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Infectious Disease Emergencies in the Cancer Patient: Rapid Fire

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SYNOPSIS

Cancer patients can be immunocompromised due to their underlying malignancy as well as the medical therapies with which they are treated. Infections frequently present atypically and can be challenging to diagnose. The spectrum of infectious diseases encountered in patients receiving chemotherapy, hematopoietic stem cell transplant, and immunotherapy is broad depending on the depth of immunosuppression. Early recognition of infectious processes followed by appropriate diagnostic testing, imaging, and empiric antibiotic therapy in the emergency department are critical to providing optimal care and improving survival in this complex patient population.

Keywords

infections; cancer; neutropenic fever; hematopoietic stem cell transplant; cytokine release syndrome; emergency department

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Case #1: Neutropenic fever

Pertinent History

A 62-year-old woman with acute lymphoblastic leukemia (ALL) undergoing chemotherapy consisting of vincristine, doxorubicin, and prednisone presents to the emergency department (ED) for a documented oral temperature of 38.3° C (100.9° F). She takes her temperature daily and has not had a fever previously. She has no history of neutropenia. Her review of systems is positive only for mild lower abdominal pain. She denies headache, neck pain, cough, dyspnea, nausea, vomiting, diarrhea, dysuria, hematuria, urinary urgency or frequency, rash, odynophagia, or tenderness along her port site.

Pertinent Physical Exam

T 38.6° C (101.5° F), BP 135/75, Pulse 85, RR 14, SpO2 97%

General: Well-appearing, no acute distress.

Oropharynx: No oropharyngeal lesions or plaques.

Neck: Supple without meningismus.

Cardiovascular: Regular rate and rhythm without murmurs, rubs, or gallops.

Pulmonary: Lungs clear to auscultation bilaterally.

Chest: Right chest port site without erythema, fluctuance, tenderness, or drainage.

Abdomen: Soft, mild tenderness to palpation in the right lower abdomen without rebound or guarding; bowel sounds are present.

Skin: Warm and well-perfused; no rashes, erythema, or swelling.

Neurologic: Awake, alert, oriented x4, normal strength and sensation throughout.

Diagnostic Testing

WBC	2.4 × 10 ⁹ /L	BUN	12 mg/dL
ANC	370 cells/μL	Creatinine	0.8 mg/dL
Hgb	12.2 g/dL	AST	34 IU/L
Platelets	380 × 10 ⁹ /L	ALT	18 IU/L
Na	142 mEq/L	Alk phos	160 IU/L
K	3.8 mEq/L	Bilirubin	0.7 mg/dL
Cl	101 mEq/L	CO ₂	26 mEq/L

Urinalysis: Negative nitrites, negative leukocyte esterase; no WBCs, RBCs, or bacteria.

Plan

Obtain blood cultures (one set from port, one set from peripheral venipuncture) and urine culture. Initiate empiric antibiotics for neutropenic fever. Perform computed tomography (CT) of the abdomen and pelvis.

Update

CT demonstrates bowel wall thickening of the cecum and distal ileum without stranding or pneumatosis. Due to concern for neutropenic enterocolitis, general surgery is consulted and the patient is admitted to the oncology ward for empiric broad-spectrum antibiotics.

Learning Points: Neutropenic Fever

Introduction and Background

1. As the U.S. population continues to expand and age, modern advances in early cancer detection and treatment have dramatically improved cancer survivorship. More than 15 million people with a history of cancer were living in the U.S. alone in 2016.¹
2. Cancer patients are at high risk of infection due to anatomic obstruction related to tumor infiltration (*e.g.*, post-obstructive pneumonia), mucosal barrier compromise due to cytotoxic chemotherapy, and defective immunity in the context of immunosuppressive cancer therapy or hematologic malignancy.
3. Chemotherapy is a mainstay of cancer treatment, and neutropenia is a common, well-known side effect. Neutropenic fever occurs in 10–50% of patients with solid tumors and >80% of patients with hematologic malignancy undergoing chemotherapy; it carries a mortality rate of nearly 10%.^{2–4} In 2012, more than 100,000 cancer patients were admitted to U.S. hospitals for neutropenia and/or its infectious complications. These neutropenia-related hospitalizations result in significant morbidity and mortality, incurring substantial medical costs.^{3–5}
4. Emergency physicians play a critical role in the time-sensitive diagnosis, stabilization, and management of patients presenting to acute care with neutropenic fever and other common infectious complications of chemotherapy.

Pathology/Pathophysiology

1. Essentially all chemotherapeutic agents have immunosuppressive effects. While different agents act on a variety of cellular functions, the common thread is that they interfere with the proliferative capacity of immune cells through bone marrow suppression,⁶ the most significant side effect being neutropenia.⁷
 - The absolute neutrophil count (ANC) reaches its nadir about 7–14 days after treatment and begins to return to normal levels 3–4 weeks after treatment.⁸
2. Hematologic malignancies and myelodysplastic syndromes resulting in bone marrow failure as well as solid organ tumors infiltrating the bone marrow also lead to neutropenia. Neutropenia is commonly defined as an ANC <1500 cells/ μ L in adults. Neutropenia can be further classified by severity:
 - Mild: ANC 1000–1500 cells/ μ L
 - Moderate: ANC 500–1000 cells/ μ L

- Severe: ANC <500 cells/ μ L⁹
- Profound: ANC <100 cells/ μ L¹⁰
 - The risk of infection is inversely proportional to the ANC. Infection is unlikely with ANC >1000 cells/ μ L, greatly increased with ANC <500 cells/ μ L, and severely increased with ANC <100–200 cells/ μ L.⁹

Absolute Neutrophil Count (ANC) Calculation

$$\text{ANC} = (\% \text{ neutrophils} + \% \text{ Bands}) \times \text{WBC Count (cells}/\mu\text{L})$$

Example: WBC = 2000 (cells/ μ L) AND neutrophils = 10% and bands = 2%

Then ANC = 12% x 2000 (cells/ μ L) = 240 (cells/ μ L)

