

Review

Risk Factors for Infections, Antibiotic Therapy, and Its Impact on Cancer Therapy Outcomes for Patients with Solid Tumors

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Abstract: Infections represent a significant cause of morbidity and mortality in cancer patients. Multiple factors related to the patient, tumor, and cancer therapy can affect the risk of infection in patients with solid tumors. A thorough understanding of such factors can aid in the identification of patients with substantial risk of infection, allowing medical practitioners to tailor therapy and apply prophylactic measures to avoid serious complications. The use of novel treatment modalities, including targeted therapy and immunotherapy, brings diagnostic and therapeutic challenges into the management of infections in cancer patients. A growing body of evidence suggests that antibiotic therapy can modulate both toxicity and antitumor response induced by chemotherapy, radiotherapy, and especially immunotherapy. This article provides a comprehensive review of potential risk factors for infections and therapeutic approaches for the most prevalent infections in patients with solid tumors, and discusses the potential effect of antibiotic therapy on toxicity and efficacy of cancer therapy.

Keywords: infection; risk factors; antibiotic therapy; cancer; solid tumors; targeted therapy; immunotherapy



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1. Introduction

Patients with solid tumors have an increased risk of infectious complications [1]. There are several factors contributing to the susceptibility of cancer patients to infections. The tumor itself affects the host immune system by inducing a catabolic state and malnutrition, which leads to immunosuppression [2]. Tumor growth can cause obstruction of tubular organs and disruption of anatomical barriers, leading to penetration of bacteria into the bloodstream [2,3]. Radiation therapy, targeted agents, and cytotoxic drugs used in cancer therapy may further increase the risk of infections by inducing neutropenia, mucositis, and skin toxicity [3].

The incidence of sepsis is 16.4 cases per 1000 cancer patients per year, with in-hospital mortality of 37.8% in severe cases [4]. Bloodstream infections are significantly more common in patients with hematologic malignancies than in those with solid tumors. Interestingly, while there is a significant downward trend in bloodstream infection in hematologic patients over time, the incidence remains stable in patients with solid tumors [5]. Infections are one of the leading causes of mortality in cancer patients, and the rate of fatal infections is approximately three times higher than that of the general population [6]. This underscores the importance of appropriate management of infections in cancer patients.

2. Immunosuppression in Cancer Patients

Patients with solid tumors are generally considered to be immunocompromised, with the level of immunosuppression depending on the tumor, patient characteristics, and therapy regimen used [7]. There are a number of differences between patients with solid tumors and those with hematologic malignancies. First, the neoplastic process of those with solid tumors does not involve the effectors of the host immune system. Second, the therapy of solid tumors usually does not lead to prolonged neutropenia [3]. Consequently, the incidence of infections in patients with solid tumors is significantly lower compared to hematologic patients [5,8,9]. Prophylactic use of antibiotics is, therefore, rarely used for patients with solid tumors. A possible exception is the use of trimethoprim/sulfamethoxazole for the prevention of *Pneumocystis jirovecii* pneumonia in patients receiving temozolomide together with radiation therapy, and moderate-to-high-dose corticosteroid therapy (prednisone equivalents ≥ 20 mg for ≥ 4 weeks) [7].

3. Immunosuppression Induced by Chemotherapy

The immunosuppressive activity of cytotoxic drugs is usually expressed as their potential to induce febrile neutropenia (FN; defined as oral temperature of >38.3 °C or two consecutive readings of >38.0 °C for two hours together with an absolute neutrophil count [ANC] of $<0.5 \times 10^9$ /L, or expected to decline below 0.5×10^9 /L) [10]. Chemotherapy regimens are usually divided into three risk groups according to the likelihood of FN: high risk ($>20\%$), intermediate risk (10–20%), and low risk ($<10\%$). Common chemotherapy regimens for the therapy of solid tumors with a significant risk of FN are listed in Table 1. Patients treated with high-risk regimens benefit from the primary prophylactic use of granulocyte colony-stimulating factors (G-CSF) [7,10,11]. The indication of G-CSF use in the intermediate-risk group is based on the presence of additional risk factors, including age > 65 years, advanced disease, history of FN, no antibiotic prophylaxis, poor performance status, patient's comorbidities, open wounds, previous chemotherapy or radiation therapy, bone marrow involvement with tumor, and poor nutritional status [11,12].

Table 1. Selected chemotherapy regimens with a significant risk of febrile neutropenia.

Tumor Type	Chemotherapy Regimen	Risk of FN (%)	Reference
Breast cancer	AC (Doxorubicin/Cyclophosphamide)	7–13 *	Truong et al. [13]
	AC→D (Doxorubicin/Cyclophosphamide→Docetaxel)	25	Perez et al. [14]
	TAC (Docetaxel/Doxorubicin/Cyclophosphamide)	22	Von Minckwitz et al. [15]
	TC (Docetaxel/Cyclophosphamide)	70	Kosaka et al. [16]
	TCH (Docetaxel/Carboplatin/Trastuzumab)	41	Gilbar et al. [17]
	Docetaxel	17	Marty et al. [18]
Bladder cancer	MVAC (Methotrexate/Vinblastine/Doxorubicin/Cisplatin)	26	Sternberg et al. [19]
Cervical cancer	Cisplatin/Paclitaxel	28	Rose et al. [20]
	Cisplatin/Topotecan	18	Long et al. [21]
Gastric cancer	DCF (Docetaxel/Cisplatin/5-FU) †	29	Van Cutsem et al. [22]
	TCF (Docetaxel/Cisplatin/5-FU) ‡	41	Roth et al. [23]
	ECF (Epirubicin/Cisplatin/5-FU)	13–18	Roth et al. [23], Cunningham et al. [24]
	ECX (Epirubicin/Cisplatin/Capecitabine)	11	Cunningham et al. [24]
Germ cell tumors	BEP (Bleomycin/Etoposide/Cisplatin)	13	Fossa et al. [25]
	EP (Etoposide/Cisplatin)	10	Motzer et al. [26]
	VIP (Etoposide/Ifosfamide/Cisplatin)	15	Fujiwara et al. [27]
	VeIP (Vinblastine/Etoposide/Cisplatin)	67	Miller et al. [28]
	TIP (Paclitaxel/Ifosfamide/Cisplatin)	48	Kondagunta et al. [29]
HNSCC	TPF (Docetaxel/Cisplatin/5-FU)	11	Pointreau et al. [30]

Table 1. Cont.

