Chapter 2

Pharmacologic Considerations in Oncology Critical Care

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Additional information is available at the end of the chapter

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Abstract

Critical care in the oncology population consists of diverse levels of diseases, syndromes, and emergencies that are not observed in typical medically-ill patients and, with it, comes even more specialized treatment strategies. Therefore, the uncommon or less well-understood pharmacologic considerations in this population must be discussed to better assist any clinician at the bedside. This chapter outlines some of the situations commonly encountered in this setting such as the challenge of treating and preventing infectious diseases when the patient lacks the ability to mount appropriate immune responses to conventional therapy, the paradigm of treating thromboembolism in the group of patients who are at highest risk for both bleeding and clotting and treatment of acute and long-term consequences of cancer or chemotherapy requiring escalation of care to the intensive care unit (ICU).

Keywords: pharmacology, pharmacokinetics, pharmacodynamics, treatment, therapy

1. Introduction

Common diseases and syndromes are identified in intensive care unit (ICU) oncology patients secondary to the progression of cancer or chemotherapy. Such challenges include frequent infections, thromboembolism with concomitant bleeding in lieu of sepsis, and toxicity from chemotherapy, leading to emergent ICU admission. The optimal treatment strategies for these syndromes become especially challenging in ICU patients with multi-system organ failure and tenuous clinical status. Furthermore, specific pharmacologic differences exist not only in ICU but more specifically in oncology patients. Therefore, we sought to provide clinicians with information that would help them make the appropriate and safest decisions when selecting therapy for such critically ill patients.

2. Antimicrobial therapy in oncology patients with sepsis

"Patients with cancer have a 30% higher risk for death from sepsis which accounts for approximately 10% of all cancer deaths" [1]. Hematologic cancers (66.4 per 1000) have a higher mortality rate and are more likely to develop severe sepsis compared to solid tumors (7.6 per 1000). The source of sepsis can be related to the site of the primary tumor as observed in the frequency with which lung cancer patients acquire respiratory infections or prostate cancer patients acquire genitourinary infections [1]. Disruption in mucosal and integumentary systems, neutropenia, cellular and humoral immune dysfunction, splenectomy, presences of indwelling vascular catheters, and local tumor effects are some risk factors of developing infection in cancer patients.

It is necessary to understand the preferred regimens so therapy can be tailored to the most likely source of infection. Furthermore, it is crucial to optimize the pharmacodynamics of antimicrobials in critically ill oncology patients to augment outcomes. Outlined here are several of the infectious disease-related phenomena unique to the critically ill oncology population including the treatment regimens. Guidelines should be referenced for the appropriate time to de-escalate or discontinue treatment regimens. Furthermore, primary antibiotic choice should be based on local susceptibility patterns and formulary agents.

2.1. Neurosurgical-related bacterial meningitis

Bacterial meningitis is one of the most common CNS infections in hematopoietic stem cell transplant and neurosurgical patients who are commonly transferred after surgery to the ICU for continued post-op monitoring of intracranial pressure (ICP), cerebral perfusion pressure (CPP), and neurological status. Patients with primary and systemic metastasis from brain tumors who had neurosurgical procedures account for 25% of cancer patients who develop CNS infections. Risk factors include barrier disruption, poor wound healing due to radiation therapy, and those with Ommaya reservoirs frequently used for fluid sampling and chemotherapy. A retrospective study evaluated 146 patients who developed meningitis after undergoing neurosurgery within 1 year. The most common organisms identified to cause the infections were *Staphylococcus epidermidis* (28.1%); *Staphylococcus hominis* (11.0%); *Staphylococcus haemolyticus* (9.6%); *Staphylococcus aureus* (8.2%); and *Enterococcus* (8.2%). *Propionibacter acnes* is another underappreciated gram-positive anaerobe bacteria, which is commonly associated with various types of implant-associated infections including neurosurgical shunts. With *Propionibacter acnes* belonging to the normal skin microbiota, it can easily cause early shunt infections when theses microorganisms are introduced during surgery [2]. Gram-negative bacteria must also be considered in this type of infection with *Klebsiella pneumoniae* (7.5%) being the most common, followed by *Acinetobacter baumannii* (2.1%), *Pseudomonas aeruginosa* (1.4%), and *Escherichia coli* (1.4%). Empiric therapy should consist of a beta-lactam antibiotic that has adequate CNS penetration (i.e., cefepime, meropenem, or ceftazidime) in addition to an agent that covers MRSA (i.e., vancomycin). The agents of choice for the treatment of specific organisms are listed in **Table 1**, along with other common fungi known to cause meningitis in the oncology critically ill patient.

Organism	Primary regimen	Alternative regimen
Ampicillin susceptible Enterococcus species	Ampicillin plus gentamicin	–
Ampicillin resistant Enterococcus species	Vancomycin[1] plus gentamicin	–
Enterococcus species Ampicillin and Vancomycin resistant	Linezolid	–
Escherichia coli and other Enterobacteriaceae	Ceftriaxone or cefotaxime	Aztreonam, Ciprofloxacin, meropenem, SMX/TMP
Listeria monocytogenes	Ampicillin or Pen G	SMX/TMP,, meropenem
Methicillin susceptible Staph aureus	Nafcillin or oxacillin	Vancomycin[1], meropenem
Methicillin resistant Staph aureus	Vancomycin[1]	SMX/TMP, Linezolid
Staphylococcus epidermidis	Vancomycin[1]	Linezolid
Streptococcus pneumoniae	Penicillin MIC <0.1 μg/mL: Pen G or ampicillin 0.1–1 μg/mL: ceftriaxone or cefotaxime ≥2 μg/mL: Vancomycin[1] + ceftriaxone or cefotaxime	Penicillin MIC <0.1 μg/mL: ceftriaxone cefotaxime 0.1–1 μg/mL:, meropenem ≥2 μg/mL: moxifloxacin
Propionibacterium acnes	Vancomycin[1] plus cefepime Vancomycin[1] plus ceftazidime Vancomycin[1] plus meropenem	–
Pseudomonas aeruginosa	Cefepime or ceftazidime	Aztreonam, ciprofloxacin meropenem PLUS Aminoglycoside

Pen, penicillin; SMX/TMP, sulfamethoxazole/trimethoprim.
[1] See vancomycin section for dosing.

Table 1. Agent of choice for bacterial meningitis based on culture identification [3, 4].

2.2. Catheter-associated urinary tract infections

Urinary tract infections (UTIs) are frequently encountered in oncology critically ill patients due to frequent use of indwelling urinary catheters, urological procedures including ureteric stent placements, neutropenia, and prolonged use of steroids. One hospital evaluated 115 patients with advanced cancer who had positive cultures in an eight (8)-month period. As the predominate infection, 61% of UTIs occurred in patients with indwelling catheters. Gram-negative organisms were the most common bacteria isolated, and patients receiving corticosteroids had the highest rate of UTIs [5]. One study included 22 patients with malignancy and

found in 57 original ureteric stents, 25 (44%) had bacterial colonization. Not all colonization will lead to true UTIs. However, if the urine culture is positive or the leukocyte count is greater than 30 on urinalysis, then antibiotic use and removal or change of the stent should be considered due to stent colonization [6]. A lack of strong data exists for initiating prolonged prophylactic antibiotics after stent placement to prevent such infections. Therefore, it is important to treat based on whether the patient is symptomatic and an accurate diagnosis of an active infection. Literature on empiric regimens, specifically in the oncology population, is unavailable, and therefore, it is recommended a broad-spectrum beta-lactam antibiotic be used with the addition of an antipseudomonal antibiotic if pseudomonas is suspected. Hemodynamically stable patients may be candidates for single-agent therapy such as a fluoroquinolone. Duration of therapy should be based on clinical response with therapy continued for 10–14 days if response is delayed [7].

2.3. Post-obstructive pneumonia

Post-obstructive pneumonia is frequently encountered in patients with cancer and can quickly lead to ICU admission if symptoms become severe. This type of pneumonia is defined as a "radiographic opacification resulting from complete or partial airway obstruction by a pulmonary neoplasm" [8]. The findings can be a result of non-infectious (mucus plugging, parenchymal inflammation, or tumor) or infectious causes. Patients will often present with severe cough, wheezing, and dyspnea, but these symptoms can be misleading making it difficult to determine the need for antibiotic therapy. For example, patients may not have signs of infection such as fever, chills, and leukocytosis and still have a microbe isolated. More commonly, an infection is present if the patient has an infiltrate in addition to a fever [8]. The majority of post-obstructive pneumonias are polymicrobial caused by *Haemophilus influenza, Klebsiella pneumonia, Enterobacter cloacae, Acinetobacter* species, *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Streptococcus viridans*. Management of such infections requires treating the source of obstruction through interventional bronchoscopy techniques in addition to antimicrobial therapy. Until cultures are identified, a broad-spectrum gram-negative agent (i.e., cefepime) in addition to MRSA coverage should be initiated based on local susceptibility patterns. Treatment should be considered for at least 7–10 days, similar to health-care-associated pneumonias and based on patient's clinical improvement.