3. Infectious Disease Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) guidelines define neutropenic fever as an ANC <500 cells/ μ L (or ANC <1000 cells/ μ L with expected decline to <500 cells/ μ L over the next 48 hours) and either a single oral temperature of 38.3°C (101.0°F) or a temperature of 38.0°C (100.4°F) sustained over 1 hour.^{10,11}
4. Neutrophils are the first line of defense in the innate immune system and play a key role in host response to bacterial and fungal pathogens. Neutropenic patients are therefore at high risk of infection with these organisms, particularly when cytotoxic chemotherapy compromises the integrity of mucosal barriers (*i.e.*, mucositis). Translocation of colonizing organisms across these barriers leads to invasive infection.⁷
 - Common organisms encountered in neutropenic fever include Gram-negative bacteria (*e.g.*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) and Gram-positive bacteria (*e.g.*, *Streptococcus* spp, *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Enterococci* spp).^{12–14}
 - *Candida* can cause mucosal infections (*e.g.*, oral thrush, esophagitis) as well as bloodstream and other invasive infections in the setting of chemotherapy-induced mucositis or central venous catheter infection. Invasive candidiasis is not typically encountered until after the first week of prolonged neutropenia.
 - Molds (such as *Aspergillus* spp, *Zygomycetes*, and *Fusarium*) are most likely to cause life-threatening invasive infections after two or more weeks of neutropenia, and typically only in patients with profound neutropenia. Additionally, those undergoing treatment for acute

myelogenous leukemia (AML) are especially susceptible to invasive mold infections.^{10,15,16}

Making the Diagnosis

1. Initial and timely (within 15 minutes of triage) assessment of the patient presenting with neutropenic fever to the ED should begin with:^{10,17}
 - Complete blood cell count with differential and comprehensive metabolic panel (serum electrolytes, blood urea nitrogen, creatinine, hepatic transaminases, bilirubin)
 - At least 2 sets of aerobic and anaerobic blood cultures:
 - One set of blood cultures from each lumen of any indwelling vascular access device (*e.g.*, central venous catheter, implantable port) PLUS 1 peripheral venipuncture site, OR
 - Two sets of blood cultures from different peripheral venipuncture sites
 - Fungal blood cultures
 - Fungal blood cultures should be obtained in patients at significant risk for developing candidemia (*e.g.*, active chemotherapy, hematologic malignancy, solid organ or hematopoietic stem cell transplant, patients with a central venous catheter, those receiving total parenteral nutrition).
 - Culture from other sites of suspected infection (*e.g.*, urine, sputum, wound, cerebrospinal fluid), based on clinical suspicion for a focal site of infection
2. Apart from fever, neutropenic patients may lack the necessary inflammatory response to manifest classic signs and symptoms of infection.
 - Erythema and induration can be mild with cellulitis, radiographic infiltrates subtle or absent in pneumonia, pyuria lacking despite a symptomatic urinary tract infection, and meningeal signs minimal if present at all in meningitis.¹⁰
 - Physicians should note that severely or profoundly neutropenic patients can present with suspected infection and either lack fever or be hypothermic.¹⁷
3. A detailed history of symptoms tailored to organ-specific infections as well as a thorough physical examination to identify subtle signs of infection should be performed, paying close attention to the skin, oropharynx, lungs, and gastrointestinal tract.
4. Unique considerations when diagnosing organ-specific infections in the setting of neutropenia:

- Oropharyngeal infection
 - White plaques are typical of oral candidiasis and are frequently asymptomatic. Painful oral ulcers or vesicles are more likely to represent infection with herpes simplex virus (HSV).¹¹
- Infectious esophagitis
 - Retrosternal burning, dysphagia, and odynophagia should prompt suspicion for *Candida*, HSV, or cytomegalovirus (CMV) infection.¹¹ Upper endoscopy with biopsy of suspicious lesions is necessary to differentiate etiology and guide therapy.
- Sinusitis
 - Sinus tenderness, periorbital swelling and/or cellulitis, unilateral eye tearing, or nasal erosions should prompt further evaluation. The sinuses are a common site for bacterial infection in neutropenic patients. High-risk patients (prolonged neutropenia, high-dose glucocorticoids, or graft-versus-host disease) are susceptible to sinusitis caused by invasive molds.¹¹
 - Symptomatic patients should undergo computed tomography (CT) of the sinuses, with a low threshold to consult an otolaryngologist and/or ophthalmologist. Magnetic resonance imaging (MRI) of the orbits and brain should be performed if proptosis or cranial nerve deficits are present to evaluate for orbital abscess (FIGURE 1) and septic cavernous sinus thrombosis.¹¹
- Skin and soft tissue infection (SSTI)
 - Due to inhibition of the normal inflammatory cascade, patients with SSTI may have minimal if any erythema, warmth, induration, or purulent drainage.¹⁰
- Pulmonary infections
 - Chest radiography should be obtained in any patient with respiratory symptoms. Recognize, however, that neutropenic patients with pneumonia may not demonstrate pulmonary infiltrates on plain films.¹⁰
 - CT of the chest may better characterize early infiltrates concerning for pneumonia.¹¹
 - Consider respiratory virus (including influenza) testing and urine *Legionella* antigen testing as clinically appropriate.^{11,17}

- Neutropenic enterocolitis
 - Also known as typhlitis or ileocecal syndrome, neutropenic enterocolitis is rare but potentially life-threatening. Microbial invasion of the bowel wall leads to inflammation, edema, and ulceration that can progress to transmural necrosis and perforation. Untreated, multisystem organ failure and death ensue, with mortality rates approaching 30–50%.
 - Symptoms include abdominal pain, nausea, vomiting, diarrhea, gastrointestinal hemorrhage, and peritonitis.
 - Patients with neutropenic fever and right-sided abdominal pain (the classic presentation for neutropenic enterocolitis), as well as those with neutropenia and a clinically concerning abdominal examination (*e.g.*, significant tenderness, peritoneal signs) should undergo CT of the abdomen and pelvis to rule out neutropenic enterocolitis (FIGURE 2).^{10,18,19}
- *Clostridium difficile* infection (CDI)
 - Patients presenting with unexplained, new onset diarrhea (≥ 3 unformed stools in 24 hours) should undergo stool testing for *C. difficile*.^{11,20} Recent antibiotic exposure and chemotherapy are risk factors for CDI.
 - Patients recently diagnosed with CDI (within 7 days) do not require retesting when presenting during the same episode of diarrhea.²⁰
 - Patients without diarrhea should not be tested for *C. difficile* as asymptomatic colonization is possible and shedding of spores may persist even after CDI treatment.²⁰
- Urinary tract infection
 - Obtain both a urinalysis with microscopy and urine culture in neutropenic patients with dysuria, frequency, urgency, suprapubic pain, and/or hematuria.¹¹
 - Neutropenic patients with UTI may not exhibit pyuria.¹⁰
- Bloodstream infection
 - Infected vascular access devices can serve as a portal of entry for bacteria or fungi into the bloodstream.
 - If inflammation is present at the site of vascular access, culture any visible drainage and obtain blood cultures from each lumen of the device.¹¹