Tumor Type	Chemotherapy Regimen	Risk of FN (%)	Reference
NSCLC	Cisplatin/Paclitaxel	16	Schiller et al. [31]
	Cisplatin/Vinorelbine	22	Pujol et al. [32]
	Cisplatin/Docetaxel	5–11	Fossella et al. [33], Schiller et al. [31]
	Cisplatin/Etoposide	54 [§]	Font et al. [34]
	Docetaxel/Carboplatin	12 [¶]	Cardenal et al. [35]
Ovarian cancer	Topotecan	26	Millward et al. [36]
	Docetaxel	42	Swisher et al. [37]
	Paclitaxel	33	Verschraegen et al. [38]
Pancreatic cancer	FOLFIRINOX (5-FU/Leucovorin/Oxaliplatin/Irinotecan)	22	Omura et al. [39]
SCLC	FOLFIRINOX (5-FU/Leucovorin/Oxaliplatin/Irinotecan)	17	Hosein et al. [40]
	Etoposide/Carboplatin	14	Yilmaz et al. [41]
	Topotecan	28	Von Pawel et al. [42]
	ICE (Ifosfamide/Carboplatin/Etoposide)	24	Lorigan et al. [43]
Soft tissue sarcoma	CAV (Cyclophosphamide/Doxorubicin/Vincristine)	14	White et al. [44]
	MAID (Mesna/Doxorubicin/Ifosfamide/Dacarbazine)	58	Binh Nguyen et al. [45]
	Ifosfamide	18 [#] , 20 ^{##}	Lorigan et al. [46]

5-FU–5-fluorouracil, HNSCC–Head and neck squamous cell carcinoma, NSCLC–Non-small cell lung cancer, SCLC–Small cell lung cancer, * Results from a systematic meta-analysis (randomized controlled trials and observational studies, respectively), [†] Docetaxel 75 mg/m² D1 + Cisplatin 75 mg/m² D1 + 5-FU 750 mg/m²/day D1–5 q3w, [‡] Docetaxel 85 mg/m² D1 + Cisplatin 75 mg/m² D1 + 5-FU 300 mg/m²/day D1–14, [§] Cisplatin 35 mg/m² D1–3 + Etoposide 200 mg/m² D1–3, [¶] Cisplatin 100 mg/m² D1 + Etoposide 100 mg/m² D1–3, [#] Ifosfamide 3 g/m² 3-h infusion D1–3, ^{##} Ifosfamide 9 g/m² continuous D1–3. For more information, see Aapro et al. (2011) [11].

4. Immunosuppression Induced by Targeted Therapy

Besides cytostatic therapy, some targeted agents used in the therapy of solid tumors show immunosuppressive activity. Inhibitors of the mammalian target of rapamycin (mTOR inhibitors—everolimus, temsirolimus) are known to induce immunosuppression by altering the balance between effector T cells and regulatory T cells (Tregs), and inhibiting NK cells, B cells, antigen presenting cells, neutrophils, and mast cells [47]. Consequently, patients treated with mTOR inhibitors have an increased risk of all-grade (RR = 2.00; 95% CI, 1.76–2.28, P < 0.001) and high-grade (RR = 2.60; 95% CI, 1.54–4.41, P < 0.001) infections [48]. Most infections affect the respiratory tract (61.7%), followed by genitourinary tract (29.4%) and skin/soft tissue (4.2%) infections [48]. In addition, patients treated with mTOR inhibitors can develop non-infectious pneumonitis, which may cause diagnostic problems [49]. Currently, there are no specific recommendations for antimicrobial prophylaxis in patients treated with mTOR inhibitors, although a high level of alertness is required [50].

Other targeted agents, such as BRAF kinase inhibitors (dabrafenib, encorafenib, vemurafenib) and multi-target protein kinase inhibitors (sorafenib), do not show a direct immunosuppressive effect, but the therapy may be associated with neutropenia and/or lymphocytopenia [7]. Similarly, therapy with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors used in the therapy of breast cancer (palbociclib and ribociclib) is associated with a high incidence of neutropenia [51]. However, despite this relatively high incidence, few patients develop FN, and infectious complications are rare [51]. This can be attributed to the fact that CDK 4/6 inhibitor-induced bone marrow suppression occurs through cell-cycle arrest with no apoptosis and is therefore reversible upon therapy withdrawal [52]. This is in contrast to chemotherapy, which can induce apoptosis of hematopoietic precursor and progenitor cells. Furthermore, mucositis and skin toxicity, which are considered risk factors for infections in chemotherapy-related neutropenia, are rare in CDK 4/6 inhibitor therapy [51]. Leucopenia is rare in another CDK 4/6 inhibitor, abemaciclib, which is explained by it being a more potent inhibitor of CDK4 than CDK6 [53].

Immune checkpoint inhibitors (ICIs), including anti-CTLA-4, anti-PD-1, and anti-PD-L1 monoclonal antibodies, do not confer a higher risk for infectious complications.

However, they can induce immune-related adverse events (irAEs), necessitating the use of corticosteroids and other immunosuppressive drugs [50]. Adequate prophylaxis should be used, depending on the level of induced immunosuppression and the drugs used [7]. One of the most common irAEs—immune-mediated colitis—can lead to disruption of the mucosal barrier, resulting in bacteremia and intestinal perforation with peritonitis [54].

5. Risk Scores for Febrile Neutropenia

Considering the complexity of risk factors for FN, there has been an effort to develop risk scores capable of predicting the risk for individual patients. Several studies developed risk scores for FN [55–59], some of which have been prospectively validated [56,58]. The overview of these studies, including independent risk factors for FN, is shown in Table 2. Aagaard et al. introduced an internally validated risk score for FN during the first cycle of chemotherapy (the FENCE Score) [57]. Recently, an update providing cycle-specific risk for FN (during cycle 2–6) in solid tumors has been published [59]. Such risk scores could be used to predict the risk of FN in a particular patient and initiate preventive measures, including the use of G-CSF in high-risk patients, although external validation in large prospective trials is required [59].

Table 2. Independent risk factors for FN in solid tumors (risk score model studies).

Reference	Study Population	Risk Factors (Multivariate Analysis)
Aagaard et al. (2018) [57]	Patients with solid tumors and DLBCL treated with first-line chemotherapy ($n = 9458$)	Female sex, age > 65 years, cancer type, disease stage, low albumin, elevated bilirubin, low estimated glomerular filtration rate, infection before baseline, treatment with more than one chemotherapy drug (two to four), receiving taxane-based chemotherapy
Aagaard et al. (2020) [59]	Patients with solid tumors who initiated cycle 2 of standard first-line chemotherapy ($n = 6885$)	Higher predicted risk for FN in the first cycle, platinum- and taxane-containing regimens, concurrent radiotherapy, treatment in cycle 2 compared to later cycles, previous FN or neutropenia, not receiving G-CSF
Hosmer et al. (2011) [55]	Elderly patients with breast, lung, colorectal, and prostate cancer ($n = 58,053$)	Advanced age at diagnosis, number of associated comorbid conditions, receipt of immunosuppressive chemotherapy, receipt of chemotherapy within one month of diagnosis
Lyman et al. (2011) [56] *	Patients with breast, lung, colorectal, ovarian cancer, and lymphoma patients ($n = 4458$)	Prior chemotherapy, use of other immunosuppressive medications, abnormal hepatic and renal function, low white blood count, chemotherapy and planned delivery $\geq 85\%$, small cell lung cancer, specific classes of chemotherapy (anthracyclines, taxanes, certain alkylating agents [cyclophosphamide, ifosfamide], class I/II topoisomerase inhibitors, platinum derivatives [cisplatin, carboplatin], gemcitabine, vinorelbine)
Razzaghdoust et al. (2018) [58] *	Patients with various solid tumors and lymphomas ($n = 305$)	High-risk chemotherapy regimen without G-CSF, intermediate-risk regimen without G-CSF, age > 65 years, elevated ferritin, BMI < 1.73 kg/m ² , BSA < 2 m ² , estimated glomerular filtration rate < 60 mL/min/1.73 m ² , elevated C-reactive protein

