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When Planets Collide: The Intersection of Internal Medicine & Oncology

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07/23/2023

HEALTHTRUST UNIVERSITY CONFERENCE

Disclosures

- The presenter has served as a consultant on advisory boards for Pfizer Inc. and Daiichi Sankyo
- All relevant financial relationships have been mitigated
- This presenter will discuss off-label use of Vedolizumab

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Learning Objectives

At the end of this session, participants should be able to:

1. Recall mechanisms of action of pathologic phenomena regarding oncologic emergencies.
2. Recognize signs and symptoms of disease processes and diagnostic criteria of oncologic emergencies.
3. Identify management strategies and supportive care plans for oncologic emergencies.

Topics to Cover

- Febrile Neutropenia
- Tumor Lysis Syndrome
- Differentiation Syndrome
- Immune-related Adverse Events
- Cytokine Release Syndrome (CAR-T Toxicities)

Febrile Neutropenia

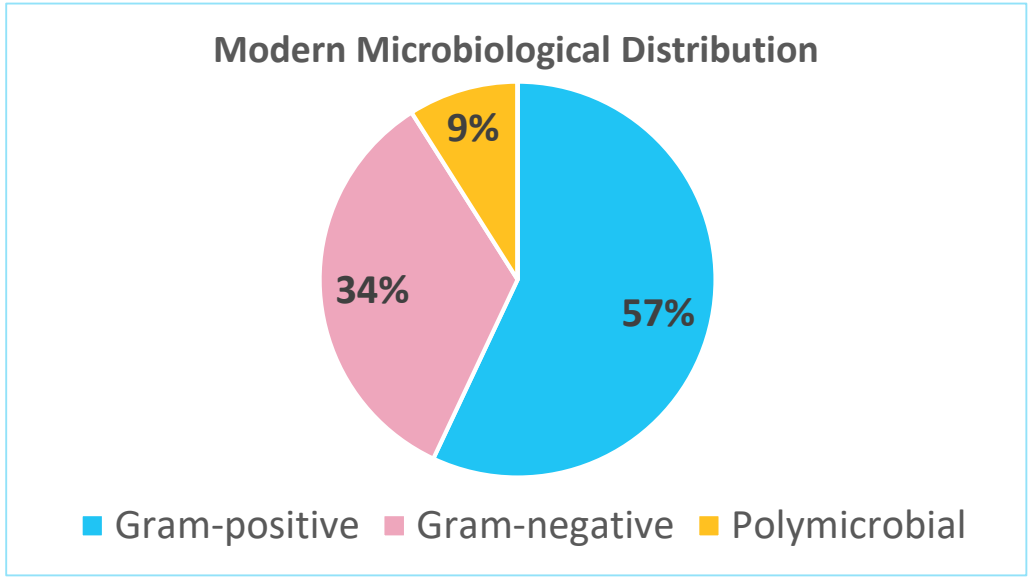
Febrile Neutropenia

- Chemotherapy agents damage rapidly dividing cells – act upon myeloproliferative cells in the bone marrow, resulting in neutropenia
- Unopposed gram-negative bacteremia has a mortality rate of up to 70% in neutropenic patients with no antibiotics
  - Mortality rate has reduced to as low as 4% with refinement of febrile neutropenia treatment
- Fever definition:
  - > 38.3 C (101 F): single oral measurement **OR** > 38.0 C (100.4 F) sustained over a 1-hr period
- Neutropenia definition:
  - ANC (absolute neutrophil count) of < 500 cells/mm^3 **OR** ANC that is expected to decrease to < 500 cells/mm^3 during the next 48 hr
- Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection

Source: Zimmer AJ, Freifeld AG. Optimal management of neutropenic fever in patients with cancer. J Oncol Pract. 2019;15(1):19-24.
Freifeld AG, Bow EJ, Sepkowitz KA, et al. 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.

Febrile Neutropenia

- Up to 50% of patients with solid tumors and >80% of those with hematologic malignancies will develop febrile neutropenia during ≥1 chemotherapy cycle
- Documented infections occur in 20%–60% of febrile episodes
  - Common cause of fever is translocation of enteric bacteria into the bloodstream[1]



Source: Zimmer AJ, Freifeld AG. Optimal management of neutropenic fever in patients with cancer. J Oncol Pract. 2019;15(1):19-24.
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Febrile Neutropenia

Assessment (Risk for infectious complications)

High-risk (Requires admission and empiric therapy):

- Anticipated prolonged (>7 days) and profound neutropenia (ANC <100 cells mm^3)
- Significant co-morbid conditions (e.g. hypotension, pneumonia, new-onset abdominal pain, or neurologic changes)

Low-risk patients (outpatient oral empiric therapy)

- Anticipated brief (<7 days duration) neutropenic periods or no or few comorbidities

Formal risk classification with the Multinational Association for Supportive Care in Cancer (MASCC) scoring system:

- High-risk: MASCC score < 21
- Low-risk: MASCC score > 21

Source: Freifeld AG, Bow EJ, Sepkowitz KA, et al. 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.

Febrile Neutropenia

Assessment (Risk for infectious complications)

MASCC Risk-Index Score	
Characteristic	Weight
No–mild illness symptoms	5
Moderate illness symptoms	3
No hypotension	5
No COPD	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age < 60	2

Source: National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections(Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed May 17, 2023.