2.4. Fever in the oncology patient

In both the critically ill and cancer patient, fever can be a common symptom not always secondary to infection. Among 371 patients (477 episodes), fever was identified due to non-infectious causes in 23% of patients and due to unknown origin in 10% of patients [9]. Non-infectious causes, independent of tumors, can be related to an allergic reaction, thromboembolism, or an inflammatory disease. Cancer-related fever is classically associated with non-Hodgkin's and Hodgkin's lymphoma, leukemia, and solid tumors [10]. A recent study defined tumor fever as no microbiological, radiological, or clinical evidence of infection and lack of response to empirical antimicrobial therapy for at least 7 days or experienced a positive response to a naproxen test. Using this definition, the investigators evaluated the

role of a procalcitonin (PCT) test for differentiating infectious from non-infectious fever in non-neutropenic patients. The baseline PCT level was not different between those with tumor-related fever and blood stream infections. However, there was a statistically significant difference in the decrease in PCT levels between the two groups in response to antimicrobials suggesting one method for differentiating fever due to infectious versus non-infectious causes [11]. Other sources of fever which must be considered are chemotherapy (azathioprine, hydroxyurea, interleukin-2, rituximab, and interferon), transfusions, surgery, or procedures [9, 10]. Drug-induced fever is often overlooked and should be highly considered especially if the fever resolves after stopping the expected culprit. Such medications in the ICU that should be evaluated in the patient are antimicrobials, succinylcholine or inhaled anesthetics antipsychotics possibly causing neuroleptic malignant syndrome, or antidepressants leading to serotonin syndrome [12]. Fever in these patients may not present in any particular pattern, and signs of infection are attenuated due to the decreased inflammatory response so fever tends to be the only sign of ensuing infection. Therefore, it is imperative to identify fever associated with other symptoms such as rigors and chills to suggest an infectious source and initiate appropriate targeted therapy.

2.5. Vancomycin dosing in oncology patients

Since the 1950s, studies have evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) profile of vancomycin to determine the best parameter that predicts its efficacy in clinical practice. National guidelines provide broad recommendations, which should be applied as the foundation for creating institution level policies [13]. However, they lack recommendations specific to oncology patients, whose vancomycin PK is greatly altered when compared to the general population. Furthermore, critically ill patients are subject to frequent alterations in drug PK due to fluctuations in creatinine clearance, shifting of fluid leading to changes in volume of distribution, decreased tissue perfusion, and decreased metabolism with organ dysfunction all of which must be accounted for when dosing antibiotics. Several pharmacokinetic (PK) studies have shown an increased vancomycin volume of distribution (Vd) and clearance (Cl) in cancer patients, requiring these patients to receive nearly double the average dose than patients without cancer (60 vs. 30 mg/kg/day) to obtain therapeutic levels [14]. More specific data with regards to cancer type or other patient factors contributing to these changes have not been elucidated.

The PD parameter that best reflects clinical efficacy of vancomycin against *S. aureus is* AUC/MIC with a target of ≥400 h [13, 15]. It has been proposed that 3–4 g of vancomycin per day would be required for 90% probability of attaining an AUC/MIC of 400 h for an MIC of 1 mg/L and ≥5 g per day for vancomycin-intermediate susceptible *S. aureus* (VISA) strains [13]. However, readily calculating the AUC/MIC is challenging and cannot easily be performed. Subsequently, most clinical pharmacists have continued to use trough levels for determining therapeutic concentrations. Therefore, until more efficient tools are available for applying pharmacodynamics methods with AUC/MIC, it is suggested that multiple daily doses (three or four as opposed to two with same total daily dose) may be preferred to achieve target therapeutic levels in patients with hematologic malignancy and normal renal function [16]. In

the critically ill patient, vancomycin can be also be effected by augmented renal clearance (ARC) due to sepsis, trauma, autoimmune disorders, or major surgery. With AUC inversely related to renal clearance, ARC can extensively impact the PK of vancomycin and lead to subtherapeutic levels [17]. These combined factors in both oncology and critically ill patients further support the need for possibly higher doses in this population.

2.6. Extended-infusion beta-lactam therapy

Studies have shown improvement in clinical outcomes (i.e., patient survival and duration of hospitalization after onset of infection) by optimizing the pharmacodynamics with use of extended-infusion (EI) dosing regimens. The best predictor of bacterial killing for β-lactams is the time during which the free drug concentration exceeds the MIC of the organism ($fT > MIC$). Near-maximal β-lactams bactericidal effect is typically observed when the free drug concentration exceeds the MIC for 50%, and 40% of the dosing interval for penicillins and carbapenems, respectively [18–20]. With the increase in resistance among gram-negative organisms, optimizing activity of β-lactam antibiotics through dosing strategies becomes crucial to preserve clinical efficacy.

Of the most common β-lactams used in critically ill oncology patients, piperacillin–tazobactam and meropenem administered via extended infusion are associated with the most positive clinical outcomes and have a higher probability of achieving target attainment. One retrospective study assessed 194 patients who received 3.375 g IV every 4 or 6 h over a 30-min infusion, vs. 3.375 g IV every 8 h over a 4-h infusion for treatment of *P. aeruginosa* infections. Higher mortality and longer length of stay were seen with intermittent infusions (31.6% of patients) compared to EI (12.2% of patients) in the more critically ill patients. Furthermore, the Monte Carlo simulation showed the probability of target attainment (PTA) was only 20% with intermittent infusion vs. 100% PTA with EI at an MIC of 16. With the MIC breakpoint for *P. aeruginosa* to PTZ being ≤16/4, it is evident that intermittent infusions may not achieve optimal levels to be efficacious [18].

Creatinine clearance (mL/min)	Dose
Extended infusion	
≥20 mL/min	3.375 g (30-min infusion) × 1 dose STAT Followed by 3.375 gm IV q8 h via 4 h infusion
<20 mL/min (including IHD/PD)	3.375 g (30-min infusion) × 1 dose STAT, 3.375 g IV q12 h via 4 h infusion
CRRT	3.375 g (30-min infusion) × 1 dose STAT, 3.375 gm IV q8 h via 4 h infusion

CRRT, continuous renal replacement therapy; PD, peritoneal dialysis; IHD, intermittent hemodialysis.

Table 2. Extended and conventional Piperacillin-tazobactam dosing [22].

The use of loading doses prior to initiating extended infusion and time to exceeding the MIC breakpoint has also been studied. A PK model demonstrated that 90% of the patients would be expected to have PTZ and meropenem drug concentrations exceed the MIC breakpoint

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within 6 min if both agents were preceded by a loading dose versus 8 h and 36 min, respectively, without a loading dose [21]. Therefore, with sepsis guidelines providing evidence to support a mortality benefit in administering antibiotics within 60 min for patients in septic shock, a loading dose should be highly considered. Loading doses may be less important for meropenem and susceptible organisms as optimal drug concentrations were achieved with any regimen in no later than 36 min [21]. From the evidence outlined, the dosing regimens for PTZ listed in **Table 2** are recommended for critically ill oncology patients.

A retrospective, pre/post-observation study of intermittent vs. extended-infusion meropenem was conducted in hematopoietic stem-cell transplant patients and those treated with induction chemotherapy for AML. Meropenem 1 g every 8 h via short 30-min infusion (SI) was compared with 1 g every 8 h via extended 4-h infusion (EI). After 5 days of treatment, therapy was successful in more cases in the EI group than the SI group (69.4 vs. 40.9%, $p = 0.001$) [23]. Various meropenem regimens were also reviewed in a Monte Caro simulation. The probability of achieving drug concentrations above the MIC for >40% of the dosing interval for *Pseudomonas aeruginosa* were 87.9, 93.5, and 96.7% for doses of 500, 1000, and 2000 mg, respectively, and thus, higher doses may be needed for immunocompromised patients with bacteria exhibiting higher meropenem MICs (e.g., MIC >4 mg/L) [24]. Minimal evidence is available on the appropriate dosage adjustments in renal failure. However, one study did evaluate the effects of augmented renal clearance in critically ill patients on achieving target attainments with extended-infusion meropenem (1 g IV every 8 h via 3-h infusion). Patients with a creatinine clearance (CrCl) of 50 mL/min had a predicted probability of target attainment of approximately 90% which inversely declined with increases in creatinine clearance ($fT > MIC$ of ~50 and ~20% at CrCl of 100 and 150 mL/min, respectively). Therefore, critically ill patients who commonly exhibit augmented clearance should have dosing regimens optimized whenever feasible with lower doses possibly not considered until the CrCl is less than or equal to 50 mL/min [25]. Consequently, we would recommend a regimen of meropenem 2 g IV every 8 h via 3-h infusion for most critically ill oncology patients.

2.7. Treatment of multi-drug resistant organisms

As stated by the CDC, "antimicrobial resistance is one of our most serious health threats" [26]. The rate of infections caused by gram-negative organisms continues to rise and significantly contribute to morbidity and mortality worldwide [27]. First- and second-line antibiotics are no longer effective for such organisms, and thus, efforts to discover and approve new antimicrobials continue to strengthen. The patient populations deemed to be most vulnerable to resistant organisms are those receiving chemotherapy, recent hospital and intensive care unit admission, and those with invasive devices. Due to their frequent exposure to antibiotics and hospitalizations, risk of acquiring such organisms is significantly increased. Much of the data for treatment of multi-drug resistant organisms are based on case studies or retrospective studies. The multitude of data concerning appropriate treatment options for all multi-drug resistant organisms exceeds the capacity of this chapter. Therefore, primary and secondary regimens for only CRE and ESBL organisms have been described in **Tables 3** and **4**.