* prospectively validated studies, DLBCL—Diffuse large B-cell lymphoma, FN—febrile neutropenia, G-CSF—Granulocyte colony-stimulating factors, BMI—body mass index, BSA—body surface area.

6. Risk Factors for Infections in Patients with Solid Tumors

Patients with solid tumors are a heterogeneous group regarding the risk of infection complications [1]. The National Comprehensive Cancer Network (NCCN) guidelines determine three risk categories based on the overall risk of developing an infection (low-, intermediate-, and high-risk categories) [7]. Most patients with solid tumors belong to the low-risk (standard chemotherapy regimens with anticipated neutropenia <7 days) and intermediate-risk categories (anticipated neutropenia 7–10 days) [7]. Besides the depth and

duration of immunosuppression, the presence of specific risk factors must be considered. The most common are depicted in Figure 1. Usually, multiple risk factors are combined in one patient [3].

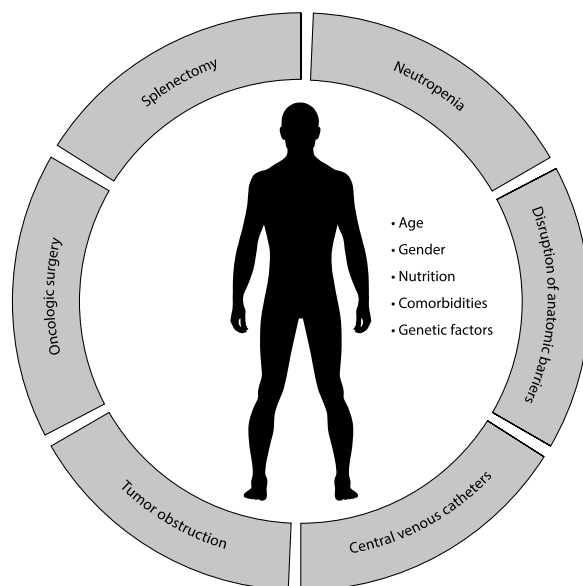


Figure 1. Factors affecting risk of infection.

6.1. Neutropenia

Severe neutropenia (grade 4) is defined as the ANC of <500 cells/ mm^3 according to the Common Terminology Criteria for Adverse Events (CTCAE) [60]. A drop of ANC below this threshold is associated with an increased risk of infections [61]. The incidence and severity of infections are inversely related to ANC, with the highest risk when ANC drops below 100 cells/ mm^3 . Duration of neutropenia is another important risk factor. Chemotherapy regimens resulting in neutropenia lasting >10 days are considered high risk [7]. However, most regimens used in the therapy of solid tumors result in neutropenia lasting <7 days and are therefore considered low risk [7].

6.2. Disruption of Anatomic Barriers

Mucositis is another important factor increasing the risk of bloodstream infections. Mucosal barriers in the gastrointestinal, urogenital, and respiratory tract constitute the first line of host defense against various pathogens [7]. The damage of mucosal barriers opens the colonizing pathogens' gateway to the bloodstream. Coexisting neutropenia allows for the rapid development of severe infections, even in the case of a low bacterial load [62]. Chemotherapy-induced mucositis is associated with an increased risk of infections caused by viridans group streptococci, gram-negative rods, and *Candida* spp. [7]. Although the risk and grade of mucositis is higher in hematologic patients receiving high-dose chemotherapy regimens with autologous hematopoietic stem cell transplantation, some of the cytotoxic drugs used in the therapy of solid tumors can induce mucositis. These include 5-fluorouracil, capecitabine, cyclophosphamide, ifosfamide, cisplatin, carboplatin, docetaxel, paclitaxel, and vinorelbine [3]. A high risk of oral mucositis is associated with some chemotherapy regimens, including DCF (86%), FOLFIRI (80%), CAF (79%), AC (71%), and FOLFOX (60%) [63]. Mucosal toxicity is also frequent in some targeted therapies, including bevacizumab, erlotinib, gefitinib, lapatinib, sorafenib, and sunitinib [64]. Oral mucositis is a typical adverse event in patients treated with mTOR inhibitors, affecting as much as 73% of patients [65]. Additionally, mucositis is a common adverse event in radiation therapy [66].

6.3. Central Venous Catheters

Central venous catheters (CVCs) are widely used in cancer patients and offer benefits to those who receive chemotherapy. However, the presence of CVCs is considered a risk factor for infections in cancer patients and may affect the etiology of bacteremia [62]. The incidence of CVC-associated bloodstream infections in cancer patients is estimated to be 0.5–10 per 1000 CVC days, with mortality ranging from 12% to 40% [67].

There are two main types of indwelling CVCs used for chemotherapy administration—centrally inserted totally implanted vascular access ports (PORTs) and peripherally inserted central catheters (PICCs) [68]. PICCs are an alternative to traditional PORTs, and their use has increased owing to their lower cost and ease of insertion and removal [68]. Several studies have compared these CVCs in terms of infection complications, with conflicting results [68–70]. A recent meta-analysis found a significantly higher risk of infectious complications in the PICC groups (RR 3.43; 95% CI 2.58–4.56; $P < 0.05$) [69]. Both the local infections of punctures and catheter-related infections were more frequent in patients with PICCs [69]. In addition, infection complications are more frequent in multi-lumen CVCs than in single-lumen CVCs [71].

Most CVC infections originate from the skin flora (65%), catheter or catheter joints (30%), or other pathways (5%) [72]. The most commonly detected pathogens causing CVC-related infections in cancer patients are coagulase-negative staphylococci, followed by other gram-positive bacteria, including *Staphylococcus aureus*, enterococci, and streptococci [67,73]. As in other bloodstream infections in cancer patients, a shift toward gram-negative flora (including *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* spp.) has been noted in CVC-related infections [74,75]. Therefore, a broad-spectrum empirical therapy covering gram-negative pathogens should be considered in CVC-related bloodstream infections [74].