- Mucositis predisposes patients to translocation of oropharyngeal or gut organisms across mucosal barriers leading to bloodstream infection.
- Central nervous system (CNS) infection
 - Patients with headache and/or altered mental status should undergo head CT or brain MRI, lumbar puncture (if possible), and neurology consultation.¹¹
 - Cerebrospinal fluid (CSF) should be sent for glucose, protein, cell count and differential, Gram stain and bacterial culture, and HSV polymerase chain reaction (PCR) at a minimum.
 - Neutropenic patients with meningitis may not exhibit a pleocytosis on CSF analysis, and normal CSF profile does not rule out meningitis and should not hinder initiation of treatment in those with suspected meningitis.^{10,21,22}

Treating the Patient

1. Initial empiric antibiotic therapy

- Start empiric antibiotics early (within 1 hour) in the setting of neutropenic fever, preferably once appropriate cultures have been obtained. Timely antibiotic administration has been shown to reduce mortality.^{17,23}
- Antibiotic selection should be bactericidal and include coverage of *Pseudomonas aeruginosa*, accounting for local antibiotic resistance patterns and patient risk factors.
- For patients requiring inpatient admission, initial monotherapy with an anti-pseudomonal beta-lactam (*e.g.*, cefepime), a carbapenem (*e.g.*, meropenem), or piperacillin-tazobactam is recommended.^{10,11}
 - Additional Gram-positive coverage with vancomycin or another antibiotic is NOT recommended as part of initial empiric therapy except in the setting of SSTI, bloodstream infection, severe pneumonia, or hemodynamic instability.
 - A combination of vancomycin plus aztreonam or clindamycin plus ciprofloxacin is appropriate for patients with a TRUE penicillin allergy.
- Patients already on fluoroquinolone prophylaxis should not receive a fluoroquinolone as part of empiric antibiotic therapy for neutropenic fever.¹⁰

2. Expanding empiric antibiotic therapy to cover antibiotic-resistant organisms

- Oncologic patients may be at increased risk of infection with antibiotic-resistant organisms due to:

- Increased frequency of healthcare exposure due to diagnostic procedures, surgery, radiation, or chemotherapy.
 - Frequent and broad exposure to antibiotics either for prophylaxis or treatment of prior infections.
 - Empiric antibiotic therapy should be modified based on previous culture-proven infection, colonization, or treatment in a hospital with high infection rates involving antibiotic-resistant organisms (TABLE 1):
3. Expanding empiric antibiotic therapy to cover fungi
 - Empiric antifungal coverage is generally reserved for high-risk patients who have had persistent fever despite 4–7 days of a broad-spectrum antibacterial regimen and no identified source of fever.¹⁰
 - However, patients with systemic inflammatory response syndrome (SIRS) and neutropenia may benefit from additional antifungal coverage with voriconazole, an echinocandin (*e.g.*, caspofungin), or liposomal amphotericin B, if the suspicion for fungal infection (*e.g.*, *Candida* spp, *Aspergillus* spp) is high.¹⁰
 4. Unique considerations for tailoring empiric antibiotic therapy to organ-specific infections
 - Oropharyngeal infections and infectious esophagitis
 - Fluconazole is considered first-line antifungal therapy for oral candidiasis and esophagitis.¹¹
 - Endoscopic findings should ultimately guide treatment for *Candida*, CMV, or HSV esophagitis.¹¹
 - Sinusitis
 - Broad-spectrum antibiotics, including anaerobic coverage, should be initiated in those with concern for bacterial sinusitis.
 - Vancomycin should be added in those with concern for periorbital cellulitis (often caused by *S. aureus*).
 - Liposomal amphotericin B should be added for high risk patients with CT or MRI findings concerning for invasive fungal sinusitis to cover molds (*e.g.*, *Aspergillus*, *Zygomycetes*, *Mucor*).¹¹
 - Skin and soft tissue infections
 - Initial empiric therapy for neutropenic fever, plus early addition of vancomycin, daptomycin, or linezolid to cover broadly for Gram-positive bacteria.^{10,11}
 - Pulmonary infections

- Initial broad-spectrum coverage should consist of a beta-lactam or carbapenem plus aminoglycoside or anti-pseudomonal fluoroquinolone.^{10,11} In severe pneumonia (hypoxia or extensive infiltrates) or if MRSA is suspected, vancomycin or linezolid should be added.¹⁰
- In high-risk populations (hematologic malignancy, hematopoietic stem cell transplant, graft-versus-host disease), nodular or cavitary pneumonia, segmental consolidation, or ground glass infiltrates on chest radiograph or CT should raise concern for *Aspergillus* infection.¹¹ Empiric antifungal therapy should be considered in this setting.
- Antiviral therapy is strongly recommended for all patients with neutropenic fever and suspected or confirmed influenza, even if symptoms have been present for more than 48 hours.^{11,24}
 - ◆ Prospective studies demonstrating modest reductions in influenza illness duration and risk of progression to lower respiratory tract infection were conducted primarily in otherwise healthy adults. Observational studies have shown a decrease in severe clinical outcomes associated with influenza in hospitalized and elderly patients. Although there is a paucity of data addressing immunocompromised patients with influenza, they are likely to have prolonged viral replication and more severe disease and are likely to benefit from antiviral therapy.^{25–33}
- Neutropenic enterocolitis
 - Antibiotic coverage should include Gram-negative and anaerobic bacteria using piperacillin-tazobactam, a carbapenem, or combination therapy with an anti-pseudomonal cephalosporin plus metronidazole.¹⁰
 - While some patients can be managed medically, those with sepsis, peritonitis, bowel ischemia, perforation, or gastrointestinal bleeding warrant urgent surgical consultation.^{10,18,19}
- *C. difficile* infection
 - Oral vancomycin is preferred initial therapy to treat *C. difficile* infection.^{11,20}
- Urinary tract infections