Infection	Regimen options
UTI	Ceftazidime/avibactam 2.5 g IV q8 h
	Fosfomycin One packet (3 grams) orally q2 to 3 days for 3 doses (can be extended to 21 days in some cases)
	Meropenem IV 2 g q8 h (3-h infusion)[3] plus Ertapenem 1 g IV q24 h (1 h after meropenem)
	Colistin IV[1,2,4] plus Meropenem 2 g q8 h (3-h infusion)[3]
Bacteremia	Colistin IV[2,4] plus Meropenem IV 2 g q8 h (3-h infusion)[3]
	Polymixin B[2] plus Meropenem 2 g IV q8 h (3-h infusion)[3]
Intra-abdominal	Ceftazidime/avibactam 2.5 g IV q8 h plus Metronidazole 500 mg IV q8 h
	Colistin IV[2,4] plus Meropenem 2 g q8 h (3 h infusion)[3]
	Polymixin B[2] plus Meropenem 2 g IV q8 h (3 h infusion)[3] plus Tigecycline 200 mg IV loading dose then 100 mg IV q12 to 24 h if meropenem MIC >16 mcg/mL and polymyxin B MIC >2 mcg/mL
ASSSI	Tigecycline 200 mg IV loading dose then 100 mg IV q12 to 24 h plus Polymixin B[2] plus Meropenem 2 g q8 h (3-h infusion)[3]

ASSSI, acute skin/skin structure infection; UTI, urinary tract infection.
[1] Colistin IV is recommended over Polymixin B for treatment of urinary tract infections based on pharmacokinetic properties. Urinary concentrations of Polymixin B remain low compared to Colistin due to Polymixin B is eliminated primarily by non-renal mechanisms.
[2] Refer to references [33] and [96] for appropriate dosing.
[3] Monitor patient closely for development of seizures with high-dose carbapenems.
[4] Not recommended for organism with MIC ≥4.

Table 3. Regimens for treatment of CRE by site of infection [25, 28–33].

Antimicrobial	Comments
Carbapenem (imipenem, **m**eropenem, ertapenem)	First-line agents
Ceftolozane/tazobactam	Only indicated for treatment of complicated intra-abdominal infections and complicated urinary tract infections including pyelonephritis (*in vitro data*)
Ceftazidime/avibactam (add Metronidazole for intra-abdominal infections)	
Tigecycline	Only indicated for treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia Limited penetration in urinary tract and blood
β-lactam/β-lactamase inhibitor combinations (amoxicillin-clavulanate, piperacillin–tazobactam, ampicillin-sulbactam)	Such agents should be reserved for treatment of ESBL organisms from the urinary tract with poor efficacy data for other sites of infections due to these organisms
Colistin	High-risk for renal toxicity
Fosfomycin	IV formulation not available in the USA Oral formulation only indicated for UTI

Table 4. Antimicrobial therapy regimens for treatment of extended-spectrum beta-lactamases (ESBL) [34–36].

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2.8. Clostridium difficile infection (CDI)

The rates of CDI continue to increase exponentially with strains becoming more virulent and difficult to treat in addition to more patients becoming colonized. Oncology patients, especially those with hematological malignancies, are particularly susceptible due to multiple risk factors such as frequent and prolonged hospitalizations, exposure to multiple courses of antibiotics, and chemotherapeutic agents. It has even been proposed that chemotherapeutic agents without concomitant antibiotics have been associated with CDI. Such incidences are most commonly reported to be caused by methotrexate and 5-FU. Methotrexate is suspected to cause severe disruption of intestinal protein metabolism causing a pronounced inflammatory cytokine response and promoting CDI. Similar effects have been seen due to irinotecan and topotecan; thus, clinicians should monitor for signs of CDI even after chemotherapy administration. Appropriate diagnostic work-ups with combination testing (i.e., glutamate dehydrogenase followed by confirmatory testing with enzyme immunoassay and quantitative real-time PCR) should be performed to differentiate between colonization and true infections (**Figures 1** and **2**) [95].

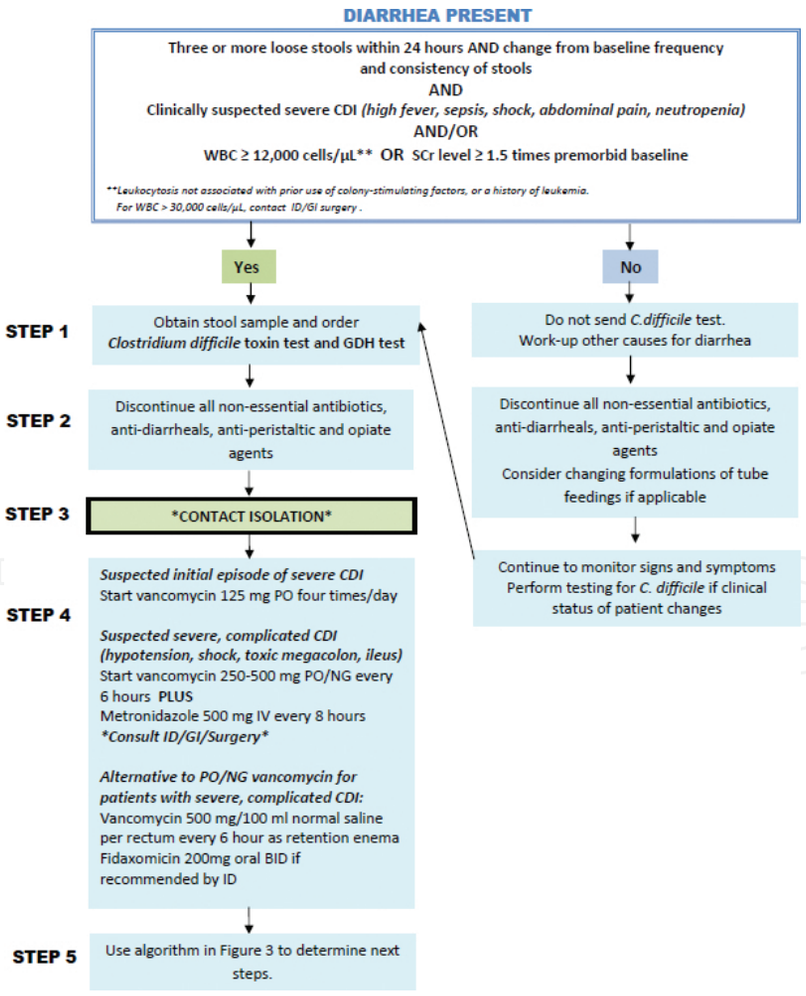

Figure 1. Diagnosis and Treatment of CDI.

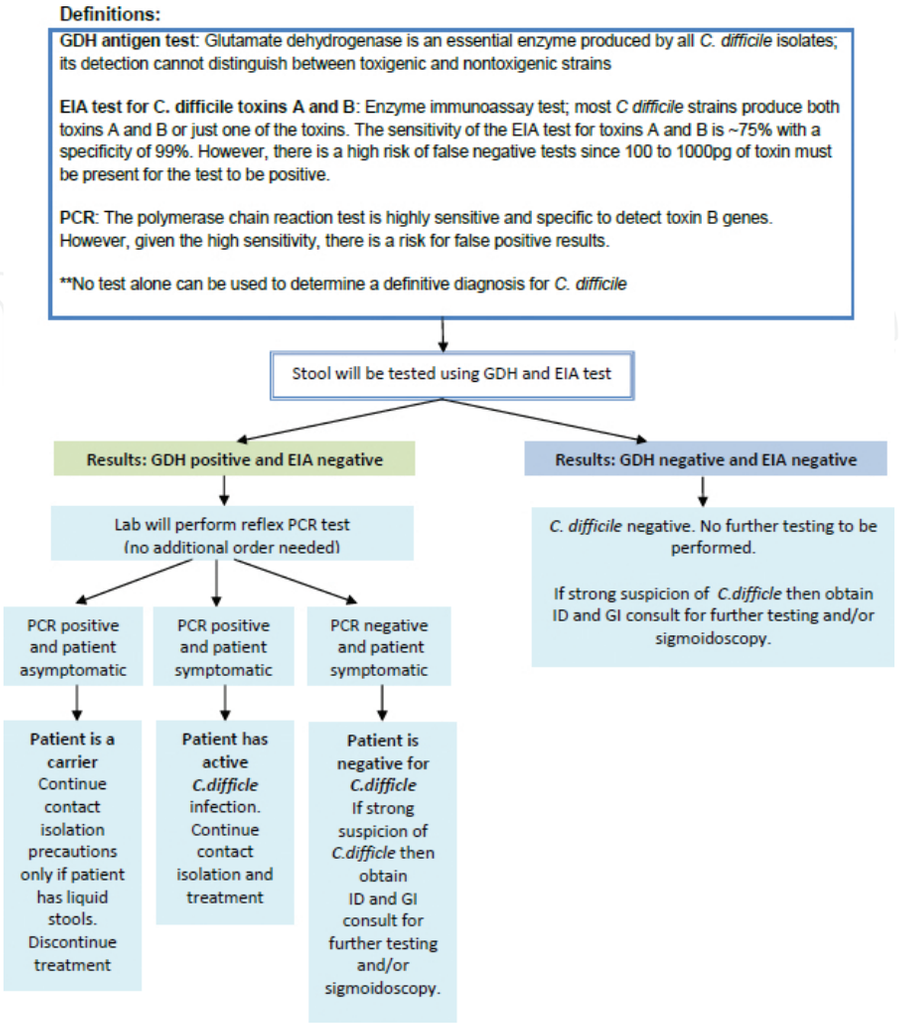

Figure 2. Appropriate *C.difficile* Testing and Interpretation.