Febrile Neutropenia

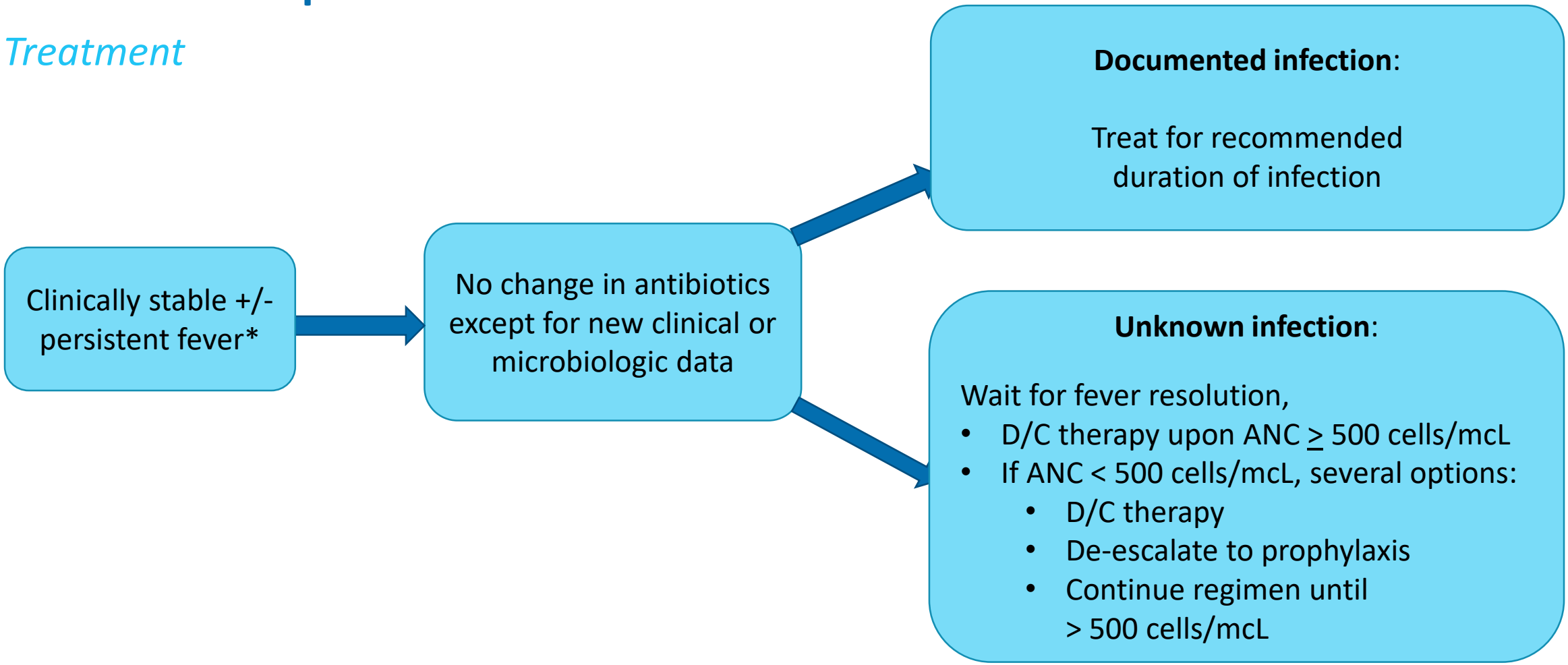
Treatment

- Approach: Administer initial empirical antibiotic therapy to prevent serious morbidity and mortality.
- Due to its association with high mortality rates, coverage of P. aeruginosa has driven the recommended antibiotic choices.
  - Despite gram-positive organisms being more common, gram-negative bacteremias are associated with greater mortality (5% vs. 18%).
- High-risk patients (Hospitalization for **IV empirical antibiotics**):
  - Cefepime (antipseudomonal b-lactam agent)
  - Meropenem or imipenem-cilastatin (carbapenem)
  - Piperacillin-tazobactam
- No single empirical therapeutic regimen has emerged as clearly superior to others.

Source: National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections(Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed May 17, 2023.

Febrile Neutropenia

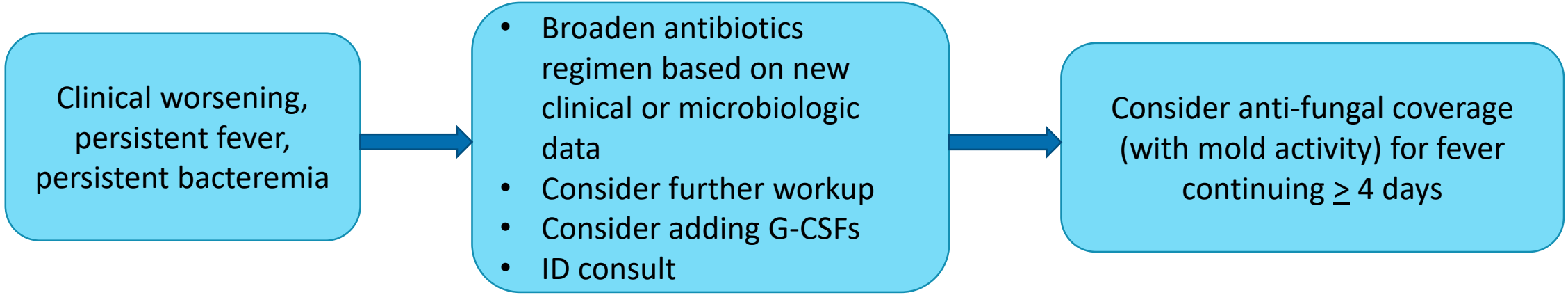
Treatment



Source: National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections(Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed May 17, 2023.

Febrile Neutropenia

Treatment



Source: National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections(Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed May 17, 2023.

Febrile Neutropenia

Vancomycin

- Vancomycin is not recommended as a standard part of the initial antibiotic regimen for febrile neutropenia
- Only consider for the following:
  - Suspected catheter-related infection
  - Skin or soft-tissue infection
  - Pneumonia
  - Hemodynamic instability
  - Blood cultures demonstrating growth for G+ bacteria before final identification & susceptibility
  - Known colonization of MRSA
- If initiated, reassess within 2–3 days of initiation

Source: Freifeld AG, Bow EJ, Sepkowitz KA, et al. 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.
National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections(Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed May 17, 2023.

Febrile Neutropenia

Special Considerations

- Penicillin Allergy:
  - Patients with immediate-type hypersensitivity reaction to penicillin should be treated with ciprofloxacin plus clindamycin or aztreonam plus vancomycin
  - Very lower rate of carbapenem cross-reactivity (0.87%), compared to with cephalosporins (2.1-16.5%)[4]
- G-CSF Use During Febrile Neutropenia[2]:
  - G-CSFs are not generally recommended for treatment of febrile neutropenia, unless for serious infections

Source: Freifeld AG, Bow EJ, Sepkowitz KA, et al. 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.
Kedzior SK. Overcoming Resistance: Antibiotic Guidance for Multidrug-Resistant Febrile Neutropenia in Patients with Cancer. Journal of Hematology Oncology Pharmacy . 2021;11(2):95-104.

Febrile Neutropenia

Take Home Points

- Complete a full patient work-up & distinguish patients from high-risk or low-risk based on the MASCC criteria
- Initiate broad-spectrum antibiotics that have gram-negative Pseudomonal coverage
- Vancomycin may be considered depending on risk factors & is not to be started empirically
- Evaluate the patient day-by-day & adjust antibiotics based on clinical features & laboratory findings

