appear to have minimal infectious risks. These include inhibitors of ALK (anaplastic lymphoma kinase), EGFR (epidermal growth factor receptor), BRAF (B Raf kinase), and MEK (MAP/ERK kinase). EGFR and MEK inhibitors are associated with a hyperproliferative rash, which may be superinfected; thus, these should be monitored closely. Oral doxycycline or minocycline is recommended for grade 2 (eruptions involving at least 10-30% of body surface area) [192]. Inhibitors of vascular endothelial growth factor (VEGF) are commonly used in renal and hepatocellular cancers, and in combination with chemotherapy in ovarian and lung cancers. These agents impair wound healing, which can predispose to post-surgical or other wound infections. Several studies have suggested that monoclonal antibodies targeting VEGF in combination with chemotherapy are associated with higher rates of infection [193,194], although the infectious risks of anti-VEGF TKIs as monotherapy do not appear to be severe.

Cellular therapies, a new class of therapeutics, have also made inroads in recent years. Chimeric antigen receptor T cells (CAR-T) involve the genetic insertion of a T cell receptor specific for a cell surface antigen, which does not require binding of human leucocyte antigen (HLA) [195]. Approved therapies currently focus on CD19, an immature B cell surface protein, resulting in long-term depletion of B cells. Thus, patients may be at higher risk of infectious complications, although the long-term risks are not well defined. In addition, patients may also experience cytokine release syndrome (CRS), which mimics sepsis in many cases. Thus, patients with fever and hypotension (which are often already

cytopenic from lymphodepleting chemotherapy) may require empiric antibiotics. Tumor infiltrating lymphocyte (TILs) regimens involve surgical resection of a tumor, lymphocyte harvest and stimulation, lympho-depleting therapy, reinfusion of T cells, and high-dose interleukin-2 (IL-2) and although not currently approved have shown promising activity in melanoma and cervical cancer [196]. These therapies, which are not associated with infectious risks (apart from the lympho-depleting chemotherapy), present similar infectious considerations as CAR-T, specifically fever and hypotension, which may mask or mimic infection.

10. Expert opinion

Notwithstanding advances in bone marrow/hematopoietic stem cell transplantation, gene therapy and gene editing represent future innovations that may enable correction of single gene abnormalities in hematological cancers, as well as some types of solid cancers. With respect to current clinical management, prevention of neutropenic fever using G-CSF is a vital strategy to decrease the risk of infections in patients undergoing myelosuppressive chemotherapy. In the past, the use of G-CSF has been limited by cost. However, the development of biosimilar formulations will decrease such costs and will increase access to these treatments globally.

Although the outcome of patients with low-risk neutropenic fever is favorable, the prognosis of patients at high risk remains poor. Low-risk patients should be managed ambulatory or admitted to hospital and discharged early. The MASCC risk index and the CISNE risk index have helped identify low-risk patients. In the future, the identification of novel biomarkers may refine these indexes. In high-risk patients, the ultimate goal in managing neutropenic sepsis is to develop both early pathogen panels to identify causative infective organisms within 24 hours of presentation and establish the role of adjuvant therapies, such as antibody therapies, in the management of those with high-risk neutropenic sepsis.

Early pathogen identification and further delineation using clinical and biomarker parameters will also improve ambulatory outpatient management of patients presenting with neutropenic fever. It is essential to maintain the safety and sustainability of emergency oncology services alongside provision of personalized toxicity management that mirrors routine cancer care.

Emerging bacterial resistance remains a significant problem in the treatment of infective complications in cancer patients. Novel antibiotics should be prescribed under strict regulations.

Treatment advances have largely included development of new antibiotics, albeit at a slow pace, characterized by novel mechanisms of action and enhanced spectrum of activity against resistant bacterial pathogens. Recent approaches have focused on the use of alternative therapeutics in combination with antibiotic therapies in countering multi-drug resistant pathogens. Strategies such as engineered lytic bacteriophages, neutralizing antibodies, and synthetic antimicrobial peptides are currently in the preclinical, as well as the early and advanced clinical phases of development and hold promise as potential pathogen-directed therapies. Preclinical models also suggest a potential role for ICIs and chimeric antigen receptor therapies in augmenting pathogen clearance in acute severe infections. Inhaled TLR agonists/antagonists also have the potential to modulate innate immune responses against bacterial and viral infections in preclinical models and may have broad application in the prevention of infection in the immunocompromised cancer patients.