2.9. Intra-abdominal infections

Intra-abdominal infections in cancer patients are especially common following surgery. One of the high-risk procedures being performed in several oncology centers is hyperthermic intraperitoneal chemotherapy (HIPEC) which can be associated with severe complications such as peritonitis. These patients are often transferred to the ICU for post-op monitoring and thus the ICU becomes the unit where such infections are managed. A retrospective study noted 9% of 52 patients required reoperation for post-operative peritonitis following complete cytoreductive surgery (CCRS) combined with HIPEC. The infections were most frequently caused by *E. coli* in 5 samples (71%) and Enterobacter species in two samples (29%), with seven of the nine bacteriological species being multi-drug resistant. Unfortunately, this is only one of the many intra-abdominal infections these patients can experience.

In the elderly population (>65 years), it was noted that the spectra of diseases that cause intra-abdominal sepsis are different from younger populations. The most common types in the

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elderly were diverticulitis, cholecystitis, cholangitis, and perforation of the colon from obstructing adenocarcinoma. Advanced tumors leading to perforation and then abscesses or peritonitis have been reported as frequently as 2.6–10%. This can quickly lead to severe sepsis or septic shock that requires management in the ICU. The common offending organisms identified are those of the gastrointestinal tract, *Enterococcus* species, *Candida* species, *Staphylococcus epidermidis, E. coli, Enterobacter* species, *B. fragilis*, and *Pseudomonas* species [40]. There are no guidelines available for recommendations on antimicrobial therapy specific to critically ill oncology patients, and therefore, it is recommended that combination therapy is initiated with a broad-spectrum agent with anaerobic coverage, a second gram-negative agent with activity against *Pseudomonas aeruginosa* if suspected, and an antifungal agent with activity against *Candida glabrata*.

Per IDSA guidelines, it is recommended that intravenous (IV) metronidazole is added to vanco-26mycin oral only in the "severe, complicated" cases defined by hypotension, shock, the presence of an ileus, or megaco-27lon, and not in "severe" cases (white blood cell (WBC) count of ≥15,000 cells/mL or serum creatinine ≥1.5 times base-28line) [37]. A recent retrospective, observational study evaluated mortality amongst critically ill patients who received 29 oral vancomycin vs. oral vancomycin with IV metronidazole defined by primarily clinical criteria. A total of 88 pa?30tients were evaluated including 23 immunocompromised patients. Mortality were found to be significantly better in31the combination therapy group, compared to the monotherapy group (36.4 vs. 15.9%, p = 0.03). This suggests the need32to further consider the true definition of "severe disease" vs. "critically ill" and whether selection of therapy should be33based on clinical criteria in addition to laboratory data. The study design cannot definitively provide support for all34critically ill patients receiving combination therapy; however, it does propose that IV metronidazole in addition to van-35comycin should be considered in the most severely ill patients [38]. Per IDSA guidelines, it is recommended that intravenous (IV) metronidazole is added to vanco-26mycin oral only in the "severe, complicated" cases defined by hypotension, shock, the presence of an ileus, or megaco-27lon, and not in "severe" cases (white blood cell (WBC) count of ≥15,000 cells/mL or serum creatinine ≥1.5 times base-28line) [37].

The administration of probiotics is also a common topic amongst patients who are on prolonged antibiotic2therapy for primary or secondary prevention of C. difficile. As IDSA guidelines recommended in 2010, there are limited3data to support its use and potential risk for bloodstream infections [37]. A report released by the World Health Organ-4ization (WHO) noted probiotics may be theoretically responsible for four types of side effects: (1) systemic infections,5(2) deleterious metabolic activities, (3) excessive immune stimulation in susceptible individuals, and (4) gene transfer.6There have been several case reports of infections caused by organisms consistent with probiotic strains including but7not limited to Saccharomyces boulardii, Lactobacilli, Lactobacillus acidophilus, and Lactobacillus casei [39]. Due to the use of8probiotics remaining controversial and with the lack of clinical trials to confirm the safety of these products, clinicians9are advised to remain cautious when using such products in immunocompromised patients, including those started on 10 corticosteroids, which is common in ICU patients [39].

Empiric regimens for necrotizing fasciitis	
Primary regimen	Alternative regimen
Piperacillin–tazobactam extended infusion (preferred) or intermittent infusion plus vancomycin[1]	Levofloxacin plus (clindamycin or metronidazole) plus aminoglycoside
Imipenem-cilastatin	
Meropenem	
Ertapenem	
Cefotaxime plus metronidazole or clindamycin	
Regimens based on culture data	
Streptococcus	Penicillin plus clindamycin
Clostridium species	
Aeromonas hydrophila	Doxycycline plus (ciprofloxacin or ceftriaxone)
Vibrio vulnificus	Doxycycline plus (ceftriaxone or cefotaxime)
Gram-negative organisms	Based on local susceptibility (Carbapenem for ESBL-producing organisms)

[1] See vancomycin section for dosing.

Table 5. Treatment regimens for necrotizing fasciitis [44].

2.10. Skin and soft tissue infections

Chemotherapy, radiation, and multiple surgical procedures place oncology patients at risk for developing skin and soft tissue infections. One particularly lethal skin infection that requires immediate transfer to the ICU is necrotizing fasciitis (NF) which has been more commonly associated with certain debilitating conditions such as immunosuppression. No true risk factors have been delineated, and the cause of ≥20% of necrotizing soft tissue infections is idiopathic making it challenging to determine precipitating factors. The onset and progression of signs and symptoms are rapid especially with Group A *Streptococcus* or *Clostridium* making it crucial that both surgical intervention and antibiotic intervention are considered immediately when suspecting NF [41]. In a retrospective review with 8534 hematological malignancy patients, nine (9) were diagnosed with NF. Interestingly, pathogens isolated were all gram-negative organisms (*Salmonella, Vibrio vulnificus, Aeromonas*, ESBL *Klebsiella*, ESBL *Escherichia coli*, and *Enterobacter cloacae*) [42]. Another case report was published of a febrile neutropenia patient with myelodysplastic syndrome (MDS) that experienced a blunt injury to the left upper extremity. This resulted in rapid progression of the wound with fluid accumulation that extended from the left upper arm to the proximal medial forearm. All blood cultures revealed *S. maltophilia*, and the patient was treated both surgically and with IV trimethoprim/sulfamethoxazole [43]. Although group A *Streptococcus* has

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most commonly been known as the leading cause of NF, more than one retrospective review has identified gram-negative NF associated with malignancy making it imperative for clinicians to consider broad-spectrum antibiotics that adequately cover for possible resistant organisms as shown in **Table 5** [42].

Another common skin infection in oncology patients known to be closely related to lymphedema is cellulitis. Unfortunately, every incidence of cellulitis can further damage the lymphatic system which in turn leads to secondary episodes of lymphedema. Due to the protein-rich lymphatic fluid which accumulates due to impaired drainage, bacteria can easily invade such areas and cause local cellulitis infections. Therapy should be directed at likely organisms such as *streptococcus* and patients with three to four episodes per year of recurrent cellulitis should be considered for prophylactic antibiotics (~4–52 weeks) [44, 45]. As suggested by IDSA guidelines, non-purulent soft tissue skin infections in immunocompromised patients are categorized as "severe" and should be considered for broader therapy with piperacillin–tazobactam plus vancomycin [44]. Purulent skin and soft tissue infections should undergo incision and drainage with the addition of antibiotics (**Figure 3**).

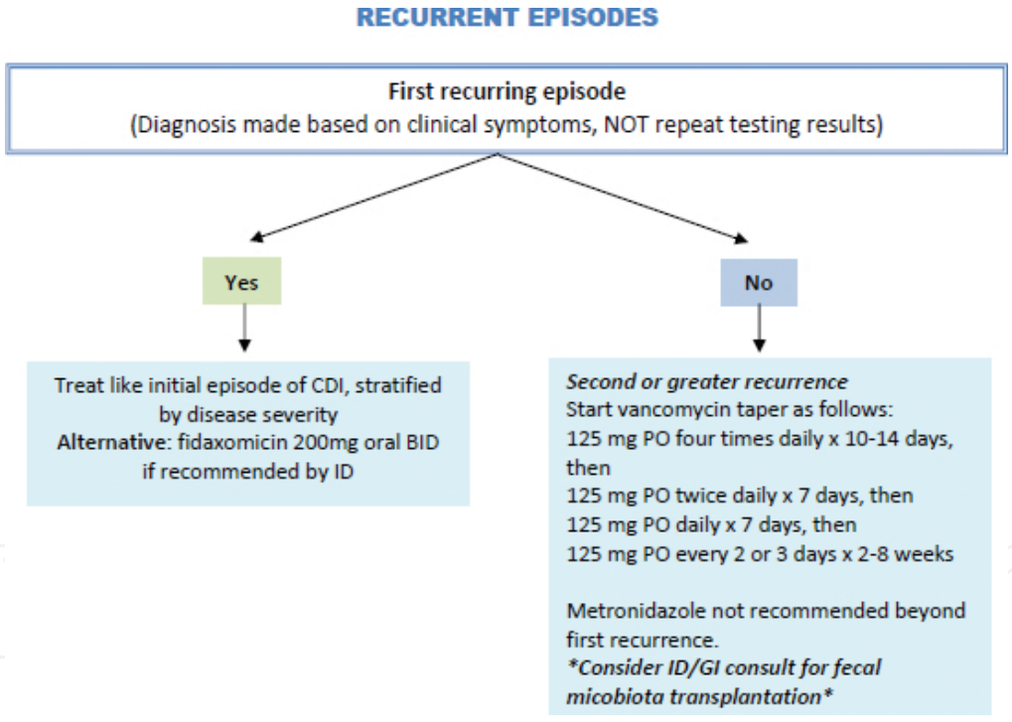

Figure 3. Treatment Algorithm of Recurrent Episodes.