Differentiation Syndrome

Differentiation Syndrome

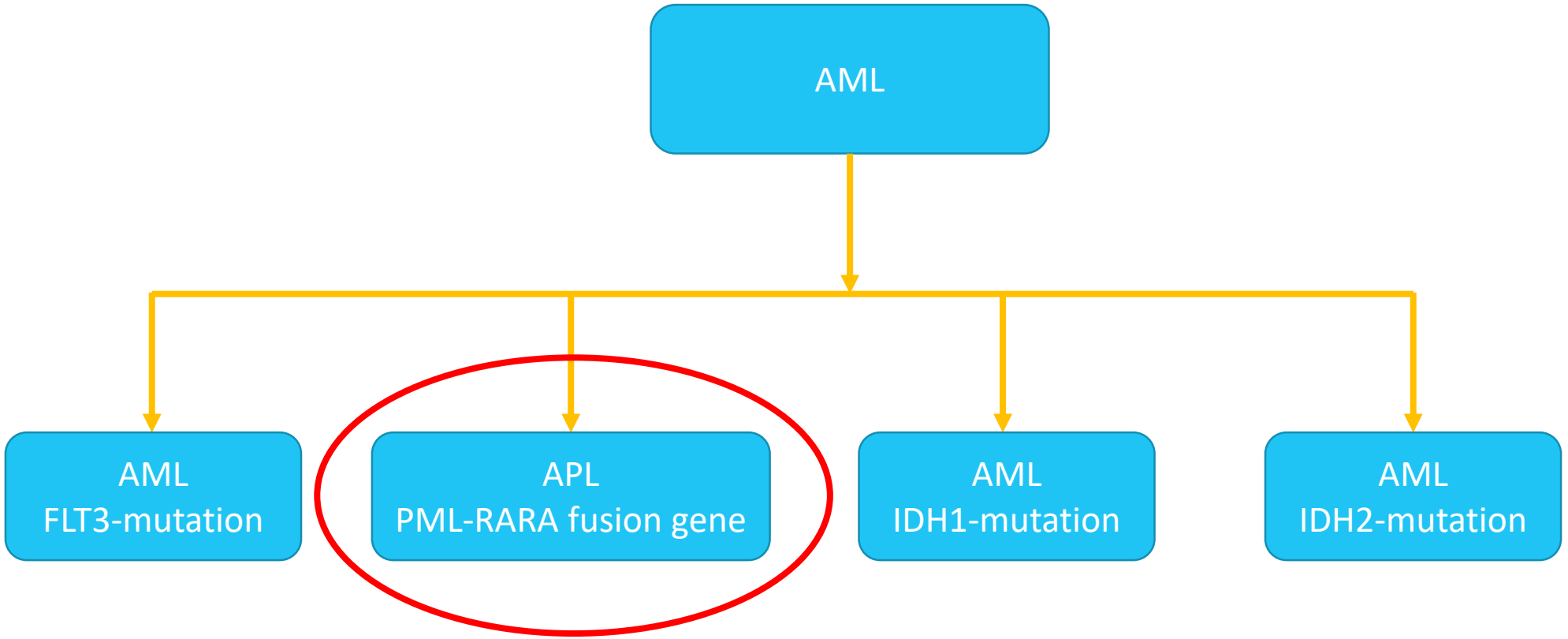
Introduction

- Acute promyelocytic leukemia (APL) is an aggressive subtype of acute myeloid leukemia (AML)
- Promyelocytes accumulate in the blood & bone marrow & displace other blood cells, (RBC, WBC, & platelets)
- Symptoms of APL
  - Neutropenia: Fevers, susceptibility to infection
  - Anemia: Fatigue
  - Thrombocytopenia: Bleeding – associated with DIC

Source: Rego EM, De Santis GC. Differentiation syndrome in promyelocytic leukemia: clinical presentation, pathogenesis and treatment. Mediterr J Hematol Infect Dis. 2011;3(1):e2011048.

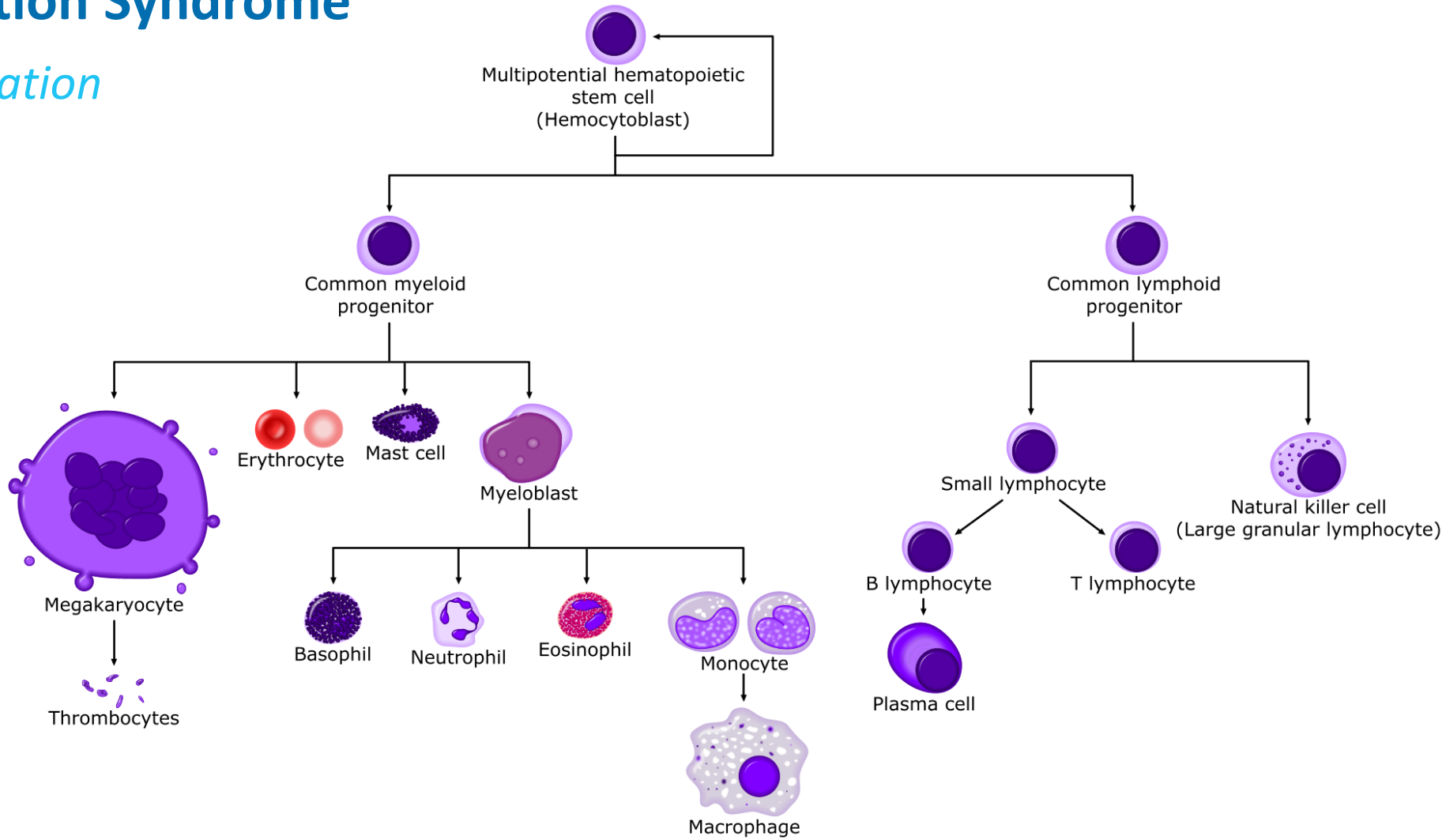
Differentiation Syndrome

AML Classification



Differentiation Syndrome

AML Classification



Differentiation Syndrome

- Differentiation syndrome (DS) is a serious complication that can be life-threatening in patients with acute promyelocytic leukemia (APL)
- Cumulative incidence of DS across all treatment regimens was 17.7%.[6]
- Occurs during Induction therapy (all-trans retinoic acid (ATRA) and/or arsenic trioxide) activates:
  - Cascade of pathophysiologic mechanisms into cytokine release (IL-1, IL-β, IL-6, IL-8 & TNF-α)
  - Systemic inflammatory response syndrome (SIRS), leading to endothelium damage with capillary leak syndrome & occlusion of microcirculation.