6.4. Tumor Obstruction

Direct expansion of the tumor may cause obstruction of tubular organs [3]. Bronchial obstruction caused by local growth of bronchogenic carcinomas and metastatic tumors may cause post-obstructive pneumonia and occasionally be the first manifestation of the disease [76]. The post-obstructive component can be found in ~45–55% of patients with pulmonary neoplasms who develop pneumonia [77]. Bronchial obstruction develops more commonly in tumors arising centrally, such as small cell lung cancer (SCLC) and squamous cell carcinoma (SCC) [78]. Pathogens causing post-obstructive pneumonia include gram-positive organisms (*St. aureus* [incl. MRSA], viridans group streptococci, beta-hemolytic streptococci [groups A, B, C, F, and G]), gram-negative organisms (*E. coli*, *Klebsiella* spp., other Enterobacteriaceae, *Ps. aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* spp.), anaerobes (*Peptococcus* spp., *Peptostreptococcus* spp., *Fusobacterium nucleatum*, *Bacteroides* spp.), and fungi (*Candida* spp.) [79]. Despite therapy with broad-spectrum antibiotics, responses tend to be low, and persistent or recurrent infections are common. Moreover, ~10–15% of patients develop severe complications, including lung abscess, empyema, hemorrhage, and fistula formation [77].

Obstructive uropathy is a frequent complication of advanced solid tumors, especially prostate, retroperitoneal, and pelvic tumors [80]. It is usually managed by placing a ureteral stent or permanent nephrostomy tube (PNT) [81]. However, the presence of PNT in cancer patients is associated with a high risk of PNT-associated pyelonephritis (with a rate of 19%) [82]. Patients with a history of previous urinary tract infection (UTI) and neutropenia are at higher risk [82]. Many pathogens are capable of forming biofilms on indwelling implants, including *E. coli*, *Enterococcus faecalis*, *Ps. aeruginosa*, *Proteus mirabilis*, *St. aureus*, and *Candida* spp. [82]. Eradication of these microorganisms is challenging, and long-term suppressive antibiotic therapy may be required in patients with recurrent urosepsis [3]. Nevertheless, prophylactic antibiotic therapy does not seem to prevent the development of pyelonephritis and asymptomatic bacteriuria in cancer patients with PNT [82]. In addition to complicated UTIs, patients with prostatic carcinoma may develop prostatitis and prostatic abscesses [3].

Malignant biliary obstruction (MBO) is caused by pancreatic adenocarcinoma, cholangiocarcinoma, ampullary/duodenal adenocarcinoma, gallbladder carcinoma, lymphoma, and compressive metastatic proximal lymph nodes [83]. Pancreatic adenocarcinoma is the most common cause of MBO, and as many as 70–90% of pancreatic cancer patients develop jaundice during the course of their disease [84]. MBO frequently results in ascending cholangitis, which may be the initial manifestation of underlying malignancy [3]. In cases of persistent obstruction, hepatic abscesses may develop [85]. The etiology is usually polymicrobial, with enteric gram-negative rods, *Enterococcus* spp., and anaerobes being most common [86]. Management of MBO includes percutaneous transhepatic biliary drainage [87] and endoscopic retrograde cholangiopancreatography (ERCP) with the placement of plastic or self-expandable metallic stents (SEMS), which is considered the current mainstay of treatment [84,88]. In patients with resectable disease, up-front surgery without a stent placement is an option and does not increase the risk of complications compared to preoperative biliary drainage [84].

Additionally, large tumors can overgrow the capacity of their blood supply and become necrotic, forming the seeds of infection. Direct invasion of colorectal cancer through the mucosa may lead to abscess formation and sepsis by enteric bacteria [7].

6.5. Oncologic Surgery

Patients who undergo extensive tumor resection are at increased risk for postoperative nosocomial infection, especially in tumors involving the respiratory and gastrointestinal tract [1]. In a large retrospective study, the rate of serious postoperative infections was 9.4% and led to a nearly 12-fold increase in the odds of in-hospital mortality [89]. Surgical procedures associated with the highest risk of serious infections were esophagectomy (25%), gastrectomy (19%), pancreas resection (17%), and lung resection (10%). The incidence of infections is significantly lower in high-volume centers than in low-volume hospitals [89]. Besides the type of surgery, the risk of infection may be related to the tumor burden, preoperative performance status, and previous therapy [7]. However, it seems that surgical and intensive care unit-related factors play a more significant role than previous oncologic therapy [62].

6.6. Splenectomy and Function Asplenia

The number of indications for splenectomy in cancer patients has declined over the years. In the case of solid tumors, splenectomy is traditionally performed in gastric cancer to dissect the splenic hilar lymph nodes, although it seems to have no benefit in tumors located at lesser curvature [90]. Splenectomy may also be performed in cases of oligometastatic disease from other sites, especially ovarian cancer [91]. Additionally, intraoperative splenic injury during abdominal surgery may result in splenectomy [92]. Besides surgical splenectomy resulting in asplenia, radiotherapy and some pathologic conditions (including graft versus host disease following allogeneic hematopoietic stem cell transplantation) lead to a decreased function of the spleen—hyposplenism (function asplenia) [7].

The spleen is a lymphoid organ that plays an important role in regulating immune homeostasis through both innate and adaptive immunity. The function of the spleen is crucial in the elimination of encapsulated bacteria [93]. Asplenic patients are therefore at risk of sepsis caused by encapsulated bacteria—most commonly *Streptococcus pneumoniae* (50–70%), but also *Haemophilus influenzae* and *Neisseria meningitidis* (15–25% each) [94]. Other pathogens causing serious infections in asplenic patients include *Capnocytophaga canimorsus* after animal bites, *Bordetella holmesii*, *Ehrlichia* spp., and intraerythrocytic parasites such as *Babesia* spp. after tick bites [94].

6.7. Patient-Related Factors

6.7.1. Age

Age is an important factor regarding the risk for infections. Age-related changes in the immune system, referred to as immunosenescence, play a major role in increased sus-

ceptibility to infections in elderly patients [95]. Other risk factors for infections frequently present in elderly patients include malnutrition, comorbidities, age-related organ changes, functional dysfunction (i.e., impairments in the performance of activities of daily living), polypharmacy, and social factors [96,97]. Furthermore, age is associated with an increased risk of FN [98], owing to reduced bone marrow reserves and reduced renal and hepatic functions [99].

6.7.2. Gender

Men are at increased risk for most infections. The explanation for this observation is rather complex and involves both biological and social factors [100]. Sexual steroid hormones play an important role in susceptibility to infections through differential modulation of pro-inflammatory and anti-inflammatory cytokine expression, toll-like receptor expression, antibody production, metabolism, growth, and virulence of pathogenic bacteria [101]. Estrogens can enhance both cell-mediated and humoral immune responses, while progesterone and testosterone have anti-inflammatory effects and suppress innate immune responses [100–102]. Additionally, it seems that genetic factors related to sex chromosomes (X and Y) may play a part [103], and differences in occupational activities and lifestyle result in different exposures to pathogens [100].