The ideal treatment options for the numerous infections that oncology critical care patients encounter have yet to be defined. Subsequently, therapy should always be optimized with respect to pharmacokinetic and pharmacodynamic properties of antimicrobials when regimens are selected. It is also well understood that therapy is often most aggressive in the immunocompromised and severely ill population. Therefore, side effects and toxicities of all agents must be weighed against efficacy to ensure safety is not compromised.

3. Prophylactic and therapeutic anticoagulation

3.1. Epidemiology

It is well known that the risk of thrombosis in oncology patients far exceeds the risk encountered by those without a cancer diagnosis. Thrombosis accounts for 10% of fatal events in oncology patients, making it the second leading cause of death in this patient population. Patients with cancer experience between a twofold to 20-fold increased risk of developing venous thromboembolism (VTE), which is most likely to occur within the first six months of cancer diagnosis [46, 47]. Patients diagnosed with cancer of the pancreas, stomach, colon, brain, lung, and ovaries are at higher risk of developing VTE in addition to treatment with antiangiogenic agents, such as thalidomide and lenalidomide used in multiple myeloma [46–49]. Unfortunately, this VTE risk is only further exacerbated in critically ill ICU patients. It has been noted that the incidence of deep venous thrombosis ranges from 28 to 32% in general medical ICU patients with nearly 95% being clinically silent [50]. One single-center prospective cohort identified four risk factors for ICU-acquired VTE including personal or family history of VTE, end-stage renal failure, platelet transfusion, and vasopressor use [51]. Catheters may be subject to thrombotic events, leading to pulmonary embolism in 10–15% of patients and loss of access in 10% of patients [52]. Such complications place a patient in danger of the effects of VTE and impede cancer-directed therapy, enabling progression of the disease.

Not only do VTEs affect a patient's cancer prognosis, but they also increase the risk of complications, such as bleeding, which is 2.5 times more likely to occur in oncology patients receiving anticoagulant therapy within the first year of VTE [46, 48]. Unfortunately, this does not preclude patients from being at risk for recurrence of thrombosis during anticoagulant therapy. Thrombosis during anticoagulant therapy occurs in 6–17% of cancer-related VTE, nearly three times higher than in non-oncology patients with a history of thromboembolism [46–48]. Given the increased risk of VTE in oncology patients contributing to morbidity and prolonged hospitalizations, it is important to adequately understand the options available for treatment and the recommended guidelines for the use of such medications in an oncology population.

3.2. Thromboprophylaxis and first-line treatment

Several well-published guidelines provide recommendations for prophylaxis and treatment of thrombosis in oncology and ICU patients, all of which have slightly different suggestions for appropriate therapy. Thus, it was necessary to provide summaries for several of these publications to allow clinicians to consider multiple view points and make the best clinical decision. Recommendations only applicable to the critically ill oncology population are provided for thromboprophylaxis, treatment of established VTE, and recurrence management in **Tables 6–8**. Additionally, per CHEST guidelines, mechanical prophylaxis alone should be considered only in ICU patients at high risk of bleeding with pharmacologic agents resumed when such bleeding risks are resolved [55]. Combination of pharmacologic and mechanical modalities should be considered in all patients as a meta-analysis published in the Cochrane Library suggested the combination was superior to either alone [58].

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Criteria	Prophylaxis options
Non-surgical	
General ICU or hospitalized patients with active malignancy and acute medical illness or reduced mobility. (Not routinely recommended for patients admitted for minor procedures, short chemotherapy infusion, or patients undergoing stem-cell/bone marrow transplantation)	Unfractionated heparin 5000 units SQ q8 h Dalteparin 5000 SQ units daily Enoxaparin 40 mg SQ daily Fondaparinux 2.5 mg SQ daily
Surgery	
All patients with malignant disease undergoing major surgical intervention unless contraindicated because of active bleeding or high bleeding risk.	Unfractionated heparin 5000 units 2–4 h preoperatively and once q8 h thereafter or 5000 units 10–12 h preoperatively and 5000 units twice daily thereafter
Prophylaxis should be continued for at least 7–10 days in patients undergoing major surgery, and up to 4 weeks in patients receiving major abdominal and pelvic surgery with high-risk factors such as restricted mobility, obesity, history of VTE, or with additional risk factors noted in ASCO guidelines.[1]	Dalteparin 2500 units SQ 2–4 h preoperatively and 5000 units SQ daily thereafter or 5,000 units SQ 10–12 h preoperatively and 5000 units SQ once daily thereafter Enoxaparin 20 mg SQ 2–4 h preoperatively and 40 g daily thereafter or 40 mg SQ 10–12 h preoperatively and 40 mg SQ once daily thereafter
LMWH or UFH commenced	Fondaparinux 2.5 mg SQ daily beginning 6–8 h post-operatively
Post-operatively for the prevention of VTE in oncology patients undergoing neurosurgery.	Additional recommendations for when to initiate prophylactic therapy post-surgery is available through NCCN guidelines

UFH, unfractionated heparin; LMWH, low molecular weight heparin; VTE, venous thromboembolism; SQ, subcutaneous.
[1] Multiple risk assessment models have been proposed but yet to be validated before strong recommendations are made for inpatient screening. ASCO guidelines should be referenced for predictive models.

Table 6. Thromboprophylaxis [52–56].

Criteria	Treatment options
LMWH is preferred over UFH for the initial 5–10 days of anticoagulation for VTE in patients without renal impairment (CrCl <30 mL/min)	Unfractionated heparin 80 units/kg IV bolus, then 18 U/kg per h IV; adjust dose based on aPTT Dalteparin 100 units/kg SQ q12 h or 200 units/kg SQ daily Enoxaparin 1 mg/kg SQ q12 h or 1.5 mg/kg daily Fondaparinux <50 kg: 5 mg SQ daily 50–100 kg: 7.5 mg SQ daily >100 kg: 10 mg SQ daily

Criteria	Treatment options
For long-term anticoagulation (at least 6 months), LMWH is preferred over VKAs (VKA is acceptable if LMWH is not available)	Dalteparin 200 units/kg SQ daily for 1 month, then 150 units/kg SQ daily
Consider anticoagulation beyond 6 months for patients with active cancer (metastatic disease) or those receiving chemotherapy	Enoxaparin 1.5 mg/kg SQ daily or 1 mg/kg once q12 h
For catheter-associated thrombosis, anticoagulate as long as the catheter is in place for at least 3 months	Warfarin Adjust dose to maintain INR 2–3
Consider insertion of vena cava filter in patients with contraindications to anticoagulant therapy or as adjunct to anticoagulation in patients with progression of thrombosis.	
Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not formally recommended by national guidelines at this time.	

CrCl, creatinine clearance; UFH, unfractionated heparin; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 7. Treatment of newly established VTE [52–54, 57].

Treatment patient was receiving when recurrence of VTE diagnosed	Secondary treatment options
VKA	LMWH[6] or fondaparinux or UFH
LMWH	Increase the dose of LMWH dose in patients treated with LMWH Consider twice daily dosing if patient experiences recurrent VTE while receiving once-daily dosing of LMWH
UFH	LMWH or fondaparinux Increase dose of UFH
Failure of any agent	Consider placement of an inferior vena cava filter

UFH, unfractionated heparin; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 8. Treatment of VTE recurrence in oncology patients receiving anticoagulation [52, 54].

3.3. Direct oral anticoagulants (DOACs)

Alternatives to treatment include new, direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban. Limited research has been conducted on their use in patients with cancer and the critically ill population [47]. While the standard approach to treating VTE is currently with use of LMWH or fondaparinux followed by warfarin, DOACs simplify anticoagulation therapy as they are administered in fixed doses and do not require routine monitoring [59, 60]. Warfarin therapy, though effective, is accompanied by burdensome

disadvantages, including constant monitoring due to the small therapeutic window and multiple drug interactions [60]. Large clinical trials have proven the DOACs to be non-inferior to LMWH/warfarin therapies in efficacy, are associated with fewer bleeding events, and have fewer food/drug interactions [60, 61]. Although the Food and Drug Administration (FDA) has approved rivaroxaban, apixaban, dabigatran, and edoxaban in the USA, the use of DOACs is not formally recommended in oncology patients due to limited clinical data [61]. Furthermore, the use of DOACs especially in ICU should be considered only for those patients who are clinically stable and are not scheduled to have a procedure in the ICU. Despite the lack of randomized trials, many clinicians are beginning to incorporate such oral agents into long-term treatment options for oncology patients due to their ease of administration compared to warfarin and LMWH.