- Additional antibiotic coverage beyond empiric therapy for neutropenic fever is generally not indicated until urine cultures have resulted.¹¹
 - Bloodstream infections
 - For patients with suspected vascular access device infection, vancomycin should be added to empiric antibiotic therapy.^{10, 11}
 - The decision to remove an infected device frequently hinges on the infecting organism isolated in blood culture.¹⁰ Emergent device removal in the ED should involve consultation with hematology/oncology, infectious disease, and/or the inpatient provider unless urgent source control is necessary (*e.g.*, sepsis, septic shock).
 - Central nervous system infections
 - Initial empiric therapy should include an anti-pseudomonal antibiotic with adequate CSF penetration (*e.g.*, cefepime, ceftazidime, or meropenem), vancomycin, and ampicillin (for coverage of *Listeria monocytogenes*).¹¹
 - For patients with encephalitis, high-dose acyclovir should be added to empirically cover for HSV infection.¹¹
5. Management of sepsis and septic shock
- Early empiric antibiotic administration, fluid resuscitation, source control, and vasopressor therapy remain key principles of contemporary sepsis care.³⁴
 - As many patients receive glucocorticoids as part of their cancer therapy, consider adrenal axis insufficiency and the role of hydrocortisone (100 mg of hydrocortisone IV) in its treatment in the setting of refractory hypotension and septic shock.
6. Outpatient Management of Neutropenic fever
- Current recommendations support that carefully selected patient can be considered for outpatient oral therapy. These patients should still receive antibiotics within 1 hour of ED presentation and be monitored for 4 hours. In the ED setting, this decision should be made in conjunction with the patient's oncologist as well as taking into consideration the psychosocial considerations outlined in the NCCN guidelines below.¹⁷
 - For patients not requiring inpatient admission, empiric oral antibiotic therapy comprised of ciprofloxacin (or levofloxacin) PLUS amoxicillin-clavulanate (or clindamycin if penicillin-allergic) is recommended.^{10,11,17} Several risk scores and professional criteria exist to evaluate

patients with neutropenic fever. None have been rigorously studied in the ED. In past retrospective studies, all patients were either admitted or discharged after a period of inpatient monitoring for clinical stability or improvement.

- As with all risk scoring systems, these criteria do not take the place of clinical judgement. If a patient does not seem low-risk for outpatient therapy based on clinical judgement, these scoring systems should not be applied, and patients should be admitted.
- Patients with known antibiotic-resistant organisms (including fluoroquinolone and beta lactam co-resistance) and those already taking prophylactic fluoroquinolones should be treated as inpatients. Additionally, patients undergoing induction chemotherapy for acute leukemia, or patients undergoing HSCT are unlikely to be appropriate candidates for outpatient therapy.^{10,17}
- Multinational Association for Supportive Care in Cancer (MASCC) Risk-Index Score
 - Scoring system derived to identify patients at low risk for poor outcomes (TABLE 2).
 - MASCC scores of 21 identified low-risk patients with a sensitivity of 71%, specificity of 68%, and positive predictive value of 91%.³⁵
 - Several studies have validated the usefulness of the MASCC score as a predictor of poor outcome in different populations,^{36–40} although some have demonstrated poor sensitivity to predict complications in febrile neutropenia.^{40–43}
 - Mixed results exist on the MASCC score's ability to identify appropriate candidates for oral antibiotic therapy and early discharge from the hospital after a period of observation.^{40,42,44–46} IDSA guidelines recommend that patients with high-risk MASCC scores be admitted for empiric antibiotic therapy while “carefully selected” patients with low-risk MASCC scores can be considered for outpatient and/or oral antibiotic therapy.¹⁰
- Clinical Index of Stable Febrile Neutropenia (CISNE) Score
 - Scoring system derived to evaluate solid tumor outpatients with febrile neutropenia at low risk of serious complications and therefore identify a group of patients potentially suitable for home treatment (TABLE 3). Low-risk patients had 0% mortality and 1.1% complication rate.^{41,47}

- The CISNE score has been prospectively validated and shown to outperform the MASCC score.^{43,47}
- Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines
 - Criteria to identify low-risk patients for oral antibiotic therapy and high-risk patients for intravenous antibiotics and inpatient admission.¹⁰ (TABLE 4)
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines
 - Criteria developed to identify patients that can be considered for outpatient therapy.¹¹ (TABLE 5)

Case Conclusion

On hospital day 2, the patient developed worsening abdominal pain and peritonitis. She was taken to the operating room and found to have a non-viable cecum. She underwent resection of her distal ileum and right hemicolon with the creation of an ileostomy. She remained hospitalized for 10 days and completed a 7-day course of piperacillin-tazobactam. She returned for reanastomosis upon completion of chemotherapy with an uncomplicated post-operative course.

Case #2: Fever in the Hematopoietic Stem Cell Transplant (HSCT) Patient

Pertinent History

Several years later, our patient from Case #1 is diagnosed with recurrent ALL. She underwent HSCT 6 weeks ago and presents to the ED with a fever of 38.1° C (100.6° F) and a 1-week history of progressive, non-productive cough. She denies chest pain, hemoptysis, or dyspnea.

Pertinent Physical Exam

T 38.1° C (100.6° F), BP 135/75, Pulse 86, RR 18, SpO2 96%

General: Well-appearing, no acute distress.

Oropharynx: No oropharyngeal lesions or plaques.

Cardiovascular: Regular rate and rhythm without murmurs, rubs, or gallops.

Pulmonary: No respiratory distress. Auscultation reveals mild fine, dry crackles in the right mid and upper lung fields.

Chest: Right chest port without erythema, warmth, fluctuance, tenderness, or drainage.

Abdomen: Soft, non-tender to palpation, no rebound or guarding.

Skin: Warm and well-perfused; no rashes, erythema, or swelling.

Neurologic: Awake, alert, oriented x4, normal strength and sensation throughout.

Diagnostic Testing

ANC 160 cells/ μ L. All other labs are unremarkable.

Chest radiograph: No pulmonary infiltrates, nodules, or consolidation.

Plan

Obtain blood cultures. Initiate empiric antibiotics for neutropenic fever (cefepime). Order respiratory virus testing (including influenza). Perform CT of the chest.

Update

Respiratory virus testing is negative. Chest CT demonstrates ground-glass infiltrates with a 1.6 cm nodule in the right upper lobe. Infectious Disease is consulted with recommendations to start empiric voriconazole in addition to cefepime and admit to the oncology service for further care.