Source: Rego EM, De Santis GC. Differentiation syndrome in promyelocytic leukemia: clinical presentation, pathogenesis and treatment. Mediterr J Hematol Infect Dis. 2011;3(1):e2011048.
Gasparovic L, Weiler S, Higi L, Burden AM. Incidence of differentiation syndrome associated with treatment regimens in acute myeloid leukemia: a systematic review of the literature. J Clin Med. 2020;9(10):E3342.
Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. Blood. 2014;123(18):2777-2782.

Differentiation Syndrome

- Symptoms
  - Mild:
    - Unexplained fever
    - Weight gain
    - Peripheral edema
  - Severe:
    - Dyspnea with interstitial pulmonary infiltrates
    - Pleuro-pericardial effusion
    - Hypotension
    - Acute renal failure

Source: Rego EM, De Santis GC. Differentiation syndrome in promyelocytic leukemia: clinical presentation, pathogenesis and treatment. Mediterr J Hematol Infect Dis. 2011;3(1):e2011048.
Image Source: https://pixabay.com/illustrations/people-emotions-feelings-7375857/

Differentiation Syndrome

Treatment

- Due to the high morbidity & mortality of DS, initiate therapy at the earliest suspicion
- Standard regimen is Dexamethasone 10 mg IV BID
- DS, however, shares signs & symptoms that are observed with other complications
- Findings supporting differential diagnosis does not rule out concomitant DS; warrants empiric therapy to cover all suspected complications
- Vast majority of patients presenting with life-threatening complications of DS have a dramatic resolution with early interventions

Source: Rego EM, De Santis GC. Differentiation syndrome in promyelocytic leukemia: clinical presentation, pathogenesis and treatment. Mediterr J Hematol Infect Dis. 2011;3(1):e2011048.
Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. Blood. 2014;123(18):2777-2782.

Differentiation Syndrome

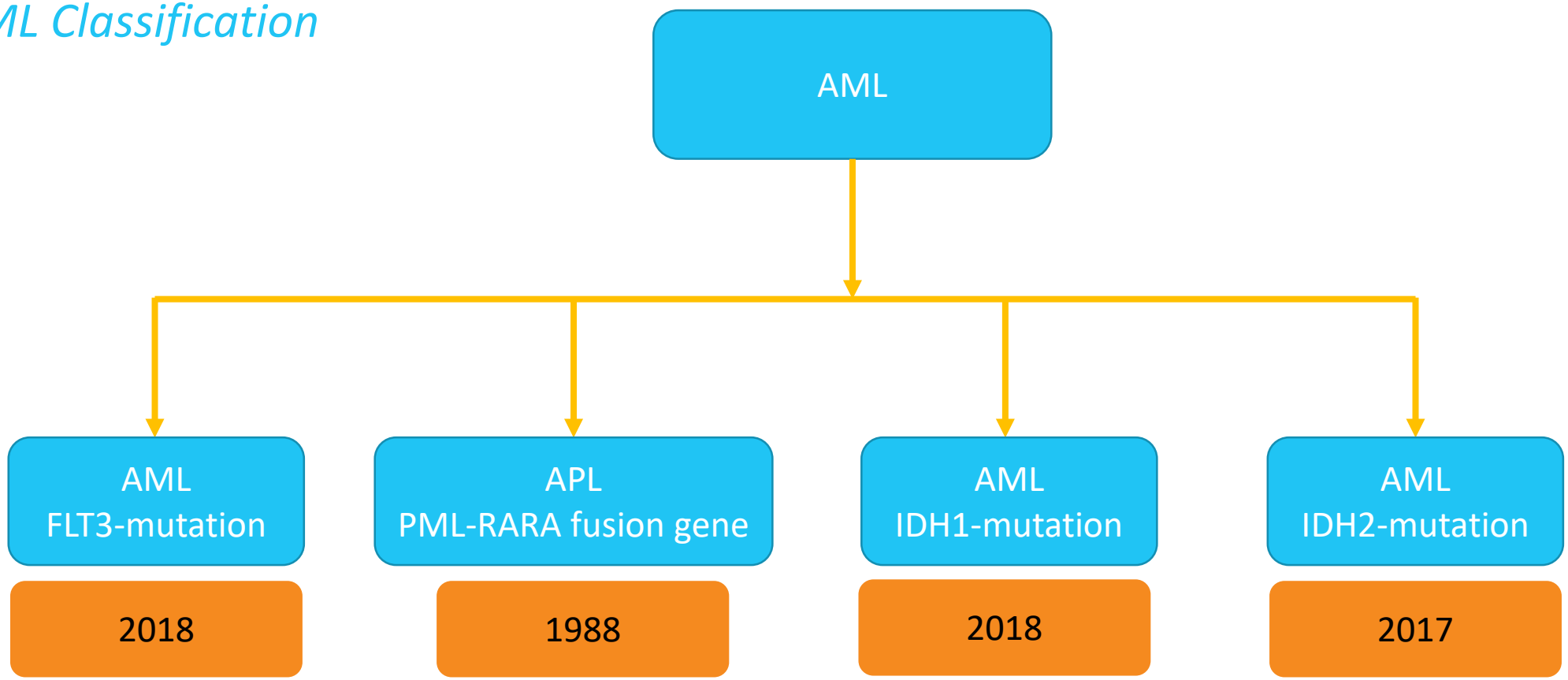
Supportive Care Measures

- Furosemide used to treat fluid overload
- Renal replacement therapy for severe, refractory acute renal failure and/or fluid overload in the context of a vascular leak syndrome
- Control the coagulopathy in the setting of high fluid overload:
  - Prefer use of cryoprecipitate, fibrinogen & coagulation factor concentrates instead of fresh-frozen plasma
- Careful fluids and/or vasopressor agents for hypotension, along with empirical therapy with intravenous antibiotics

Source: Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. Blood. 2014;123(18):2777-2782.

Differentiation Syndrome

AML Classification



Source: Zhou GB, Zhang J, Wang ZY, Chen SJ, Chen Z. Treatment of acute promyelocytic leukaemia with all-trans retinoic acid and arsenic trioxide: a paradigm of synergistic molecular targeting therapy. Philos Trans R Soc Lond B Biol Sci. 2007;362(1482):959-971.
XOSPATA® (gilteritinib) [package insert]. Northbrook, Illinois: Astellas Pharma Inc.; 2022.
IDHIFA® (enasidenib) [package insert]. Summit, NJ: Celgene Corporation; 2020.
TIBSOVO® (ivosidenib) [package insert]. Boston, MA: Servier Pharmaceuticals LLC.; 2022.