Infections in the setting of cancer will likely continue to shift from those associated with myelosuppression from cytotoxic chemotherapy towards those stemming from disruptions to the immune system by novel targeted or immune-based therapy. As such, identifying the impact of novel therapies on immune function early in development will be a key goal for maintaining patient safety and preventing infectious complications. In addition, in cancers with multiple options with similar mechanism of action and similar efficacy (for example, therapies targeting the B cell receptor in CLL), rates of infection may prove to be key considerations in determining which agent is used for individual patients.

Fortunately, many novel agents have either stimulatory or no effect on host immune function, including ICIs and novel cellular therapies. However, novel combination therapies, including chemotherapy and immune therapies, may produce complex effects on immune function and susceptibility to microbial infection. Further, as with many cellular therapies (such as CAR-T), the novel agent may be given following myelosuppressive chemotherapy and produce symptoms that are clinically indistinguishable from infection (including cytokine release syndrome). Thus, while overall rates of infection may decrease

with novel therapies, the complexity of identifying and managing diverse infections may grow over time.

11. Five-year view

Cancer treatment is changing with increased usage of targeted therapy and immunotherapy-based treatments. The use of myelosuppressive chemotherapy treatments will remain one of the primary treatment modalities in the foreseeable future. The cost of G-CSF will decrease with the introduction of biosimilar formulations. There will be a global decrease in FN incidence due to the usage of prophylactic G-CSF. Opportunistic and fungal infections will, however, remain a significant problem in cancer treatment, particularly for patients receiving intensive chemotherapy for hematological malignancies and bone marrow transplant recipients. The overall incidence of infection may decrease with the increased usage of novel therapies. However, the complexity of identifying and managing infective complications in cancer patients may increase in the future. The identification of cost-effective biomarkers of infections will be critical for the management of these patients.

12. Article highlights

- Patients with cancer have a significant risk of infection resulting in considerable morbidity and mortality;
- Hematological malignancies are associated with immune dysfunction resulting in increased susceptibility to infection from an early stage;
- Patients with solid tumors have a predisposition for the development of infections later in the course of the disease and are associated with systemic inflammation and immunosuppression, immunosenescence, comorbidities, poor nutrition, smoking, and anatomical obstruction;
- Febrile neutropenia is considered a medical emergency and treated with empirical antibiotics to cover the most likely pathogens that will cause life-threatening infections in neutropenic patients;
- Low-risk febrile neutropenic patients with a MASCC risk index greater than 21 should be considered candidates for outpatient antibiotic therapy;
- Prophylactic use of G-CSF is a therapeutic strategy for maintaining the chemotherapy relative dose intensity during treatment, decreasing the incidence of severe neutropenia and FN, and improving treatment outcomes and quality of life;

• Amphotericin B formulations, newer triazoles (posaconazole, voriconazole, isavuconazole), and the echinocandins (caspofungin, micafungin, anidulafungin) are the preferred agents for the empiric treatment of neutropenic fever and patients with severe and invasive fungal infections;
• Immune checkpoint inhibitors do not appear to produce immunosuppression; however, high-dose corticosteroids used to treat immune-related adverse events increase the risks for development of opportunistic infections.

13. Authors' contributions

All of the authors contributed equally to the conceptualization of the manuscript; BLR, TC, DBJ, VS and RA shared equally in drafting of the manuscript, while TC, BLR, DBJ and RA provided additional expert input and editorial oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

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15. Conflict of Interests

TC, RA, and VRS have no conflict of interest to declare. BR reports grants, personal fees and non-financial support from Sandoz, speaker engagements from Teva, speaker engagements from Amgen South Africa and speaker engagements from Mylan South Africa, during the conduct of the study. DBJ reports Ad board from Array Biopharma, grants and Ad board from BMS, Ad board from Catalyst Biopharma, Ad board from Jansen, Ad board from Iovance, Ad board from Merck, Ad board from Novartis and grants from Incyte, outside the submitted work.

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