Learning Points: Fever in the HSCT Patient

Introduction and Background

With the use of HSCT to treat hematologic and solid tumor malignancies comes an increased risk of common and atypical infections. Several factors influence an individual's risk of infection including underlying patient comorbidities, stem cell source, conditioning regimen, immunosuppression regimen, and history of post-HSCT complications (particularly graft-versus-host disease).⁴⁸

Pathology/Pathophysiology

1. The risk of infection after HSCT varies across time. Prior to HSCT, the recipient undergoes a "conditioning" regimen which prepares the bone marrow for engraftment and virtually eliminates the endogenous immune system, rendering the patient susceptible to a host of infections until their immune system reconstitutes post-engraftment.⁴⁹
2. Graft-versus-host disease (GVHD) can significantly delay a patient's immune reconstitution, prolonging the risk for infection. Chronic immunosuppression (*e.g.*, glucocorticoids) to treat GVHD further compounds this risk.^{49,50}
 - HLA-mismatched or HLA-matched unrelated donors (MUD) have a greater risk of infectious complications compared to HLA-matched related donor transplants due to higher incidence of GVHD.⁴⁹

Making the Diagnosis

1. HSCT patients are prone to severe and atypical infections due to the effects of immunosuppression on both myeloid and lymphoid immune cell lineages.
 - Bacterial infections

- Early after HSCT, bacterial infections associated with neutropenia, vascular access devices, and mucositis are common.^{48,49}
- Later, the risk for bacterial infection depends on the severity of GVHD and degree of immunosuppression (particularly with glucocorticoids) required to treat GVHD. HSCT patients have an increased risk of infection with encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*).^{48,49}
- Viral infections
 - Viral infections are common and can cause severe illness.
 - Several herpesviruses can cause clinically important infections, most notably CMV.^{48,49} CMV reactivation can manifest as pneumonitis, colitis, retinitis, hepatitis, or encephalitis.⁴⁸ HSV and varicella zoster virus (VZV) can cause both localized as well as disseminated infection.⁴⁸
 - Respiratory viruses can cause disease at any time but tend to follow seasonal patterns like the general population. Infections frequently progress to pneumonia with rates as high as 35%, with a mortality as high as 30%. CT is more sensitive compared to chest radiography for diagnosis of pneumonia in this population. Caution is advised when diagnosing viral pneumonia, as documented viral infection does not exclude bacterial or fungal infection.⁴⁸
- Fungal infections
 - *Aspergillus* is the most common mold species encountered in HSCT patients.⁴⁸ Pulmonary aspergillosis can present with nodular infiltrates, cavitary lesions, segmental consolidation, or ground glass opacities on chest imaging.
 - Infections involving yeast, primarily *Candida* spp, include oral candidiasis, esophagitis, candidemia, and hepatosplenic (chronic) infection.⁴⁸ Candidemic patients are likely to present with fever and SIRS/sepsis.⁴⁸
 - *Pneumocystis jirovecii* (previously *P. carinii*) infection should be considered in patients with pneumonia not taking prophylaxis (e.g., trimethoprim-sulfamethoxazole), particularly in the setting of GVHD and during periods of lymphopenia.⁴⁸
- 2. Infection risk due to obliteration and reconstitution of the immune system after HSCT follows a characteristic and predictable timeline.^{48–50} (FIGURE 3)

- Pre-transplant period
 - Period prior to infusion of stem cells.
 - Low risk of infection, which depends on underlying patient comorbidity and existing immunosuppressive therapy.^{49,50}
 - Most common infections include SSTIs, oral mucosal infections, and urinary tract infections.⁴⁹
- Pre-engraftment period
 - Period from infusion of stem cells (Day 0) until marrow engraftment.
 - Infection risk is related to neutropenia, mucosal barrier breakdown (mucositis), and invasive catheters, as seen in the case of neutropenic fever.
 - Innate immunity is the first to recover (neutrophils and epithelial barriers) 2–3 weeks after infusion. If engraftment is delayed, patients can have prolonged neutropenia, which places the patient at greater risk of invasive fungal infections (*e.g.*, *Candida* spp, *Aspergillus* spp).⁴⁹
- Early post-engraftment period
 - Period from marrow engraftment until Day 100 with early immune reconstitution.
 - Impaired T-cell function leads to poor cell mediated immunity.
 - Viral infections are common during this period.
- Late post-engraftment period
 - Period begins around Day 100 post stem cell infusion.
 - Patients without development of GVHD typically regain reasonable immunity within 1–2 years. It takes months for the restoration of adequate B-cells and CD8 T-cells. CD4 T-cells may remain inadequate for years, especially in older patients with less thymic reserve.
 - Humoral defects lead to risk of infections with encapsulated organisms, especially of the respiratory tract, as well as viral infections, for at least 1 year.^{49,50}

3. GVHD

- Development of chronic GVHD can significantly delay restoration of normal immune function, particularly cell-mediated and humoral immunity. This can prolong the timeline for risk of infection.⁴⁹

- Patients with GVHD are extremely vulnerable to infectious complications due to immunosuppression from the disease process itself as well as its treatment (additional immunosuppression with glucocorticoids).⁴⁹
 - Profound immunosuppression predisposes GVHD patients to a range of fungal (*Aspergillus* spp, *Zygomycetes*, *Pneumocystis jirovecii*), viral (e.g., CMV, VZV), and bacterial infections.⁴⁹
- 4. Post-HSCT patients, regardless of neutropenia, are functionally immunosuppressed. Any patient presenting with fever or infectious symptoms should undergo a thorough history and physical examination, targeted imaging based on symptomatology, basic laboratory testing, and microbiological cultures as clinically indicated.

Treating the patient

The initial ED management of HSCT patients presenting with fever is no different than that of other cancer patients with neutropenic fever, although the differential diagnosis for infection is significantly broader. HSCT patients presenting with fever should be rapidly started on broad-spectrum empiric antibiotics. Consider adding empiric antifungal coverage if the suspicion for fungal infection (e.g., *Aspergillus*, *Candida*) is high.

Recognize that the diagnosis and targeted therapy for many of the opportunistic infections encountered in the HSCT population will not be completed in the emergency setting. Emergency physicians should have a low threshold for inpatient admission for further diagnostic testing, and consultation with infectious disease and hematology/oncology specialists is recommended early in the care of these complex patients.

Case Conclusion

The patient was continued on cefepime and voriconazole. The next morning, she underwent bronchoscopy with biopsy of the pulmonary nodule. Blood cultures remained no growth. Histopathology of lung nodule revealed hyphae and tissue culture eventually grew *Aspergillus fumigatus* on incubation day 6. Cefepime was discontinued and the patient was discharged on hospital day 10 to complete a prolonged course of voriconazole for pulmonary aspergillosis.