Differentiation Syndrome

Drug Name	AML-Subtype	Rate of Differentiation Syndrome
Gilteritinib*	FLT-3 mutation	3%
Ivosidenib*	Isocitrate dehydrogenase-1 (IDH1) mutation	25% of newly diagnosed 19% of relapsed/refractory
Enasidenib**	Isocitrate dehydrogenase-2 (IDH2) mutation	14%

* DS seen as early as 1 day & up to 3 months starting treatment

** DS seen as early as 1 day & up to 3 months starting treatment

Source: XOSPATA® (gilteritinib) [package insert]. Northbrook, Illinois: Astellas Pharma Inc.; 2022.
IDHIFA® (enasidenib) [package insert]. Summit, NJ: Celgene Corporation; 2022.
TIBSOVO® (ivosidenib) [package insert]. Boston, MA: Servier Pharmaceuticals LLC.; 2022.

Differentiation Syndrome

Take Home Points

- Seen in AML (acute myeloid leukemia), particularly the AML-variant of APL (acute promyelocytic leukemia) – usually is a diagnosis of exclusion
- Agents that are known to induce differentiation syndrome include: ATRA (all trans retinoic acid), arsenic trioxide, enasidenib, gilteritinib & ivosidenib
- Initiate Dexamethasone at 10 mg IV Q12hr. & implement other supportive care measures as necessary

Tumor Lysis Syndrome

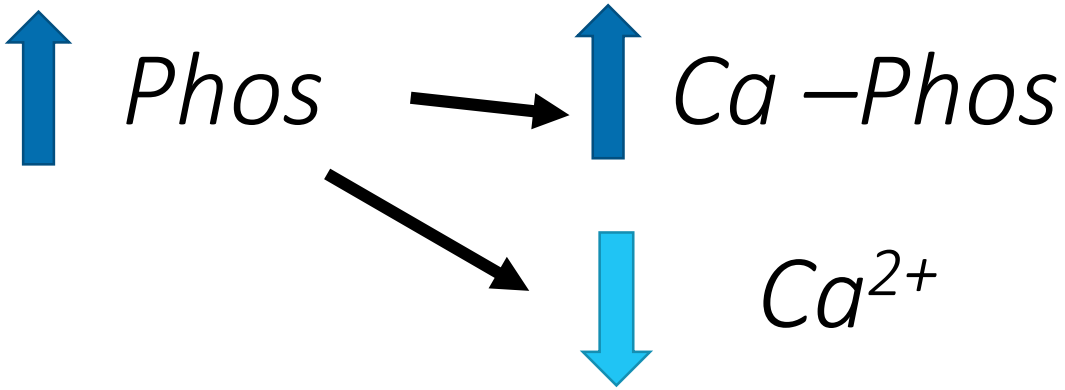
Tumor Lysis Syndrome

Introduction

- Phenomenon when a large number of cancer cells die quickly, releasing their contents into the blood
- Levels of uric acid, potassium & phosphorus rise faster than the kidneys can remove them
- Changes in uric acid, K+, Phos, Ca^{2+}, can affect organ function (kidneys, heart, brain, muscles, GI tract)
- Patients with high tumor burden of the following cancers are at greatest risk of developing TLS:
  - Non-Hodgkin lymphoma (Burkitt, Diffuse Large B-Cell Lymphoma)
  - Hodgkin Lymphoma

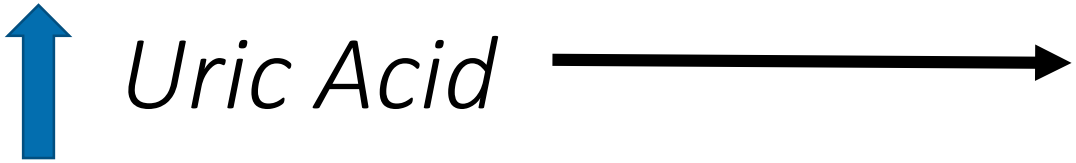
Source: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-1854.

Tumor Lysis Syndrome



Myocardial infarction, pulmonary embolism
Acute phosphate nephropathy

Paresthesia, muscle spasms, cramps, tetany, circumoral numbness & seizures



Urate Nephropathy

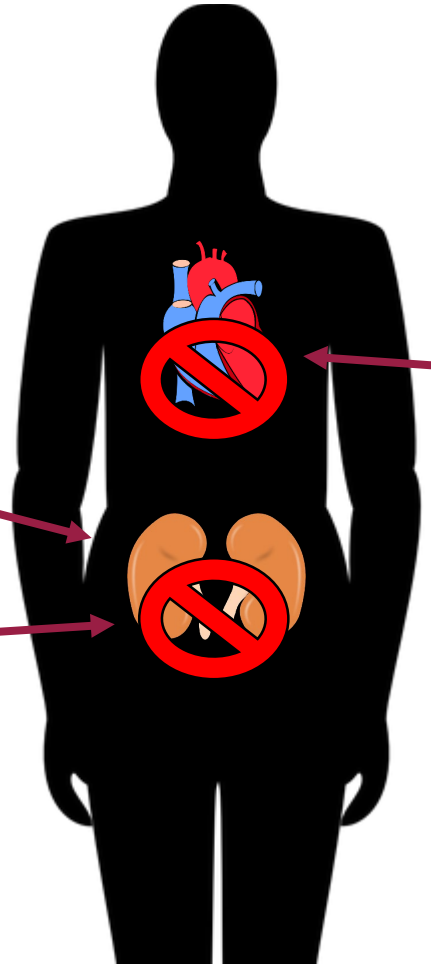
Cardiac arrhythmias, muscle weakness or paralysis → Death

Source: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-1854.

Tumor Lysis Syndrome

Urate Nephropathy

Acute Phosphate Nephropathy



Arrythmia

Cardiac Arrest

Sources
Body: https://pixabay.com/vectors/man-silhouette-stand-straight-308387/
Heart: https://pixabay.com/vectors/human-heart-blood-flow-1700453/
Kidney: https://pixabay.com/vectors/kidney-anatomy-human-man-organ-147499/

Tumor Lysis Syndrome

Prevention/Treatment

- Hydration with NS
  - 2.5–3 L/m^2/24hr to maintain urine output > 100 mL/hr
- Hyperuricemia Management
  - Allopurinol (MOA: Blocks the conversion: hypoxanthine → xanthine → uric acid)
    - Renally excreted, may require dose reduction in renal dysfunction
    - Does not remove the existing uric acid. Takes a few days to reduce uric acid concentration
  - Rasburicase (MOA: Converts uric acid into inactive metabolite, allantoin)
    - Decreases serum uric acid concentrations immediately
    - Very $$
    - Dosing is variable. Can be weight-based or flat-dose of 6 mg, 3 or 4.5 mg may be considered for uric acid levels < 12 mg/dL

Source: Matuszkiewicz-Rowinska J, Malyszko J. Prevention and treatment of tumor lysis syndrome in the era of onco-nephrology progress. Kidney Blood Press Res. 2020;45(5):645-660.