Rivaroxaban is a direct factor Xa inhibitor and was the first DOAC approved by the FDA in 2012 [61–63]. It is contraindicated with inhibitors of CYP3A4 and P-glycoprotein including ketoconazole and ritonavir due to increased plasma drug concentrations [62]. Two non-inferiority studies that included patients with cancer, proved rivaroxaban equally as effective as LMWH/warfarin therapy with similar rates of bleeding [61, 63]. Recurrent VTE occurred in 3.4% of oncology patients treated with rivaroxaban compared to 5.6% of oncology patients with enoxaparin/VKA therapy [63]. One concern with rivaroxaban in critically ill oncology patients is that doses of 15–20 mg must be taken with food to optimize bioavailability. This is often difficult in an oncology population known to have poor appetites and inadequate oral intake. The tablets can be crushed and administered via nasogastric feeding tubes; however, administration via this route must be followed by enteral feedings to optimize absorption. Furthermore, administration through feed tubes placed distal to the stomach will decrease absorption of rivaroxaban [63].

Apixaban, a direct factor Xa inhibitor, was approved by the FDA in 2014 [61]. Similar to rivaroxaban, apixaban is contraindicated with CYP3A4 inhibitors due to increased plasma drug concentrations [62]. In the double-dummy, double-blind AMPLIFY trial, apixaban was proven non-inferior compared to standard anticoagulation therapy (LMWH/warfarin) for incidence of recurrent VTE, and major bleeding events occurred less frequently with apixaban [61]. In the AMPLIFY-EXT trial, long-term anticoagulation for approximately 1 year with apixaban was evaluated in patients who had already been treated for DVT and/or PE for six to 12 months. Compared to placebo, apixaban was superior in preventing recurrent VTE and all-cause death. One additional compelling study evaluating patients with non-valvular atrial fibrillation was able to prove that apixiban 5 mg twice daily compared to aspirin 81–324 mg daily showed significant reduction in stroke and systemic embolism in addition to lower rates of bleeding. The AMPLIFY and AMPLIFY-EXT included a small portion of oncology patients (3.1 and 1.7%, respectively) in which recurrent VTE and major bleeding events occurred about half as frequently in the apixaban group compared to oncology patients treated with enoxaparin/warfarin [64]. Apixaban is further advantageous in ICU patients at risk of multi-system organ failure as it does not require renal or hepatic dosage adjustments.

Dabigatran, a direct thrombin inhibitor, was approved by the FDA in 2014 [61]. Dabigatran proved non-inferior in efficacy and had similar bleeding risks compared to warfarin in the

double-blind, double-dummy RE-COVER and RE-COVER II studies [61]. When compared to enoxaparin, rivaroxaban, and apixaban, efficacy was similar but bleeding risks were significantly higher with dabigatran. A meta-analysis comparing trials of these DOACs found that major bleeding risk was lower in those using apixaban than users of dabigatran and edoxaban [65]. Aside from the higher bleeding risk, clinicians should be cautious with its use in the oncology setting as it has a long half-life and requires discontinuation of therapy at least 1–2 days prior to surgery or even as early as 3–5 days for those with a CrCl <50 mL/min. The oral anticoagulant is not recommended for most indications in patients with a CrCl <30 mL/min and must be adjusted if administered with specific P-gp inhibitors. Due to multiple safety risks, the use of dabigatran in the oncology setting has fallen out of favor and caution is advised when treating patients who arrive to the ICU on chronic dabigatran therapy.

Few national guidelines have incorporated these agents into recommendations for treating VTE; however, a recent meta-analysis of five randomized controlled trials did prove that DOACs are comparable to VKA (warfarin) therapy in treating cancer-related VTE, which makes this class of anticoagulants promising in the future [61]. Unfortunately, the DOACs still face one major concern: managing real-world DOAC-associated bleeding, as no antidote is currently FDA-approved for these agents. Some guidelines make recommendations for managing DOAC-associated bleeding events, but the principles are based on laboratory, not clinical parameters [60]. Further research is needed to validate the use of DOACs in VTE treatment, especially in an oncology population.

3.4. Bleeding and thrombocytopenia

Thromboprophylaxis significantly reduces the rate of symptomatic VTE and is important for improving the quality of life in oncology patients, but it is associated with an increased risk of bleeding especially in ICU patients with coagulopathies abnormalities from sepsis and organ failure [48]. In patients with a high risk of bleeding who experience acute proximal DVT or PE, anticoagulation therapy may not be appropriate. The American College of Chest Physicians (ACCP) advises placing an IVC filter in this situation [61].

One common risk for bleeding in oncology critically ill patients is thrombocytopenia secondary to chemotherapy, blood loss during surgery, toxins including other drugs, macrophage-activation syndrome, disseminated intravascular coagulopathy, and massive transfusions. Anticoagulation therapy should be pursued if the platelet count remains above 50×10^9, and platelet transfusions should be considered during the high-risk period of recurrence in order to provide full anticoagulation therapy. Furthermore, it is crucial to delineate whether the cause of thrombocytopenia is related to consumptive coagulopathy that can continue to worsen over several days or if the decrease in platelets is only an acute change due to a single event such as surgery, which is likely to resolve quickly [66]. This approach can help determine the appropriate course of action such as reducing the dose of LMWH by 50% if the platelet count is between 25 and 50×10^9 and cannot be sustained by transfusions or if all anticoagulants should be held with the risk of bleeding exceeding the risk of clotting [47].

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4. Adverse effects of anticancer therapy leading to emergent ICU admissions in the adult population

Patients with malignancies are at risk for acute life-threatening illnesses that require intensive care unit (ICU) admission. Leukemia and lymphoma are the most common hematologic cancers encountered in the ICU, and lung cancer is the most common solid tumor encountered in adults [67]. In addition, as many as 40 percent of allogenic hematopoietic cell transplant (HCT) recipients develop one or more complications where transfer to the ICU is necessary [68]. Indications for ICU admission in oncology patients include decompensation secondary to progression of the cancer, treatment-related side effects, or comorbid illnesses.

Patients whose survival rates remain marginally low include allogeneic bone marrow transplant recipients with severe GVHD unresponsive to immunosuppressive therapy, patients with multiple organ failure related to delayed ICU admission, and specific clinical vignettes in patients with solid tumors [69]. They are exposed to individual or combination chemotherapy regimens with the intention of cure or remission but not without risk for developing acute or long-term side effects requiring escalation of care. The following are only a few of the many anticancer therapy-related AEs, and oncology patients may experience resulting in ICU admission.

4.1. Tumor lysis syndrome (TLS)

TLS is an oncologic emergency caused by massive tumor cell lysis with the overwhelming release of intracellular contents (potassium, phosphorus, and nucleic acids) into the systemic circulation. In turn, the kidneys are overwhelmed due to the rapid influx of these contents and inability to excrete them efficiently. This can cause potentially life-threatening metabolic and electrolyte abnormalities which can require a patient to be transferred to an ICU for more appropriate management [70]. The four key electrolyte abnormalities are hyperuricemia (uric acid >8 mg/dL), hyperphosphatemia (phosphate >4.5 mg/dL), hypocalcemia (total serum calcium <7 mg/dL), and hyperkalemia (>6 mmol/L).

TLS manifestations may occur before initiation of chemotherapy but are usually observed within 12–72 h after therapy begins and may persist for 5–7 days post-therapy. TLS occurs most frequently after the initiation of cytotoxic therapy in patients with highly aggressive lymphomas (Burkitt subtype) and acute lymphoblastic leukemia (ALL). TLS may also occur spontaneously and/or in other tumor types that have high proliferation rate, large tumor burden (reflected by serum lactate dehydrogenase levels), or high sensitivity to cytotoxic therapy. Common anticancer agents associated with TLS are listed in **Table 9**.

The Cairo-Bishop grading system is used to classify and grade TLS. TLS is diagnosed by Laboratory Tumor Lysis Syndrome (LTLS) or by Clinical Tumor Lysis Syndrome (CTLS). A retrospective analysis of 772 consecutive acute myeloid leukemia (AML) patients receiving induction chemotherapy concluded clinical TLS (not laboratory) was associated with a significantly higher risk of death during induction therapy (30 out of 38 patients; 79 vs. 23% of those patients without evidence of clinical TLS) [70]. The risk for developing TLS is stratified

as low, intermediate, and high risk with treatment strategies varying by each level of risk shown in **Table 10**. Those in the high-risk category strongly need aggressive intervention, and those in the low-risk category might need only observation, but the classification and treatment approach for the intermediate-risk patients is not as clearly defined.