Case #3: Fever in the oncology patient receiving immunotherapy

Pertinent History

Our patient returns now with relapsed ALL, diagnosed 2 months ago. She is currently receiving immunotherapy with blinatumomab, a bispecific T-cell enhancing (BiTE) antibody. Treatment was initiated 16 days ago and she was discharged from the oncology ward on continuous home infusion 2 days ago. She presents to the ED for fever to 39.2° C (102.6° F). A review of systems is notable for dyspnea, malaise, and lethargy.

Pertinent Physical Exam

T 39.3° C (102.7° F), BP 88/65, Pulse 110, RR 22, SpO2 87%

General: Appears lethargic with generalized weakness.

Cardiovascular: Rapid rate, regular rhythm without murmurs, rubs, or gallops.

Pulmonary: Mild tachypnea. Lungs clear to auscultation.

Chest: Right chest port without erythema, warmth, fluctuance, tenderness, or drainage. Current infusion of medication (blinatumomab) via port.

Abdomen: Soft, nontender to palpation, no rebound or guarding.

Skin: Delayed capillary refill. No rashes, erythema, or mottling.

Neurologic: Awake, alert, oriented x4, non-focal sensory and motor exam.

Diagnostic Testing

WBC	$3.8 \times 10^9/L$	BUN	12 mg/dL
ANC	400 cells/ μ L	Creatinine	0.8 mg/dL
Hgb	9.8 g/dL	AST	78 IU/L
Platelets	$480 \times 10^9/L$	ALT	60 IU/L
Lactate	3.2 mmol/L	Alk phos	160 IU/L
CO ₂	19 mEq/L	Bilirubin	1.1 mg/dL

Chest radiography: No pulmonary infiltrates, nodules, or consolidation.

Plan

Stop infusion of blinatumomab. Obtain blood cultures. Resuscitate with parenteral fluids and monitor blood pressure response. Administer empiric antibiotics for neutropenic fever. Consult infectious disease and hematology/oncology. Admit to the intensive care unit (ICU).

Update

Hematology/oncology raises the concern for cytokine release syndrome (CRS), recommends administration of dexamethasone in the ED, and agrees with the plan for ICU admission. Infectious disease agrees with empiric antibiotic therapy for neutropenic fever. The patient transiently responds to fluids but ultimately requires low-dose norepinephrine to maintain a mean arterial pressure >60 mmHg. She is transferred to the ICU shortly thereafter.

Learning Points: Fever in the oncology patient receiving immunotherapy

Introduction and Background

Immunotherapies, such as monoclonal antibodies and chimeric antigen receptor (CAR) T-cell therapies, are an evolving class of medications used to treat cancers and other conditions, including both solid tumors and hematologic malignancies. While there are

several currently in use, there are a large number undergoing development or testing in clinical trials.⁵¹

Pathology/Pathophysiology

Monoclonal antibodies work by boosting the host immune response to cancer cells, blocking the growth or spread of cancer cells, or targeting immune checkpoints.⁵² CARs allow major histocompatibility complex (MCH) independent activation of cytotoxic T-cells to target specific tumor antigens.^{51,53}

1. Side-effects of these medications can generally be grouped into two classes: autoimmune toxicity and cytokine-mediated toxicity.⁵³
 - Autoimmune toxicity
 - Monoclonal antibodies, notably immune checkpoint inhibitors, can have adverse effects due to general immune enhancement, termed immune-related adverse events (irAEs). These are common side effects and while most are mild and easily managed, they can also become life-threatening. IrAEs typically occur weeks to months after infusion (TABLE 6) and are treated with glucocorticoids.⁵²
 - Cytokine mediated toxicity
 - T-cell engaging immunotherapies, such as CARs or bispecific T-cell enhancing (BiTE) antibodies, can cause cytokine release syndrome (CRS). CRS is a potentially fatal condition caused by the non-physiologic activation of T-cells and subsequent release of inflammatory cytokines.^{51,53}

Making the Diagnosis

CRS typically begins within 14 days of initiation of therapy.⁵⁴ While most patients develop CRS within their hospitalization treatment period, patients who are discharged home can also develop this syndrome and present to the ED. Many of the clinical features of CRS overlap with that of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH). Patients develop a systemic inflammatory response as well as elevated inflammatory markers, with fever often being the first sign. CRS can be self-limiting, needing only supportive care, or progress to life-threatening inflammation requiring immunosuppression (TABLE 7).^{53,54} Significant overlap exists among the symptoms of CRS, neutropenic fever, and sepsis. Patients at risk for CRS are often likewise at risk for infection.⁵³ Emergency physicians must recognize this fact, maintain a broad differential diagnosis, and treat patients accordingly.

No universal grading system exists for CRS, although the most widely-accepted system used by the National Cancer Institute is summarized in TABLE 8.³⁹ Neurologic toxicity may be part of the spectrum of CRS, but is not included in this scoring system.^{53–57}

Treating the Patient

1. Treatment of CRS is aimed at supportive management and the inhibition of inflammatory cytokines.
2. Two medications are currently in use to treat CRS: glucocorticoids and tocilizumab, an IL-6 inhibitor. While activation of the immune system causes CRS, it is also what gives these therapies their anti-tumor effects. For this reason, the goal of treatment is to limit life-threatening side effects of CRS while attempting to maintain anti-tumor effects.⁴⁸
 - Treatment of CRS related to CAR T-cell therapies:
 - The mainstay of therapy for CRS related to CAR T-cell therapies is tocilizumab.⁵⁴
 - One treatment algorithm proposes therapy based on CRS grade and patient factors:⁵³
 - ◆ Grade 1: supportive care
 - ◆ Grade 2: supportive care +/- tocilizumab
 - ◆ Grade 3 or 4: Supportive care + tocilizumab
 - Treatment of CRS related to BiTE antibodies:
 - Pausing the infusion (the only approved BiTE antibody is administered via continuous infusion, which the patients go home on) +/- administration of dexamethasone is the mainstay of treatment of CRS related to blinatumomab.⁵⁴
3. All patients with suspected CRS should be admitted to the hospital, and those with severe symptoms should be admitted to the ICU.
4. Many institutions and/or oncology centers have their own protocol for when to administer immunosuppressants for CRS, or what agent should be used. Hematology/oncology should be involved immediately in any patient presenting with suspected CRS to the ED.
5. It is often prudent to start immediate antibiotics for presumed infection in patients with febrile neutropenia, severe illness, or other infectious symptoms, even if CRS is the suspected cause, as CRS and infection cannot be differentiated based on symptoms. Infectious disease should be involved early and often.