Tumor Lysis Syndrome

Prevention/Treatment (Electrolyte Abnormality Management)

- Hyperphosphatemia:
  - Oral non-calcium phosphate binders (sevelamer)
- Hyperkalemia:
  - Cardiac rhythm monitoring
  - May consider rapid-acting therapies
  - Dextrose 10% with rapid-acting insulin
  - IV Calcium gluconate
- Hypocalcemia
  - Do not correct if asymptomatic
  - Treat symptomatic patients with lowest doses of calcium required to relieve symptoms

May require renal replacement therapy (hemodialysis) in severe cases

Source: Matuszkiewicz-Rowinska J, Malyszko J. Prevention and treatment of tumor lysis syndrome in the era of onco-nephrology progress. Kidney Blood Press Res. 2020;45(5):645-660.

Tumor Lysis Syndrome

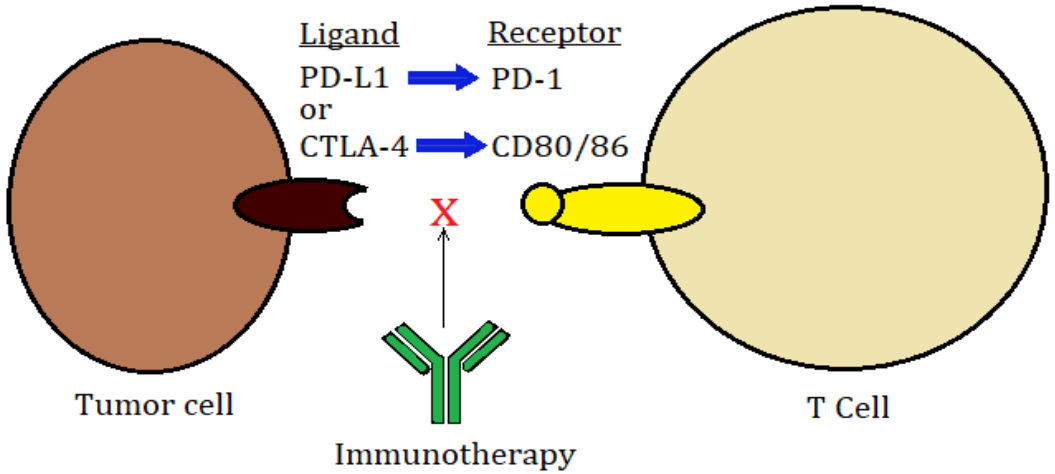
Take Home Points

- Tumor apoptosis, particularly in B-cell lymphomas, may cause changes in serum uric acid, K, Phos & Ca^{++}, which may lead to organ complications
- Management is multifactorial, but fluid hydration is a cornerstone of care & of utmost importance
- Uric acid is often managed by allopurinol, but rasburicase may be considered in severe cases
- Correct electrolyte imbalances & use supportive care measures to mitigate complications

Source: Matuszkiewicz-Rowinska J, Malyszko J. Prevention and treatment of tumor lysis syndrome in the era of onco-nephrology progress. Kidney Blood Press Res. 2020;45(5):645-660.

Immune-Related Adverse Events

Introduction to Checkpoint Inhibitor Immunotherapy



- T Cell function can be de-activated when a tumor cell's ligand binds to T cell's receptor
  - T Cell ligand = PD-L1 or CTLA-4
  - T Cell receptor = PD-1 or CD80/CD86
- Prevention of the ligand-receptor interaction with immunotherapy could prolong and reinvigorate the anti-tumor immune response

Source: "Immune Checkpoint Inhibitors and Their Side Effects." Immunotherapy, American Cancer Society, 22 Mar. 2022, https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html.

Immune-Related Adverse Event

List of Checkpoint Inhibitors

Drug Name	Mechanistic Target	Year Approved
Ipilimumab	CTLA-4	2011
Pembrolizumab	**PD-1**	**2014**
Nivolumab	**PD-1**	**2014**
Cemiplimab	PD-1	2016
Atezolizumab	**PD-L1**	**2016**
Avelumab	PD-L1	2017
Durvalumab	PD-L1	2017
Dostarlimab	PD-1	2021
Relatlimab	LAG-3	2022

Source: Twomey JD, Zhang B. Cancer immunotherapy update: fda-approved checkpoint inhibitors and companion diagnostics. AAPS J. 2021;23(2):39.
EMPERLI (dostarlimab-gxly) [package insert]. Philadelphia, PA: GlaxoSmithKline LLC.; 2023.
OPDUALAG™ (nivolumab and relatlimab-rmbw) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2022.

Immune-Related Adverse Events

Checkpoint Inhibitor Indications

- Indications:
  - Melanoma
  - Non-Small Cell Lung Cancer
  - Head & Neck Cancer
  - Hodgkin Lymphoma
  - Large B-Cell Lymphoma
  - Urothelial Carcinoma
  - MSI-H Cancer
  - Gastric Cancer
  - Cervical Cancer
  - Hepatocellular Carcinoma
  - Merkel Cell Carcinoma
  - Esophageal Cancer
  - Renal Cell Carcinoma
  - Endometrial Carcinoma
  - TMB-H Cancer
  - Cutaneous Squamous Cell Carcinoma
  - Breast Cancer
  - …and potentially more!

Source: KEYTRUDA®(pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2023.

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Immune-Related Adverse Events

Mechanism of Immune-related Adverse Events

1. T-lymphocytes attack the tumor, resulting in tumor cell death & collateral damage to nearby healthy cells
2. Release of tumor antigens & self-antigens
3. APCs (antigen-presenting cells) ingest both these antigens & activate more T cells
4. T cells will now recognize & attack normal tissues

Source: “What Are Immunotherapy Side Effects - ESMO.” Immunotherapy Side Effects, European Society of Medical Oncology , https://www.esmo.org/content/download/124130/2352601/1/ESMO-Patient-Guide-on-Immunotherapy-Side-Effects.pdf.

Immune-Related Adverse Events

Lungs: Dyspnea, Pneumonitis

Liver: Hepatitis

Endocrine: Pituitary gland or thyroid gland dysfunction

GI (Colon): Diarrhea, Colitis

Skin: Rash, Itching

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Immune-Related Adverse Events

Core Ideas

- Majority of irAEs occur within 3–6 months of therapy, but may manifest up to 1 year after discontinuation of treatment
- Early intervention with corticosteroids is the mainstay of treatment for most irAEs & crucial to limiting severity & duration
- Severe irAEs refractory to steroids after 48–72 hours; may use other agents particular to each disease.