Continuous hydration is the cornerstone of TLS prevention and is recommended prior to therapy in all patients that fall into the intermediate- or high-risk category. The goal is to improve renal perfusion, to improve glomerular filtration rate, and to produce a high urine output to lessen the likelihood of uric acid or calcium phosphate from precipitating in the renal tubules. It is imperative to use cautiously in patients with underlying kidney injury or cardiac dysfunction. The following are key points of this section [72–76]:

- Begin continuous hydration ideally 2 days before chemotherapy is to be given. Continue therapy during chemotherapy administration and 2–3 days after chemotherapy completion. Vigorous hydration (intermediate and high risk) consists of 2–3 L/m^2/day IV solution consisting of 0.225%NS + D5W, with a urine output goal of 80–100 mL/h

- To enhance renal excretion, consider furosemide 20–40 mg IV push to maintain urine output >100 mL/m^2/h or 2 mL/kg/h. Diuretic use is contraindicated if the patient has evidence of acute obstructive uropathy or hypovolemia. Potassium must also be closely monitored due to furosemide's ability to increase renal excretion of this electrolyte.

- The role of urinary alkalization with either acetazolamide and/or sodium bicarbonate is a controversial issue; therefore, use of sodium bicarbonate is only indicated in patients with metabolic acidosis [70].

Bendamustine	Ibrutinib
Bortezomib	Imatinib
Brentuximab Vedotin	Lenalidomide
Carfilzomib	Mechlorethamine
Cetuximab	6-Mercaptopurine
Cisplatin	Nilotinib
Cytarabine	Obinutuzumab
Dasatinib	Omacetaxine
Daunorubicin	Paclitaxel
Doxorubicin	Rituximab
Epirubicin	Romidepsin
Etoposide	Thalidomide
Fludarabine	Vincristine

Table 9. Anticancer agents associated with tumor lysis syndrome (TLS) [71].

Risk category[1]	Treatment options
Low-risk patients	• Observation • Normal hydration with IV fluids • Monitor laboratories once daily throughout chemotherapy, then as clinically indicated post-treatment manage fluid and electrolyte abnormalities • +/− Allopurinol
Intermediate-risk patients	• Vigorous hydration and inpatient monitoring • Initiate allopurinol or rasburicase if uric acid >7.5 mg/dL (Some practices report administering a single dose of rasburicase in this setting, which is a reasonable alternative) • Monitor laboratories every 8–12 h throughout chemotherapy, then as clinically indicated post-treatment • Initiate rasburicase
High-risk patients	• Increase hydration and maintain urine output • Cardiac monitoring • Initiate rasburicase for 1 dose and repeat only if uric acid ≥7.5 mg/dL • Monitor laboratories every 6–8 h throughout chemotherapy, then every 1–2 days post-treatment and as clinically indicated • Manage fluid and electrolyte abnormalities • Consult nephrology
Established TLS in patients	• Admission to Intensive Care Unit • Increase hydration and maintain urine output • Cardiac monitoring • Initiate rasburicase for 1 dose and repeat only if uric acid ≥7.5 mg/dL • At the end of rasburicase treatment, patients should start allopurinol • Monitor laboratories every 4–6 h daily

S/S, signs and symptoms; IVP, intravenous push; CrCl, creatinine clearance; IV, intravenous; NS, normal saline; D5W, 5% dextrose in water; G6PD, glucose-6-phosphate dehydrogenase deficiency; WBC, white blood cells.
[1] Refer to reference [73] for definitions and criteria defining low-, intermediate-, and high-risk patients.

Table 10. Tumor lysis syndrome (TLS) treatment based on risk stratification [72–75].

Allopurinol is a xanthine oxidase inhibitor, which means it blocks the enzyme responsible for the conversion of xanthine to uric acid. Allopurinol is preferred for patients that fall into the low-risk category explained in **Table 10**. It is recommended to start 1–2 days prior to initiating chemotherapy to prevent excess uric acid, but it will not reduce uric acid levels in patients who have existing hyperuricemia [77]. Unfortunately, the excess xanthine levels could precipitate

into the kidneys leading to the renal dysfunction. Another limitation of allopurinol is it interferes with the excretion of other chemotherapy agents (high-dose methotrexate, cyclophosphamide, mercaptopurine, and azathioprine). If concomitant use cannot be avoided, reduce 6-mercaptopurine and/or azathioprine doses by 65–75% when used with allopurinol [78]. Allopurinol should never be administered with capecitabine because it may decrease its effectiveness [71]. The recommended oral allopurinol dose per the manufacturer is 600–800 mg daily in divided doses or 100–300 mg oral every 8 h daily (maximum of 800 mg/day). Alternative dosing (off label for intermediate risk for TLS) is 10 mg/kg/day divided every 8 h (maximum of 800 mg per daily) or 50–100 mg/m^2 every 8 h (max dose 300 mg/m^2 daily) beginning 1–2 days before initiation of chemotherapy induction. This may be continue for 3–7 days after chemotherapy [74]. IV allopurinol can be used in patients not tolerating oral at a dose of 200–400 mg/m2/day in one to three divided doses (maximum of 600 mg/day) beginning 1–2 days before initiation of chemotherapy induction and may be continued for 3–7 days after chemotherapy [78]. Allopurinol should be continued until uric acid levels are normalized and tumor burden, WBC count, and other laboratory values have returned to low TLS risk levels as defined in **Table 10**. Refer to **Table 11** for appropriate renal adjustments.

Creatinine Clearance (ml/min)	Daily Oral Allopurinol Dose
Manufacturer Recommended Allopurinol Dosing [78]	
10–20	200 mg
<10	100 mg
<3	100 mg at extended intervals (more than 24 h if necessary)
Alternative Allopurinol Dose Adjustments [74]	
140	400 mg
120	350 mg
100	300 mg
80	250 mg
60	200 mg
40	150 mg
20	100 mg
10	100 mg every 2 days
0	100 mg every 3 days

CrCl, creatinine clearance.

Table 11. Recommended allopurinol dosing.

Rasburicase is a recombinant urate oxidase produced by a genetically modified *S. cerevisiae* strain. Rasburicase is used to treat hyperuricemia by converting uric acid to allantoin thereby

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reducing uric acid levels and helping to control serum potassium, phosphorus, calcium, and creatinine levels [70]. Allantoin is highly effective with it being five to ten times more soluble in the urine than uric acid. The duration of rasburicase therapy can vary, with a majority receiving 2 days of therapy, but success has been seen with a single dose. Uric acid levels should be monitored regularly and used as a guide for dosing. Rasburicase works quickly with decreases in the level of uric acid by 0.5–1 mg/dL being observed within 4 h of administration [70]. Patients with larger tumor burden may need longer therapy (up to 7 days) or twice daily treatment [70, 78]. Rasburicase is dosed at 0.2 mg/kg/day infused over 30 min with the first dose at least 4 h prior to start of cytotoxic therapy and continued for up to 5 days. Dosing beyond 5 days or administration of more than one course is not recommended [79]. The FDA-approved dose is 0.2 mg/kg dose, but 0.15 mg/kg has demonstrated efficacy, which may be an option for intermediate-risk patients with baseline uric acid ≤7.5 mg/dL [70]. Many institutions are also utilizing fixed dosages (3, 6 or 7.5 mg) versus weight based dosing [97]. Once serum uric acid levels normalize, rasburicase can be stopped and allopurinol treatment can be initiated/resumed. Concomitant allopurinol should not be administered in order to avoid xanthine accumulation and lack of substrate for rasburicase.

4.2. Pulmonary complications (non-infectious causes) following hematopoietic stem cell transplantation (HCT)

Hematopoietic stem cell transplantation (HCT) is a treatment option for many malignant hematological disorders. The conditioning chemotherapy regimens used are considered either myeloablative where lethal doses of chemotherapy are given, with or without irradiation, or non-myeloablative where lower doses of chemotherapy are administered. Our lungs contain an enormous capillary bed that is uniquely sensitive to the side effects of chemotherapy and radiation therapy. Subsequently, a myeloablative conditioning regimen with lethal doses of chemotherapy has a high likelihood of causing pulmonary complications. The estimated incidence of pulmonary complications in HCT recipients ranges between 40 and 60% [80]. Such complications can be further divided into infectious and non-infectious causes. The non-infectious causes include pulmonary edema, engraftment syndrome (ES), diffuse alveolar hemorrhage (DAH), idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans organizing pneumonia (BOOP), and pulmonary sarcoidosis. The risk of developing these complications can occur at three different phases following a HCT. The neutropenic phase is described as <30 days post-HCT, the early phase includes 30–100 days post-HCT, and the late phase is known as >100 days post-HCT. The following section will focus on a few of the non-infectious pulmonary complications that occur in the neutropenic phase (<30 days) post-HCT.

Engraftment syndrome is equally common in autologous and allogenic HCT patients (7–11 and 10%, respectively). The median time to onset is 10 days post-transplant and can manifest up to 11 days. The syndrome is multifactorial consisting of the overproduction and release of pro-inflammatory cytokines and interaction between T cells, monocytes, and complement activation during engraftment. A majority of the cases are mild and self-limiting but the moderate-to-severe cases require treatment with corticosteroids. Lack of response to corticosteroid therapy leading to mechanical ventilation is a predictor of poor prognosis [76].

Treatment for mild ES (transient low-grade fevers with limited rash) includes discontinuing G-CSF and initiating empiric broad-spectrum antibiotics. Moderate-to-severe ES with pulmonary involvement often requires treatment with corticosteroids such as methylprednisolone doses ranging from 0.5 to 10 mg/kg/day or methylprednisolone 1–2 g/day × 3 days followed by rapid taper over 2–3 weeks. A decrease in O_2 requirement should be observed with symptoms improving in 2–4 days [13, 81, 82].