Case Conclusion

Overnight in the ICU, our patient began to show signs of hypoperfusion. Echocardiography demonstrated global cardiomyopathy with a left ventricular ejection fraction of 35%. Inotropic support was added. By the next afternoon, her fever had resolved, and she required less and less cardiovascular support. Blood cultures returned no growth at 48 hours and antibiotics were discontinued as her symptoms were felt to be related to CRS. She was

discharged on hospital day 5. Outpatient follow up showed resolution of her cardiomyopathy and she is scheduled to resume blinatumomab.

Discussion

In all three cases, our patient was immunocompromised and at risk for infection, but for different reasons. Consequently, the differential diagnosis for infection varied widely based on cancer therapy. Patients with chemotherapy-related neutropenia are at risk for common bacterial as well as fungal infections. The differential diagnosis for infection in the HSCT population is wide-ranging. Due to significant immunosuppression and potential for GVHD, HSCT patients are at risk for a broader range of organisms including bacteria, viruses, and fungi, both common and atypical. Patients receiving T-cell engaging immunotherapies are at risk of neutropenia (and the infections that accompany this) as well as CRS. While CRS is not infectious in origin, its presentation is indistinguishable from infection. Emergency physicians caring for patients receiving cancer immunotherapy must be aware of this phenomenon, because treatment of infection alone will not improve the patient's clinical status.

Emergency physicians should maintain a high index of suspicion for infection in cancer patients seeking care in the ED. Atypical presentations abound, and fever may often be the only presenting symptom. Initial evaluation should include basic laboratory testing, microbiological cultures, and appropriate imaging. Timely initiation of empiric antibiotic therapy in the ED is paramount to reducing mortality, particularly in critical illness. A low threshold for inpatient admission is advisable, particularly for significantly immunocompromised cancer patients (*e.g.*, severe, profound, or prolonged neutropenia; HSCT; GVHD). Early involvement of hematology/oncology and infectious disease specialists in the care of these complex patients helps guide empiric antibiotic therapy, diagnostic evaluation, and definitive care (Box 1).

Box 1

Pattern Recognition

- Fever + Neutropenia + Clinically stable: Empiric antibiotics [anti-pseudomonal beta-lactam (*e.g.*, cefepime), a carbapenem (*e.g.*, meropenem), or piperacillin-tazobactam]
- Neutropenic fever + SIRS: Add antifungal coverage
- Neutropenic fever + hemodynamic instability: Go broad-spectrum! Consider adrenal axis insufficiency
- Neutropenia + Abdominal pain: Neutropenic enterocolitis (typhlitis)
- Fever and/or SIRS + Immunotherapy (T-cell engaging): Consider cytokine release syndrome
- GVHD = Very immunocompromised!

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Key Points

- Infections in the cancer patient can be difficult to diagnose due to their immunocompromised status, lack of typical inflammatory signs and symptoms, and atypical presentations. Fever may often be the only presenting symptom.
- Emergency physicians should maintain a high index of suspicion for infection in cancer patients seeking care in the emergency department. Timely initiation of empiric antibiotic therapy is paramount, and a low threshold for inpatient admission is advisable.
- Patients with chemotherapy-related neutropenia are at risk for common bacterial as well as fungal infections. Hematopoietic stem cell transplant patients are at risk for infection due to a broader range of organisms including bacteria, viruses, and fungi, both common and atypical.
- Cytokine release syndrome can occur in patients receiving T-cell engaging immunotherapies. While not infectious in origin, its initial clinical presentation can be indistinguishable from that of an infection.

Figure 1. Orbital Cellulitis. CT showing marked proptosis of the right eye and a collection above the right orbital floor tracking from the laminal papyracea.
From: Mahmood H, Flora H, Murphy C, Sutton D. Retrobulbar abscess: rare complication after repair of an oroantral communication. *Br J Oral Maxillofac Surg.* 2018 Mar 2. pii: S0266-4356(18)30054-8. doi: 10.1016/j.bjoms.2018.02.011

Figure 2.

CT scan through the base of the cecum shows a circumferential wall thickening of distal ileum (arrow) with a slight distension of surrounding small bowel and marked sub-mucosal.

(b) Coronal CT image shows the wall thickening (arrow) with increased edema of distal ileum and inflammatory changes in the adjacent mesenteric fat.

From: Tiseo M, Gelsomino F, Bartolotti M, Barili MP, Ardizzoni A. Typhlitis during second-line chemotherapy with pemetrexed in non-small cell lung cancer (NSCLC): A case report. *Lung Cancer*. 2009 Aug;65(2):251–3. doi: 10.1016/j.lungcan.2009.02.021.

Figure 3.

Infection timeline after HSCT for most common pathogens.

Data from Marr KA. Infections in Hematopoietic Stem Cell Transplant Recipients. In Cohen J, Powderly WG, Opal SM, ed. *Infectious Diseases*. 4th ed. Elsevier, 2017:739–745.

Ramaprasad C, Pursell KJ. Infectious complications of stem cell transplantation. *Cancer Treat Res*. 2014;161:351–70. doi:10.1007/978-3-319-04220-6. Tomblyn M, Chiller T, *et al*. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143–1238. doi:10.1016/j.bbmt.2009.06.019.]

Table 1

Additions to empiric antibiotic therapy for patients with known antibiotic-resistant organisms.

Pathogen	Addition to Empiric Therapy
Methicillin-resistant <i>S. aureus</i> (MRSA)	Consider the addition of vancomycin, linezolid, or daptomycin [†] .
Vancomycin-resistant Enterococci (VRE)	Consider the addition of linezolid or daptomycin.
Extended spectrum beta-lactamase (ESBL) producing Gram-negative bacteria (e.g., <i>K. pneumoniae</i> , <i>E. coli</i>)	Consider early use of a carbapenem.
Carbapenemase-producing Gram-negative bacteria (e.g., Enterobacteriaceae and <i>Pseudomonas</i> spp)	Consider tigecycline or polymyxin-colistin.

[†] Recognize that daptomycin is inhibited by pulmonary surfactant and is therefore not an appropriate antibiotic for treating pneumonia. Data from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. 2011;52(4):e56–93. doi:10.1093/cid/cir073.

Table 2

MASCC Risk Index scoring criteria.

21: low risk, <21: high risk, maximum: 26.