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Immune-Related Adverse Events

Basic Management Strategy

Grade	Approach
Grade 1 (mild)	• Manage symptoms • Continue treatment
Grade 2 (moderate)	• May skip one or more treatment doses • Manage symptoms • Corticosteroids (initial dose of **0.5 to 1 mg/kg/d** of prednisone)
Grade 3 (severe)	• Hold immunotherapy • High-dose corticosteroids (prednisone **1 to 2 mg/kg/d** or methylprednisolone 1 to 2 mg/kg/d)
Grade 4 (very severe)	• **Permanent discontinuation of immunotherapy** • Consider inpatient admission

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Immune-Related Adverse Events

Strategies for Refractory Syndrome

irAE	Secondary Agent
Colitis	• Infliximab • Vedolizumab
Pneumonitis	• Infliximab • Mycophenolate mofetil • IVIG
Hepatitis	• Mycophenolate mofetil

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Immune-Related Adverse Events

Take Home Points

- Checkpoint inhibitors enhance the immune system's attack patterns on cancer cells
- Byproduct of this process is that it may induce an autoimmune-like response toward the individual's healthy tissues (irAE)
- irAEs may occur at any time, even months after treatment has completed
- Standard of care is high-dose corticosteroids that must be slowly tapered
- Secondary agents may be required for steroid-refractory cases

Cytokine Release Syndrome & Neurologic Toxicities (CAR-T Toxicities)

Introduction to CAR-T (Chimeric Antigen Receptor)

- T-cells are collected from the patient
- An engineered viral vector inserts a gene to encode proteins on the T-cell surface
- These proteins, called CARs, act as receptors to target surface molecules of cancer cells
- CAR-T cells are then returned to the patient
- Binding to tumor cells activates cytokine release:
  - Induction of T cell multiplication & inflammatory factors at cancer cell site
  - Enhances response & persistence

Source: “Car T-Cell Therapy and Its Side Effects.” Immunotherapy, American Cancer Society, 1 Mar. 2022, https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html.
“Remodeled Car T-Cell Therapy Causes Fewer Side Effects.” Cancer Currents Blog , National Cancer Institute, 20 Feb. 2020, https://www.cancer.gov/news-events/cancer-currents-blog/2020/car-t-cell-therapy-lymphoma-reduced-side-effects.
Portell, Craig. “How Does Car T-Cell Therapy Work in Treating Cancer?” Cancer.Net Blog, American Society of Clinical Oncology, 17 June 2021, https://www.cancer.net/blog/2021-06/how-does-car-t-cell-therapy-work-treating-cancer.

Cytokine Release Syndrome

List of CAR-T Therapies

Drug Name	Disease Indication	Year Approved
Tisagenlecleucel	• Pediatric B-cell acute lymphocytic leukemia • Large B-cell lymphoma • Follicular lymphoma	2017
Axicabtagene Ciloleucel	• Large B-cell lymphoma • Follicular lymphoma	2017
Brexucabtagene Autoleucel	• B-cell acute lymphocytic leukemia • Mantle cell lymphoma	2020
Lisocabtagene Maraleucel	• Large B-cell lymphoma • Follicular lymphoma	2021
Idecabtagene Vicleucel	• Multiple myeloma	2021
Ciltacabtagene Autoleucel	• Multiple myeloma	2022

Source: "CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers." Cancer Treatment Research, National Cancer Institute, 10 Mar. 2022, https://www.cancer.gov/about-cancer/treatment/research/car-t-cells.

Cytokine Release Syndrome

CAR-T Toxicity Warnings

- Cytokine Release Syndrome (CRS)
- Neurologic Toxicities (CRES)

Both complications are life-threatening & require registration into REMS program to use these agents

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

Bi-specific T-cell engager ('BiTe')

- Bi-specific T-cell engager ('BiTe' for short)
  - Mechanism: Brings the body's native T-cells (by binding to the CD3 site of the T-cells) to the site of cancer cells, activates T-cell attack on cancer cells & pro-inflammatory cytokines release

Drug Name	Disease Indication	Target	Year Approved	Rate of CRS
Blinatumomab[28]	Acute lymphoblastic leukemia	CD19 – CD3	2014	14%
Tebentafusp[29]	Uveal melanoma	gp100 peptide-HLA – CD3	2022	89%
Teclistamab[30]	Multiple myeloma	BCMA – CD3	2022	72%
Mosunetuzumab[31]	Follicular lymphoma	CD20 – CD3	2022	39%

Source: BLINCYTO (blinatumomab) [package insert]. Thousand Oaks, CA: Amgen Inc.; 2022.
KIMMTRAK (tebentafusp-tebn) [package insert]. Conshohocken, PA: Immunocore Commercial LLC.; 2022.
TECVAYLI (teclistamab-cqyv) [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2022.
LUNSUMIO (mosunetuzumab-axgb) [package insert]. San Francisco, CA. Genentech, Inc.; 2022.

Cytokine Release Syndrome

- Toxicity associated with high levels of inflammatory cytokines (GM-CSF, IL-6, IL-1B, CRP), induced by activated myeloid CAR-T cells
- Overactivation of immune effector cells results in endothelial injury & capillary leak, hemodynamic instability & organ dysfunction
- Symptoms:
  - Mild: Fevers, sinus tachycardia, nausea, fatigue, myalgias, malaise, headache
  - Severe: Hypotension, hypoxia, decline in cardiac function, organ dysfunction (liver & renal), Afib/Vtach, capillary leak
- Typically develops 2–3 days post-infusion or as late as 10–15 days post infusion
- Peaks & resolves within 7 days

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.
Fischer JW, Bhattarai N. Car-t cell therapy: mechanism, management, and mitigation of inflammatory toxicities. Front Immunol. 2021;12:693016.
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Yáñez L, Sánchez-Escamilla M, Perales MA. Car t cell toxicity: current management and future directions. Hemasphere. 2019;3(2):e186.

Neurotoxicities

- Toxicity associated with high levels of inflammatory cytokines as with CRS
- Symptoms:
  - Mild: Tremors, somnolence
  - Severe: Delirium, hallucinations/psychosis, cognitive, dysphasia, nerve palsies, focal motor or sensory deficits, myoclonus, obtundation (may require mechanical ventilation), seizures
- Develops 4–10 days post-infusion

Source: Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321-3330

Cytokine Release Syndrome

Monitoring Parameters

- Vital signs & cardiac rhythm
- Neurologic assessment
- Blood counts
- Electrolytes
- Coagulation assays
- Inflammatory markers (CRP, lactate, LDH, ferritin)

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

Tocilizumab

- Mechanism: IL-6-R inhibitor
- Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)
- Repeat in 8 hours if no improvement
- Do not exceed 3 doses in 24 hours, with a maximum of 4 doses total
- 2 doses reserved per patient, mandated by REMS program

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

CRS Treatment

Grade	Approach
Grade 1 • Fever (≥ 38 C)	• Consider tocilizumab (if prolonged > 3 days) • In general, avoid steroids*
Grade 2 (moderate) • Fever (≥ 38 C) • Hypotension (not requiring pressors) • Hypoxia requiring low-flow cannula	• Tocilizumab • Consider Corticosteroids for refractory** hypotension: • Dexamethasone 10 mg IV Q12–24hrs

*For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS

** Refractory after 1–2 doses of anti-IL-6 therapy

Consider pressors with Grade 2

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

CRS Treatment

Grade	Approach
Grade 3 (severe) • Fever (≥ 38 C) • Hypotension (requiring pressor(s)) • Hypoxia requiring high-flow cannula	• Tocilizumab • Corticosteroids: Dex 10 mg IV Q 6–12 hrs

Grade 4 (very severe)
• Fever (≥ 38 C)
• Hypotension (requiring pressors)
• Hypoxia requiring mechanical ventilation
	• Tocilizumab
	• Corticosteroids:
	  • Dex 10 mg IV Q 6hrs
	  • Methylprednisolone 1000 mg/day x 3 if refractory