In contrast to the overall lower risk of infections in the female population, UTIs and genital tract infections are more common in women owing to anatomic and physiological differences [104]. Available data suggest that female gender is a risk factor for the development of FN [98,105]. One possible explanation is that female patients are more frequently treated with breast cancer chemotherapy regimens, which confer a higher risk for FN (up to 23% in standard chemotherapy and 98% in high-dose chemotherapy regimens) [106]. Gender-related differences in pharmacokinetics and pharmacodynamics of anticancer drugs provide another rationale [107]. A recent study has found that polymorphisms of genes involved in drug metabolism are distributed unevenly in women and men, and that these polymorphisms have different impacts on adverse event occurrence (including FN) between genders [108].

6.7.3. Nutrition

Malnutrition affects as many as 75% of cancer patients, with the highest prevalence in those with tumors of the gastrointestinal tract [109]. The association between malnutrition and infections is well-established and can be explained by impaired cell-mediated immunity, phagocyte function, cytokine production, and complement system function [110]. Therefore, improvement of the patient's nutritional status is of great importance to reduce the risk of infections and improve survival [111].

Obesity is associated with an increased risk of infections when compared to normal-weight subjects [112,113]. The highest increase was observed for skin infections in both genders and for gastrointestinal tract infections, UTIs, and sepsis in obese women [113]. The underlying mechanisms involve altered adipokine signaling (e.g., leptin, adiponectin), immune system dysregulation, impaired chemotaxis, and metabolic changes [112,114].

6.7.4. Comorbidities

Many internal diseases are associated with an increased risk of infection. Patients with type 1 and 2 diabetes are at increased risk of all infections, particularly bone and joint infections, sepsis, and cellulitis [115]. Chronic kidney disease is associated with an increased risk of infections, especially in patients undergoing hemodialysis [116,117]. Patients with chronic obstructive pulmonary disease (COPD) are more likely to develop respiratory infections, but the incidence of infections outside the respiratory tract does not seem to be affected [118]. An increased risk of infections is observed in patients with rheumatological disorders owing to both altered function of the immune system and immunosuppressive therapy [119]. Opportunistic infections, including *P. jirovecii*, are

particularly common [120]. Other comorbidities with increased risk of infection include chronic heart failure [121] and cirrhosis [122].

6.7.5. Genetic Factors

Defects in innate and adaptive immunity are naturally associated with an increased risk of infections [123]. Single nucleotide polymorphisms (SNPs) in genes involved in cytotoxic drug metabolism are associated with an increased risk of FN [98]. In breast cancer patients treated with the FEC (5-FU + epirubicin + cyclophosphamide) regimen, *MDM2* SNP309 and *TP53* R72P genotypes [124], as well as SNPs of the *ABCC1/MRP1*, *UGT2B7*, and *FGFR4* genes [125], were significantly associated with an increased risk of FN. *UGT1A1* gene polymorphism is associated with increased risk of FN in patients treated with irinotecan [126–128]. Similarly, *DPYD* gene polymorphism resulting in dihydropyrimidine dehydrogenase (DPD) deficiency is associated with significant toxicity, including FN, in patients treated with fluoropyrimidines [127]. Prospective validation of these polymorphisms as predictive factors for FN could identify patients at high risk of infectious complications and suggest treatment deescalation or application of prophylactic measures in affected individuals [127].

7. Antibiotic Therapy in Patients with Solid Tumors

Early detection of infections is essential in cancer patients. Clinical signs of infection might be vague, especially in neutropenic patients, but fever remains an early, although non-specific, sign of infection [129]. Approximately 50–60% of patients who became febrile have an underlying infection [130]. However, non-infectious causes of fever, including paraneoplastic etiology (neoplastic fever) and drug reactions, are not rare in cancer patients [131]. Moreover, laboratory markers of infection, including elevated C-reactive protein and leukocytosis, are frequently present in cancer patients [132,133], making the diagnosis of infection challenging. In such circumstances, additional markers such as procalcitonin can be used [134].

The symptoms-oriented diagnostic process should be initiated as soon as possible with identification of the most likely infection source. The empiric antibiotic should be initiated immediately after obtaining cultivation samples. The antibiotic choice should be tailored according to the suspected infection site, microbial colonization of the patient (i.e., known presence of multiresistant strains in previous cultivation samples), and the local epidemiological situation [10]. The most likely tumor-specific infections should be ruled out first, including cholangitis in pancreatic cancer, obstructive pneumonia in lung tumors, urinary infection in prostate cancer patients, etc. [135].

The use of antibiotics with broad-spectrum coverage, including anti-pseudomonal activity, is recommended in patients presenting with severe neutropenia [7]. Deescalation of the antibiotic therapy should be performed as soon as the results of cultivation samples are available, and the duration of antibiotic therapy should be tailored to the type of infection, level of immunosuppression, and other risk factors (type of malignancy, anticancer therapy, patient's comorbidities, etc.). It should be kept in mind that prolonged antibiotic therapy can lead to severe complications, including vulvovaginal candidosis in women, *Clostridioides difficile* infection (CDI), and possible detrimental effects on anticancer therapy effectiveness due to dysmicrobia [136].

The rise in multiresistant strains of bacteria (including extended-spectrum β -lactamase [ESBL]-producing *Enterobacteriaceae*, methicillin-resistant *St. aureus* [MRSA], and vancomycin-resistant *Enterococcus faecium*) has become a significant problem, especially in oncologic patients [1]. Antimicrobial stewardship and strict adherence to infection control recommendations are essential to reduce the risk of emergence and spread of multiresistant bacteria strains [3]. However, approximately one third of antibiotics prescribed in the United States acute care hospitals are either unnecessary or suboptimal [137,138]. In up to 50% of cases, the treatment indication, choice of agent, or duration of antibiotic therapy may even be incorrect [139]. This is of utmost importance considering that 30-day mortality can reach 70% in

patients with bloodstream infections not receiving appropriate antimicrobial treatment [140]. It is, therefore, the policy of many hospitals to restrict the use of broad-spectrum antibiotics unless approved by the hospital's antibiotic center. This approach can reduce treatment expenses and limit the emergence of multiresistant strains and CDI [141,142].