Diffuse alveolar hemorrhage (DAH) is a progressive, non-infectious pulmonary complication following HCT often leading to mechanical ventilation for respiratory failure in a majority of patients. It is thought to be due to a combination of mechanisms such as lung tissue injury from the conditioning regimen or pulmonary infections, inflammation likely due to a combination of bronchial inflammation, alveolitis, GCSF induced neutrophil influx into the lungs, or cytokine release which contributes to alveolar capillary endothelial membrane damage. DAH occurs equally in approximately 5% of allogeneic and autologous HCT recipients with the most common cause of death being multi-organ failure and sepsis [76, 83–85]. Standard therapy includes high-dose corticosteroids with methylprednisolone 500–1000 mg/day for 3–4 days followed by 1 mg/kg for 3 days then taper over 2–4 weeks. Doses of 125–250 mg IV every 6 h for the first 4–5 days followed by a taper over 2–4 weeks have been associated with higher overall survival as well. One retrospective study of 14 patients also showed an overall higher survival benefit with aminocaproic acid 1000 mg IV q6 h plus methylprednisolone 250 mg IV every 6 h followed by a taper. In addition, several case reports have shown a modest resolution in bleeding with the combination of recombinant factor VIIa 90 mcg/kg and methylprednisolone 500–2000 mg IV daily followed by gradual taper over 2–4 weeks [76, 84–86].

4.3. Cytokine release syndrome (CRS) associated with chimeric antigen receptors (CARs)

Immunotherapy is redefining the standard of care in many malignancies. Recent advances involve the engineering of a patient's own immune cells to recognize and attack tumor cells. T cells contain a monoclonal antibody fragment (scFv) specific for a tumor target with T-cell receptor activation. The T cells are then directed to target antigens that are expressed by tumors. This initiates the patient's own immune system to target the cancer. However, CAR T-cell treatments are not without risks, and many people experience an inflammatory process called severe cytokine release syndrome (CRS) that requires hospitalization, with over 30% requiring intensive care admission [87].

Cytokine release syndrome (CRS) is marked by dramatic elevation in cytokine levels producing a systemic inflammatory response similar to that of septic shock. The onset has been noted to occur within 1–14 days of CD-19 CAR T-cell infusion and resolves typically in 2–3 weeks. With hypotension being the main criteria in the revised CRS grading system, it is important to record baseline blood pressure prior to start of therapy that could induce CRS. Potentially life-threatening complications with CRS include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation [85]. Diagnosis of CRS is made based on the presence of high levels of inflamma-

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tory markers and cytokines, increased LFTs, and increased total bilirubin [88]. Appropriate treatment is based on the CRS grading system explained in **Table 12**.

CRS-revised grading system	Treatment Associated with revised grading system
Grade 1 Symptoms are not life threatening and require symptomatic treatment only: Fever and constitutional symptoms (nausea, fatigue, headache, myalgias, malaise)	• Assess for infection in all grades • Vigilant supportive care including antipyretics and analgesics in all grades[1]
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement <40% or Hypotension responsive to fluids or Vasopressor if unresponsive to fluids or Grade 2 organ toxicity	• Monitor cardiac function (s/s cardiac decomposition). Cardiac decompensation can be sudden and severe, but usually reversible. The pathophysiology of acute cardiac toxicity in the setting of CRS is not clear, but resembles cardiomyopathy associated with sepsis and stress cardiomyopathy. Monitor echocardiography frequently in patients who are a concern for cardiac dysfunction (Grade 2–4) • Monitor organ function closely • Monitor/manage complications of TLS IF, older age or extensive comorbidities: • Based on clinical judgment, may be necessary to initiate immunosuppressive therapy (refer to Grade 3/4 treatment)
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis	• Initiate **tocilizumab**: For patients weighing <30 kg: 12 mg/kg IV x1 dose For patients weighing >30 kg: 8 mg/kg IV × 1 dose (max dose 800 mg)
Grade 4 Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)	IF, lack of clinical improvement while waiting for tocilizumab response: • Initiate corticosteroid therapy (taper within one week; can generally be accomplished) **Methylprednisolone*** 2mg/kg x 1 dose, followed by 2mg/kg/d divided 4 times per day [24] to hopefully suppress the inflammatory cascade and prevent irreversible organ dysfunction
Grade 5—Death	

*Emerging evidence suggests corticosteroids may mediate a greater adverse effect on the antitumor activity of adoptively transferred T cells [26]
[1] Vigilant supportive care: antipyretics, analgesics, adequate hydration, blood pressure support, and broad-spectrum antibiotics.
[2] For patients with severe neurologic symptoms, consider dexamethasone (0.5 mg/kg; maximum 10 mg/dose) due to more efficient penetration of the blood-brain barrier although evidence for choosing one over the other has not been established.

Table 12. Cytokine release syndrome–revised grading system and associated treatment [88–90].

Tocilizumab is an antirheumatic disease modifying interleukin-6 receptor antagonist approved for adults with rheumatoid arthritis at the dose 4–8 mg/kg every 4 weeks infused over 1 h [88]. It is also the standard therapy for managing Grade 3 CRS. Reports have shown cytokines return to normal and symptoms resolve concurrently by day nine following tocilizumab administration [87, 91]. In addition, tocilizumab may have less impact on the antitumor effect of CAR t cells when compared to corticosteroids [88]. If the patient has a positive clinical response to tocilizumab, then vasopressors and supportive measures can be weaned shortly thereafter. If the patient's condition does not improve or stabilize within 24 h of tocilizumab dose, a second dose can be administered. A corticosteroid regimen should also be considered if it has not already been initiated. Adverse effects (AE) associated with tocilizumab include, but are not limited to: hypersensitivity reactions, elevated liver enzymes, fatal opportunistic infections, gastrointestinal perforation, hematologic effects, herpes zoster reactivation, hyperlipidemia, and tuberculosis. Studies are under investigation regarding the optimal timing of anti-Il-6 treatment, but some levels of CRS should be expected and possibly an inevitable consequence of the CAR T-cell therapy mechanism [92].

4.4. Pulmonary toxicity due to chemotherapy agents in general oncology patients

In the non-HCT patients, several other chemotherapy agents have high risks for causing pulmonary toxicity exhibited early with infiltrates, pulmonary edema, hypersensitivity reactions, and pleural effusions or with infiltrates or fibrosis in late onset (greater than 2 months). These injuries can be dose dependent or can manifest several years after completion of therapy [93]. As a result, the most severe and late stages of such toxicity are usually observed in patients admitted to the ICU. The most common chemotherapy agents associated with pulmonary toxicity and their respective clinical/radiologic manifestations are described in **Table 13**. The mainstay treatment for such pulmonary complications are largely steroids; however, it has yet to be determined the appropriate dose and duration of therapy that is most effective. One study evaluated the dosage pattern of corticosteroids used in 398 lung cancer patients with pulmonary toxicity. The drug-induced interstitial lung diseases were primarily treated with pulse dose therapy (≥500 mg/day methylprednisolone for 3 days followed by high-dose steroids) and high-dose therapy (≥0.5 mg/kg/day prednisolone). These cases had a mortality rate of 48.4% which was similar or less than that of the other groups. Unfortunately, response to therapy was not defined in this study by improvements in radiologic findings or carbon monoxide diffusing capacity, which has been suggested as better indicators [94]. Scarce literature exists outside of case series or small observation studies as the one described. Therefore, with the lack of established treatment guidelines for pulmonary toxicity, intensivists should customize corticosteroid regimens based on each patient's response and risk for AEs from prolonged therapy.

Despite the many advances in cancer treatment options including not only chemotherapy but also immunotherapy agents, the risks for AEs have unfortunately not been completely diminished. These agents are administered at toxic levels with multiple cycles, and each dose highly affects more than one organ system. Therefore, the risks observed from these agents far outweigh AEs due to therapies initiated in typical ICU patients. The AEs previously discussed

are only a few of the many acute and chronic consequences that are observed in cancer patients leading to ICU admission. However, the pharmacologic management of such occurrences is extremely important as they affect future treatment options and overall quality of life of the patient.

Chemotherapy agent	Clinical/radiological manifestations
Bleomycin	Bronchiolitis obliterans organizing pneumonia (now referred to as *cryptogenic organizing pneumonia*), eosinophilic hypersensitivity, or interstitial pneumonitis (most common) that can progress to fibrosis
Methotrexate	Bilateral interstitial and alveolar infiltrates or pleural effusions, accompanied by fever and peripheral eosinophilia. Fibrosis can be prevented if the medication is discontinued
Gemcitabine	Diffuse ground-glass changes accompanied by thickened septal lines, interstitial infiltrates, or diffuse alveolar infiltrates, which may lead to acute respiratory distress syndrome
Paclitaxel	Bilateral reticular or ground-glass infiltrates or focal consolidation
Oxaliplatin	Interstitial pneumonitis with fibrosis occurring after 3–6 months of therapy. Patients can present with slow progressive cough and dyspnea
EGFR-targeted inhibitors: gefitinib and erlotinib	Airspace consolidation or extensive bilateral ground-glass infiltrates

Table 13. Common chemotherapy agents associated with pulmonary toxicity and clinical/radiological manifestations [005B93].

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