Definitive pressor use with Grade 3-4

*For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS
** Refractory after 1–2 doses of anti-IL-6 therapy

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

Neurotoxicity Evaluation

- ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome) Consensus Grading
  - Level of consciousness
  - Seizure
  - Motor findings
  - Elevated ICP/cerebral edema
  - ICE score

ICE (Immune Effector Cell-Associated Encephalopathy) Assessment Tool:
Orientation
Naming
Writing
Attention

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

Neurotoxicity Treatment

Grade	Approach
Grade 1	• Supportive care
Grade 2 (moderate)	• Dexamethasone 10 mg IV, repeat Q 6–12 hrs PRN
Grade 3 (severe) *Requires ICU admission*	• Dexamethasone 10 mg IV, repeat Q 6–12 hrs PRN or Methylprednisolone 1 mg/kg IV Q12 hr
Grade 4 (very severe) *Requires ICU admission*	• High-dose corticosteroids • Treat status epilepticus per institutional guidelines • Mechanical ventilation may be required

Give tocilizumab only if concurrent CRS

Source: National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed May 17, 2023.

Cytokine Release Syndrome

Take Home Points

- Newest technologies can “train” our T-cells to be highly specific toward killing targeted cancer cells
- Two key adverse events as a result of this technology are: CRS (cytokine release syndrome) & CAR-T-associated neurotoxicity
- For CRS, high-dose corticosteroids & tocilizumab are the key agents to mitigate an elevated cytokine response
- For CAR-T neurotoxicity, corticosteroids alone are the mainstay of therapy & use of tocilizumab is not recommended at this time

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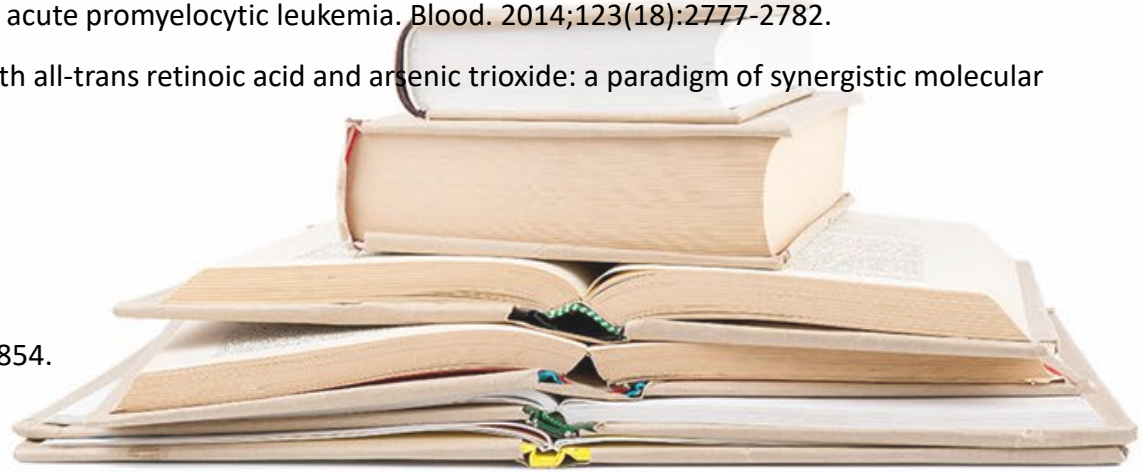

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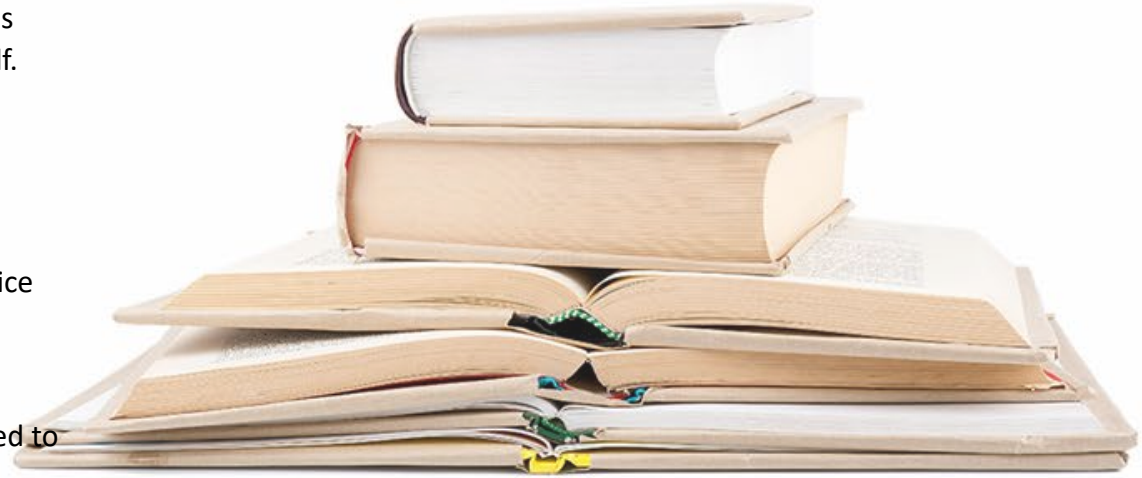

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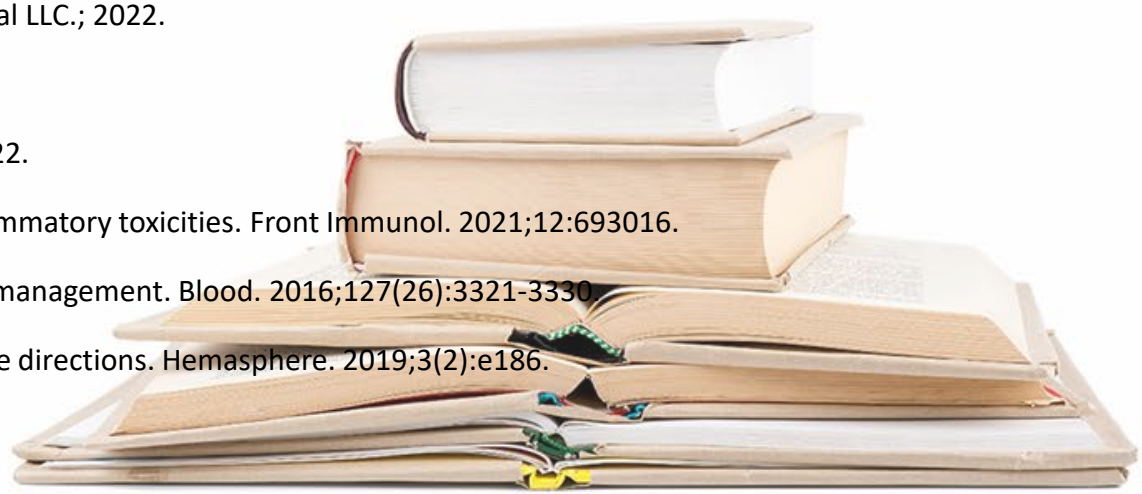

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