Data from Klastersky J, Paesmans M, Rubenstein EB, *et al.* The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol.* 2000;18(16):3038–51.

Characteristic	Weight
Burden of febrile neutropenia	
• No or mild symptoms	+5
• Moderate symptoms	+3
• Severe symptoms	+0
Hypotension	
• Systolic blood pressure ≥ 90	+5
• Systolic blood pressure <90	+0
Active COPD	
• No	+4
• Yes	+0
Cancer characteristics	
• Solid tumor	+4
• Hematologic malignancy without prior fungal infection	+4
• Hematologic malignancy with prior fungal infection	+0
Dehydration requiring parenteral fluids	
• No	+3
• Yes	+0
Status at fever onset	
• Outpatient	+3
• Inpatient	+0
Age	
• <60	+2
• ≥ 60	+0

Table 3

CISNE Score. Low-risk (0), intermediate-risk (1–2), high-risk (≥3).

Data from Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu J, et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. *J Clin Oncol*. 2015;33(5):465–71. doi:10.1200/JCO.2014.57.2347.

Characteristic	Weight
ECOG Performance Status	
• <2	+0
• 2	+2
Stress-induced hyperglycemia	
• No	+0
• Yes	+2
COPD	
• No	+0
• Yes	+1
Chronic cardiovascular disease	
• No	+0
• Yes	+1
Mucositis	
• Grade <2	+0
• Grade ≥2	+1
Monocytes	
• ≥200/μL	+0
• <200/μL	+1

Table 4

IDSA Criteria for low- and high-risk febrile neutropenia.

Data from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. 2011;52(4):e56–93. doi:10.1093/cid/cir073.

Low-Risk Criteria	High-Risk Criteria
Anticipated brief (<7 days) neutropenia	Prolonged and profound neutropenia (<100 for >7 days)
Clinically stable	Hemodynamic instability
No medical comorbidities	COPD
	Poor functional status
	Advanced age
	Pneumonia, pulmonary infiltrate, or hypoxemia
	Altered mental state
	GI symptoms
	Mucositis interfering with swallowing
	Indwelling catheter infection
	Uncontrolled pain
	Uncontrolled cancer
	Hepatic or renal insufficiency

Table 5

NCCN Guidelines for outpatient therapy of febrile neutropenia. Patients can be considered for outpatient therapy if they meet none of the high-risk, most of the low-risk, and all of the outpatient criteria. Data from Baden LR, Swaminathan S, Angarone M, et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(7):882–913.

High-Risk Criteria	Low-Risk Criteria	Outpatient Criteria
Anticipated prolonged severe neutropenia	Anticipated short duration of severe neutropenia (≥ 100 for <7 days)	No critical lab results on screening labs
Pneumonia or other complex infection	No comorbid illnesses requiring inpatient management	24-hour home caregiver available
Clinically unstable	ECOG 0–1	Home telephone
Significant comorbidity	Outpatient status at time of fever onset	<1 hour from appropriate medical care
Mucositis grade 3 or 4	MASCC low-risk (≥ 21)	Access to emergency facilities
Inpatient status at time of fever onset	No hepatic (5x upper limit transaminases) or renal (CrCl <30) insufficiency	Adequate home environment
MASCC high-risk (<21)		Patient consent
Hepatic or renal insufficiency		
Allogenic HSCT		
Alemtuzumab therapy		
Uncontrolled or progressive cancer		

Table 6

Immune-related adverse events caused by immune checkpoint inhibitors. Data from Caruana I, Diaconu I, Dotti G. From Monoclonal Antibodies to Chimeric Antigen Receptors for the Treatment of Human Malignancies. *Seminars in oncology*. 2014;41(5):661–666. doi:10.1053/j.seminoncol.2014.08.005.

Organ system	Effects	Timing after immunotherapy
Dermatologic	Rash (maculopapular), pruritus, vitiligo, blisters, SJS/TEN	3–6 weeks
Gastrointestinal	Diarrhea, colitis, intestinal perforation	5 weeks
Hepatic	Transaminitis, hyperbilirubinemia, fatigue, nausea, jaundice, fever, change in stool or urine color, pruritic, icterus, hepatomegaly.	6–14 weeks
Endocrine	Hypopituitarism with or without hypophysitis, adrenal insufficiency, hyper/hypothyroid, gonadal hypofunction.	7 weeks and on
Other	Meningitis, uveitis, pneumonitis, pancreatitis, pericarditis, myocarditis, nephritis, angiopathies, hemolysis, thrombocytopenia	

Table 7

Signs and symptoms of cytokine release syndrome. Data from Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*. 2016;127(26):3321–3330. doi: 10.1182/blood-2016-04-703751.

Organ system	Signs and Symptoms
Constitutional	Fever, malaise, fatigue, myalgias, arthralgias, anorexia
Dermatologic	Rash
Cardiovascular	Tachycardia, wide pulse pressure, hypotension, increased cardiac output, cardiomyopathy
Pulmonary	Tachypnea, hypoxemia, acute respiratory distress syndrome
Gastrointestinal	Nausea, vomiting, diarrhea
Hepatic	Transaminitis, hyperbilirubinemia
Renal	Azotemia
Vascular	Elevated D-dimer, hypofibrinogenemia, coagulopathy, bleeding, disseminated intravascular coagulation,
Neurologic	Headache, altered mental status, confusion, delirium, aphasia, hallucinations, tremor, dysmetria, seizures

Table 8

Grading of cytokine release syndrome.

Grade	Toxicity	Examples
1	Symptoms are not life threatening and require symptomatic treatment only.	Fever, nausea, fatigue, headache, myalgias, malaise
2	Symptoms require and respond to moderate intervention.	Oxygen requirement <40%, hypotension responsive to fluids or low dose vasopressor, grade 2 organ toxicity [†]
3	Symptoms require and respond to aggressive intervention	Oxygen requirement ≥40%, hypotension requiring high dose [‡] or multiple vasopressors, grade 3 organ toxicity [†] , grade 4 transaminitis [†]
4	Life-threatening symptoms.	Requirement for ventilatory support, grade 4 organ toxicity [†] (excluding transaminitis)
5	Death	

[†] Grading according to the Common Terminology Criteria for Adverse Events.

[‡] High dose vasopressors: Norepinephrine 20 µg/kg/min, Dopamine 10 µg/kg/min, Phenylephrine 200 µg/kg/min, Epinephrine 10 µg/kg/min. Data from Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188–195. doi:10.1182/blood-2014-05-552729.