The advent of modern treatment modalities, including targeted therapy and immunotherapy, has brought new challenges for the management of infections in cancer patients. Targeting checkpoints of immune response with ICIs has become a new treatment strategy in many solid tumors, including melanoma, renal cell carcinoma, lung cancer, and others. Despite great improvements in patients' survival, a new class of adverse events, known as immune-related adverse events (irAE), has emerged [143]. This form of autoimmune reaction can affect various organs and be potentially life-threatening. Importantly, the discrimination between irAE and infectious complications may be challenging. This is of high clinical significance, considering that corticosteroids and other immunosuppressants used in irAE management may aggravate the course of infectious diseases and increase the risk of opportunistic infections [144]. Improper use of antibiotics in patients treated with ICIs may weaken the treatment outcome via antibiotic-induced dysbiosis [145]. Therefore, antibiotic therapy should be prescribed cautiously in patients treated with ICIs, and the diagnosis of infection should be confirmed with appropriate tests. Narrow-spectrum antibiotics are the preferred option in this setting, and consultation with the hospital's antibiotic center before treatment initiation is highly encouraged [145].

8. Antibiotic Therapy of Specific Infections

8.1. Febrile Neutropenia

FN represents a severe and potentially life-threatening complication of cancer therapy, with an overall in-hospital mortality of ~10% [10]. The definition and risk factors for FN in patients with solid tumors have already been addressed. The management of FN follows international guidelines with slight variations reflecting national differences (i.e., local epidemiological situation and prevalence of multiresistant strains) [10,146].

The first step is to stratify patients into risk categories based on clinical characteristics (nature of the underlying malignancy, comorbidities, performance status, presence of hypotension, dehydration, and stress-induced hyperglycemia at presentation, outpatient status, and age). Evaluation of these characteristics allows us to stratify patients into low- and high-risk groups using the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index Score [10] or Clinical Index of Stable Febrile Neutropenia (CISNE) score [147], the latter having been specifically validated for patients with solid tumors. FN patients within the high-risk group or having high-risk features as assessed by the admitting physician should be admitted to hospital and administered broad-spectrum antibiotics intravenously within one hour of admission (Table 3) [7,10]. Local epidemiological bacterial isolate and resistance patterns are crucial to determining the optimal empirical antibiotic therapy [10]. Inadequate antibiotic regimen use is associated with a significantly higher ICU admission and death rate during hospital stay [148]. Culture specimens, including two sets of blood cultures (from a peripheral vein and any indwelling venous catheter), urine specimens, and specimens from any suspected site of infection, should be obtained before antibiotic therapy initiation [7,10].

Patients at low risk of developing serious complications (<10%) may receive oral antibiotics in an outpatient setting after being provided careful patient education [146]. Outpatients should be instructed on how to monitor their symptoms and when and how to contact appropriate medical services. Compliance of the patient and ability to reach the healthcare facility are prerequisites for this approach [149].

Table 3. Appropriate initial antibiotics in febrile neutropenia groups with different risk of serious infection development.

Risk of Serious Complications	Low	High
Initial antibiotic	Oral or parenteral Inpatient or outpatient Amoxicillin-clavulanate + fluoroquinolone (ciprofloxacin or levofloxacin)	Parenteral Inpatient Antipseudomonal beta-lactam * (cefepime or meropenem or imipenem or piperacillin-tazobactam)
Suspicion of catheter-related infection, severe skin and soft tissue infection, pneumonia, or risk of MRSA infection	Shift to high-risk group	Add gram-positive bacteria targeted antibiotic (vancomycin or linezolid or daptomycin [†]), in case of VRE add linezolid or daptomycin [†]
Suspicion of abdominal infection	Shift to high-risk group	Add metronidazole
Risk of multiresistant strain infection	Shift to high-risk group	Choose carbapenem (in case of ESBL), add polymyxin-colistin or tigecycline (in cases of KPC)

ESBL—extended-spectrum beta-lactamase producing strains, KPC—carbapenemase producing strains, MRSA—methicillin-resistant *St. aureus*, VRE—vancomycin-resistant enterococci, * choice depends on the local epidemiological situation, [†] not in cases of pneumonia. References: [10,146,150,151].

8.2. Central Venous Catheter-Related Infections

CVC-related infections represent ~10% of bloodstream infections in cancer patients [152, 153]. In case of suspected CVC-related infection, blood culture from the CVC and peripheral vein must be performed in order to determine differential time to positivity. A difference in time to positivity of >2 h (blood culture from CVC must be the first positive) is a highly sensitive and specific CVC-related infection indicator [154].

In particular situations, it might not be necessary to remove the infected CVC, and antimicrobial therapy alone is sufficient. The main premise for such an approach is a stable patient and the assumption of successful antimicrobial therapy without developing complications (Table 4) [155,156]. There is no consensus regarding the length of antimicrobial therapy. However, a recent meta-analysis suggests that a short-course therapy (seven days) for gram-negative bacteria, seven days for enterococci, and three days for coagulase-negative staphylococci could be sufficient in uncomplicated CVC-related infection [157]. However, the authors conclude that shorter courses may not be appropriate for immunocompromised patients, and prospective studies are warranted [157]. In case of complications, including tunnel infection, port abscess, septic thrombosis, endocarditis, and osteomyelitis, the catheter must always be removed, and appropriate pathogen-directed antimicrobial therapy should be used [155].

Another therapeutic option for stable patients with catheter-related infections caused by low-virulence pathogens—coagulase-negative staphylococci (except from *Staphylococcus lugdunensis*), *Corynebacterium* spp., and some gram-negative rods—is the use of antimicrobial lock therapy (ALT) either with or without delayed CVC removal [158]. This approach should only be used in combination with systemic administration of antibiotics [155,158]. The choice of antimicrobial agent depends on the type of isolated pathogen (Table 5). The dwell time of the lock solution differs according to the stability of the substance solution at the body temperature, but it should not exceed 48–72 h [158]. The type of CVC or port determines the volume of instilled antibiotic lock solution, which is ~2–5 mL. The most frequent antibiotics used for ALT are listed in Table 5. Appropriate duration of ALT is unknown, but generally 10–14 day therapy is recommended [155]. Importantly, the lock solution must be removed before catheter reuse.

Besides therapy for CVC-related infections, prophylactic ALT might decrease the incidence of central-line associated infections in cancer patients [159]. This approach seems promising and has demonstrated its cost-effectiveness specifically in cancer therapy [160], although further studies are warranted to optimize prophylactic ALT use.

Table 4. Appropriate antibiotic treatment of bacterial CVC-related infection according to isolated pathogens.

Isolated Pathogen	Catheter Removal	Antibiotic Therapy	
		Choice	Duration
Coagulase-negative staphylococci	Not necessary Risk factor for recurrence	Vancomycin Oxacillin * Flucloxacillin * Cefazoline *	Catheter removed: 5–7 days Retained catheter: 10–14 days + ALT 10–14 days
<i>St. aureus</i> , <i>St. lugdunensis</i>	Yes	Vancomycin Oxacillin * Flucloxacillin * Cefazoline *	≥14 days. Necessary to rule out complications. Complications: 4–6 weeks
Enterococci	Yes Long-term CVC may retain	Vancomycin Ampicillin *	5–14 days. Retained long-term CVC: 7–14 days + ALT 7–14 days
gram-negative bacilli	Yes, especially in case of multiresistant bacteria CVC retaining unsuitable for immunosuppressed patients	Based on severity of disease: Piperacillin/tazobactam *, 4th gen. Cephalosporin *, Carbapenem +/- Aminoglycoside *	7–14 days

* According to sensitivity pattern and local susceptibility data. CVC—central venous catheter, ALT—antimicrobial lock therapy. References: [155,156].

Table 5. List of the most frequently used antibiotic catheter lock solutions.

Antibiotic	Spectrum of Bacteria	Concentration * (mg/mL)	Heparin Content (IU/mL)	Stability (Hours)	References
Vancomycin	gram-positive	2.0–5.0	2500 or 5000	72	[161,162]
Teicoplanin	gram-positive	5.0–10.0	0 or 100	96	[163,164]
Daptomycin	gram-positive	5.0	0 or 5000	72	[165]
Gentamicin	gram-positive, gram-negative	1.0–5.0	0, 2500 or 5000	72	[166,167]
Amikacin	gram-positive, gram-negative	1.0–40.0 †	0 or 5000	72	[168]
Ceftazidime	gram-negative	0.5–10.0	0 or 5000	48	[167,169,170]
Cefazolin	Methicillin-sensitive staphylococci	5.0–10.0	2500 or 5000	72	[168]
Ciprofloxacin	gram-negative	0.2–5.0	0 or 5000	48	[171,172]
Ampicillin	Ampicillin-sensitive enterococci	10.0	10 or 5000	8 ‡	[161]
Ethanol	gram-positive, gram-negative	70%	0	24	[173]

* Concentration should exceed 100–1000× minimal inhibitory concentration (MIC). † Most commonly used 2.0 mg/mL, ‡ according to SPC [174]. For more detailed information on ACL see Justo et al. [168].

8.3. Pneumonia

Cancer patients are at increased risk of pneumonia due to impaired immune function caused by the tumor itself and cancer therapy [175], together with frequent tumor obstruction causing post-obstructive pneumonia [79]. The therapy of community-acquired pneumonia in cancer patients who are not neutropenic does not differ from that of the general population and should follow respective guidelines [7]. Beta-lactam antibiotics are the mainstay of therapy, but the choice depends on the local epidemiological situation (i.e., the local level of pneumococcal resistance). Antibiotics covering atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) are necessary for patients with community-acquired pneumonia [10]. In patients requiring hospital admission, respiratory fluoroquinolone or a combination of macrolide with a third generation cephalosporin (ceftriaxone or cefotaxime) or ertapenem are the options [7]. Besides gram-positive and gram-negative activity (excluding *Ps. aeruginosa* and *Acinetobacter* spp.), ertapenem has anaerobic activity useful for suspected aspiration and post-obstructive pneumonia [7,176]. Severe community-acquired pneumonia and pneumonia in neutropenic patients should be treated with a combination of an antipseudomonal beta-lactam (piperacillin/tazobactam) and a respiratory fluoroquinolone or azithromycin [7,10].

In patients who come from a medical facility or are long-term oncologically treated and repeatedly hospitalized, etiological microorganisms of pneumonia have changed, and therefore the empirical choice of antibiotic should be different, covering *St. aureus*, *Ps. aeruginosa*, or other gram-negative rods: piperacillin/tazobactam, cefepime, or carbapenems in combination with antibiotics covering gram-positive cocci (linezolid, vancomycin, or teicoplanin) [177]. In this regard, the choice of initial antibiotic regimen should be based on knowledge of the local patterns of antibiotic susceptibility [7,177]. Clinical samples, including good-quality sputum, lower respiratory tract samples for culture, viral (influenza, COVID-19), mycoplasma, chlamydial PCR detection, and urine samples for detection of pneumococcal and legionella antigens, should be obtained before antibiotic therapy initiation in case of severe pneumonia in immunocompromised patients [178,179]. Microbiological results can help to deescalate and target antibiotic treatment [177]. In patients receiving a prednisone equivalent of ≥ 20 mg for ≥ 4 months, or treated with RT and concomitant temozolomide without reliable antipneumocystis prophylaxis, the addition of high-dose trimethoprim/sulfamethoxazole should be considered [7,10].

8.4. Intra-Abdominal Infections

In addition to common intra-abdominal infections, cancer patients are at risk for infections complicating the underlying disease (infiltration of intra-abdominal organs by tumor, compression of adjacent organs by the tumor and associated stagnation of secretions, tumor disintegration with subsequent rupture, or creation of intra-abdominal or pelvic abscess) [180]. Antibiotic choice depends on the patient's condition, previous antibiotic treatment, and colonization with multidrug-resistant bacteria. A high probability of polymicrobial pathogens and the presence of endogenous anaerobic flora has to be kept in mind [7]. Initial empirical treatment is based on administration of beta-lactam antibiotics (ampicillin/sulbactam, piperacillin/tazobactam, cefotaxime, ceftriaxone, carbapenem). If second-, third-, or fourth-generation cephalosporins are used, it is necessary to add metronidazole to cover anaerobic bacteria [10,180]. Antibiotic therapy with antipseudomonal activity is required in neutropenic patients [7]. Repeated cultivation of suitable materials (i.e., secretion from the drain, deep wound sample, and puncture fluid) may be required to avoid long-term administration of broad-spectrum antibiotics [180,181].

Cancer patients are susceptible to developing CDI as a result of the malignancy itself, immunosuppression, chemotherapy administration, antibiotic exposure, and frequent hospital stays [182]. This translates into a six- to nine-fold higher risk of developing CDI compared to non-cancer patients [183]. Orally administered fidaxomicin or vancomycin are the treatment of choice in initial and subsequent CDI episodes [184]. Orally administered metronidazole should be restricted to non-severe CDI cases when the above-mentioned agents are not available [184]. Fecal microbiota transplantation seems promising in the management of recurrent CDI, albeit the data in cancer patients are limited [7].

Neutropenic enterocolitis (referred to as typhlitis when located in the caecum) is not common in patients with solid tumors, but its association with taxanes (docetaxel, paclitaxel) and vinorelbine therapy has been reported [3]. Computed tomography is the preferred diagnostic tool for revealing thickening of the bowel wall [185]. The therapy consists of general supportive measures (including bowel rest and parenteral nutrition) and broad-spectrum antibiotics with coverage for *C. difficile*, aerobic pathogens, and anaerobic pathogens [3,7]. Complications develop in ~5% of patients requiring surgical intervention [186].

8.5. Urinary Tract Infections

UTIs are common in cancer patients due to cancer therapy, immunosuppression, and indwelling urinary catheters [187–189]. Importantly, the urinary tract is the source of ~20% of bloodstream infections in cancer patients [152,153]. The most common pathogens include *E. coli* (40–58%), *Kl. pneumoniae* (10–25%), *Ps. aeruginosa* (4–11%), *Enterococcus* spp. (8–11%), *Staphylococcus* spp. (11%), and *P. mirabilis* (1–5%) [187,188]. Multidrug resistance is frequent in cancer patients with UTIs (96%) [188]. A high proportion of resistance to

fluoroquinolones (90–96%), cephalosporins (68–80%), and aminoglycosides (46–50%) has been observed [189,190].

Uncomplicated UTIs (women without risk factors) can be treated according to general guidelines with orally administered fosfomycin, pivmecillinam, or nitrofurantoin [191]. Treatment with antimicrobials penetrating the prostate tissue (trimethoprim/sulfamethoxazole or fluoroquinolone) is required in male patients, provided cystitis can be associated with prostatitis [191]. However, most UTIs in oncological patients are associated with other risk factors, including anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, stents, renal disease, cancer-related immunosuppression, oncologic therapy, and surgical intervention [3,80]. Antimicrobial therapy should be guided by cultivation results, as repeated antibiotic therapy in cancer patients may lead to the selection of non-predictable bacterial variants and multiresistant strains [192]. Antimicrobial agents with extended spectrum of activity (piperacillin/tazobactam, imipenem, meropenem, ceftazidime/avibactam, ceftolozane/tazobactam) should be used for empirical treatment of severe infections in accordance with previous individual culture or local resistance data [191]. A switch to narrow-spectrum antibiotics should be performed as soon as the results of antibiotic sensitivity tests are available to avoid unnecessary adverse effects and ecological consequences [191,192]. Treatment for 7–14 days is generally recommended, but the duration should be guided by the therapy of the underlying abnormality [191,192].

9. The Impact of Antibiotic Therapy on Cancer Therapy Outcomes

Despite the undeniable contribution of antibiotic therapy to the management of infections in cancer patients, a potential detrimental effect on treatment outcome and toxicity has to be considered [193,194]. Several contributing factors have been proposed to decrease the efficacy of cancer therapy, the most prominent being alteration of the microbiome and its interaction with the patient's immune system, potentially resulting in reduced immune surveillance [194,195].

9.1. Impact on Cancer Therapy Efficacy

There is a growing body of evidence that antibiotic therapy can negatively affect anticancer treatment efficacy and cancer-specific survival, especially in patients treated with immunotherapy [196]. It is now understood that the microbiome alters antitumor immunity and influences the efficacy of cancer therapies mediated via systemic immune response [194]. The effect of gut microbiome composition on immunotherapy outcome is supported by the finding that fecal transplants of gut microbiota from patients responding to ICI therapy to germ-free mice results in an antitumor response [197–199]. The presence of several species of microbiota have been associated with ICI efficacy, including *Bacteroides* spp. [200], *Bifidobacterium* spp. [198,201], *Faecalibacterium* spp. [202], *Akkermansia muciniphila* [199], *Collinsella aerofaciens* [198], *E. faecium* [198], and bacteria from the Ruminococcaceae family [197]. Changing the balance and diversity of the patient's microbiome by antibiotic therapy may alter the antitumor immune response induced by ICIs, resulting in poor therapeutic outcomes [145]. Multiple clinical studies have reported a negative association between antibiotic use and response to ICIs in different solid tumors, including melanoma [203,204], NSCLC [203,205–208], and RCC [203,205,209]. Additionally, several meta-analyses have confirmed these results [210–212]. Interestingly, the negative effect of antibiotics on survival was also observed in adjuvant therapy with ICIs [204]. The most detrimental effect on overall survival in the multivariate analysis was observed in patients treated with penicillins, cephalosporins, and fluoroquinolones [204]. In light of these findings, the use of broad-spectrum antibiotics should be avoided in patients treated with immunotherapy whenever possible [195]. In addition to the antibiotic class, the length of antibiotic therapy seems to play an important role, as the detrimental effect was most commonly observed in patients receiving multiple or prolonged cycles of antibiotic therapy [203,207].

Besides affecting the efficacy of immunotherapy, the use of antibiotics can potentiate the effect of radiotherapy. Vancomycin, a glycopeptide antibiotic active against gram-positive bacteria with minimal absorption from the gut when administered orally, showed a potentiating antitumor effect when combined with radiotherapy in a preclinical model [213]. The effect was mediated through changes in gut microbiota composition, which led to increased antigen presentation by CD11c⁺ dendritic cells in the tumor-draining lymph nodes of the radiotherapy-treated mice. Interestingly, the vancomycin effect was abrogated by butyrate, a metabolite produced by vancomycin-depleted gut bacteria [213]. Recently, these results were confirmed by another study, suggesting that butyrate-producing bacteria, such as Lachnospiraceae and Ruminococcaceae, could be novel therapeutic targets [214].

Conversely, antibiotic therapy during curative chemoradiotherapy in patients with locally advanced head and neck cancers was associated with a significant reduction of progression-free survival, overall survival, and disease-specific survival [215]. The potential harm of broad-spectrum and prophylactic antibiotic therapy in these patients should, therefore, be considered [215].

9.2. Impact on Cancer Therapy Toxicity

In addition to possible pharmacokinetic interactions, the use of antibiotics can lead to increased toxicity of anticancer drugs by modulation of microbiome [195]. In patients with metastatic pancreatic adenocarcinoma treated with gemcitabine, antibiotic therapy was associated with increased chemotherapy-related toxicity [216]. The authors suggest that intratumor bacteria may be responsible for a clinically meaningful portion of gemcitabine metabolism [216]. In melanoma patients treated with immunotherapy, the use of antibiotics was associated with moderate to severe immune-mediated colitis [204]. The underlying mechanism seems to involve changes in the gut microbiome, resulting in inhibition of regulatory T cells [217] together with regrowth of pro-inflammation bacterial species [204].

10. Conclusions

Infections are one of the most common causes of death in patients with solid tumors and can complicate cancer therapy. Thorough evaluation of possible risk factors could identify patients at high risk for infections and aid in the decision-making process regarding the use of G-CSF and antibiotics. In this regard, prognostic scores considering multiple risk factors together are being evaluated to calculate each individual patient's risk. Early initiation of antibiotic therapy is essential, especially in immunocompromised patients. However, other pathologic conditions mimicking infection, including irAE in patients treated with ICIs, have to be excluded first. Consultation with the hospital's antibiotic center before antibiotic therapy initiation and strict adherence to the antibiotic stewardship program is highly encouraged to reduce the occurrence of multidrug-resistant pathogens and decrease therapy costs. Potential risks of antibiotic therapy in cancer patients have to be considered, including potential detrimental effects on treatment efficacy and toxicity. This holds especially true for patients treated with ICIs, for whom antibiotic therapy should be restricted to unequivocally diagnosed infections, and broad-spectrum antibiotics should be avoided.

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