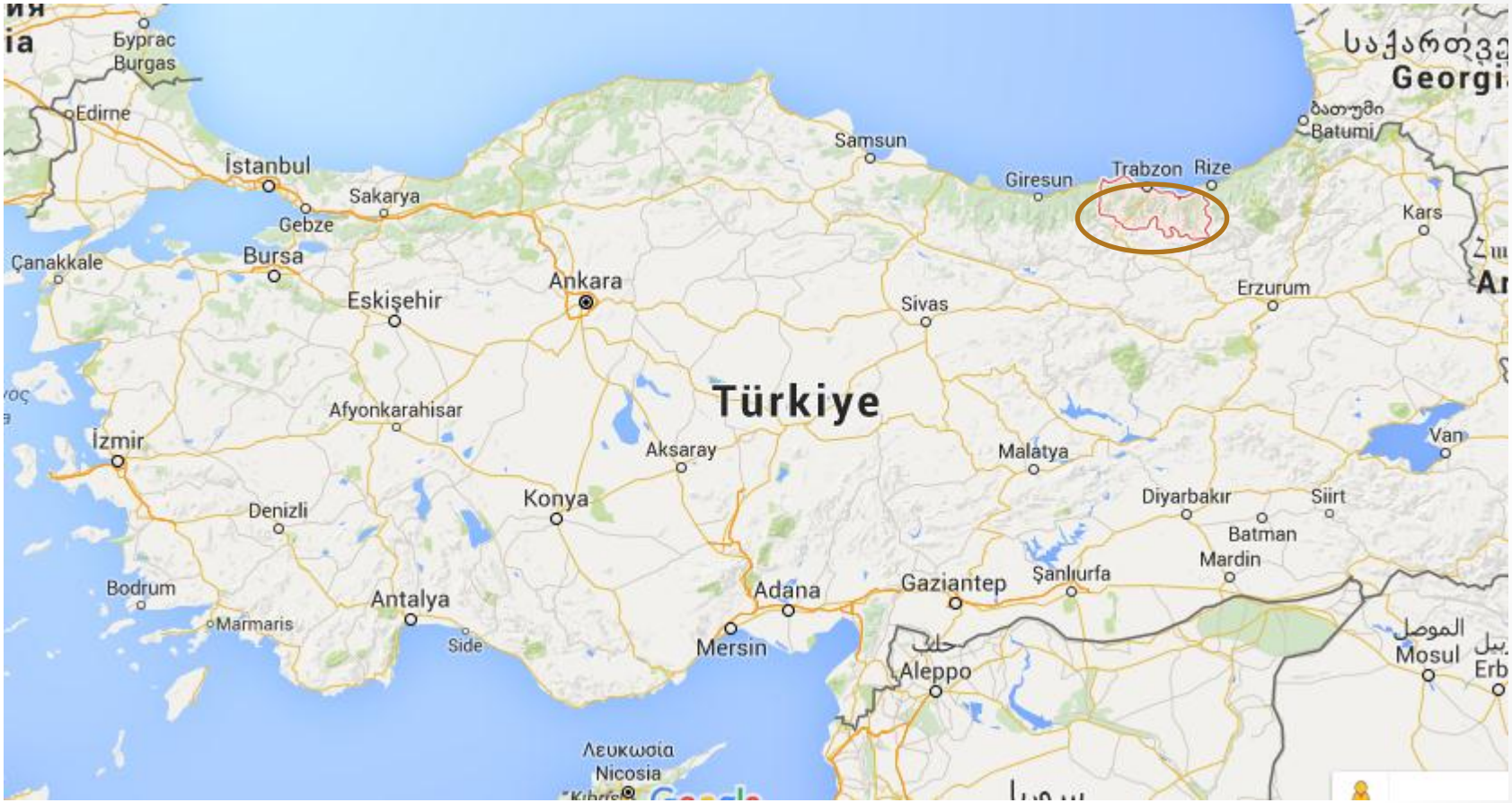
Immunocompromised Host in the Emergency Department

Should All be Treated the Same Way?

Umut Eryiğit, MD, Assist. Prof.
Karadeniz Technical University Faculty of Medicine
Department of Emergency Medicine
Trabzon, Turkey

12.Ulusal Acil Tıp Kongresi, 3rd Intercontinental Emergency Medicine Congress, 3rd International Critical Care and Emergency Medicine Congress, ANTALYA, 2016.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Objectives

- Definition of Immun system
- Definition of Immunocompromised patients
- Complications of Immunocompromisation
- Treatment of special situations

Immun System

- Immunity refers to the ability to resist almost all types of organisms or toxins that tend to damage the tissues and organs.

Guyton and Hall Textbook of Medical Physiology, 13th edition. 2016.

Immunocompromisation (IC)

- Immunocompromisation is the state in which of immune system's ability to fight infectious disease is compromised or entirely absent.

IC≈INFECTION

Immuncompromised patient in the emergency department

- Immuncompromised patients frequently visit emergency departments (EDs) for evaluation and treatment of various conditions.
- Infectious complications are common
- Clinical presentations are often subtle and atypical.
- Emergency physician should be aware of complications in immunocompromised patients.

Categories

- Primary immunodeficiency, A number of rare diseases feature a heightened susceptibility to infections from childhood onward.
- Primary immunodeficiency is also known as congenital immunodeficiencies.
- There are about 100 recognised primary immunodeficiency syndromes.

Rosen FS et al. The primary immunodeficiencies. 1995.

Secondary immunodeficiencies

- Also known as acquired immunodeficiencies
- Immunosuppressive agents
- Malnutrition
- Aging and particular medications
- Many specific diseases directly or indirectly causing immunosuppression as certain types of cancers affecting bone marrow, acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV).

Abul K. Abbas, Basic Immunology: Functions and Disorders of the Immune System, 3rd Ed. 2011.

Complications

- Neutropenic Fever
- Opportunistic Infections
  - Mucormycosis
  - Toxoplasmosis
  - Pneumocystis carinii pneumonia (PCP)
  - Cytomegalovirus (CMV)

Who is immunocompromised

- Extremes of age
- Patients on immunosuppressant drugs
  - Transplant patients, high dose steroid
- Cancer
- Cytotoxic chemotherapy
- Marrow replacement by leukaemia
- Infection: HIV
- Splenectomized patients
- Diabetes Mellitus
- Renal failure
- Cirrhosis

Neutropenic Fever

- Infectious Disease Society of America (IDSA);

Neutropenia(NP), absolute neutrophil count (ANC)<500 cells/mm^3 OR expected to decrease to less than 500 cells/mm^3 during the next 48 hours AND

Fever, in the absence of obvious environmental causes,

Single oral temperature ≥ 38.3° C (101° F) OR

Temperature 38.0° C (100.4° F) or higher for at least 1 hour.

The most common sites of infection

Lung 25%

Mouth and Pharynx 25%

GIS tract 15%

Skin, soft tissue, and intravascular catheters 15%

perineum and anorectal area (10%); urinary tract (5%); and nose and sinuses (5%).

Giamarellou H et al. Infectious complications of febrile leukopenia. 2001.

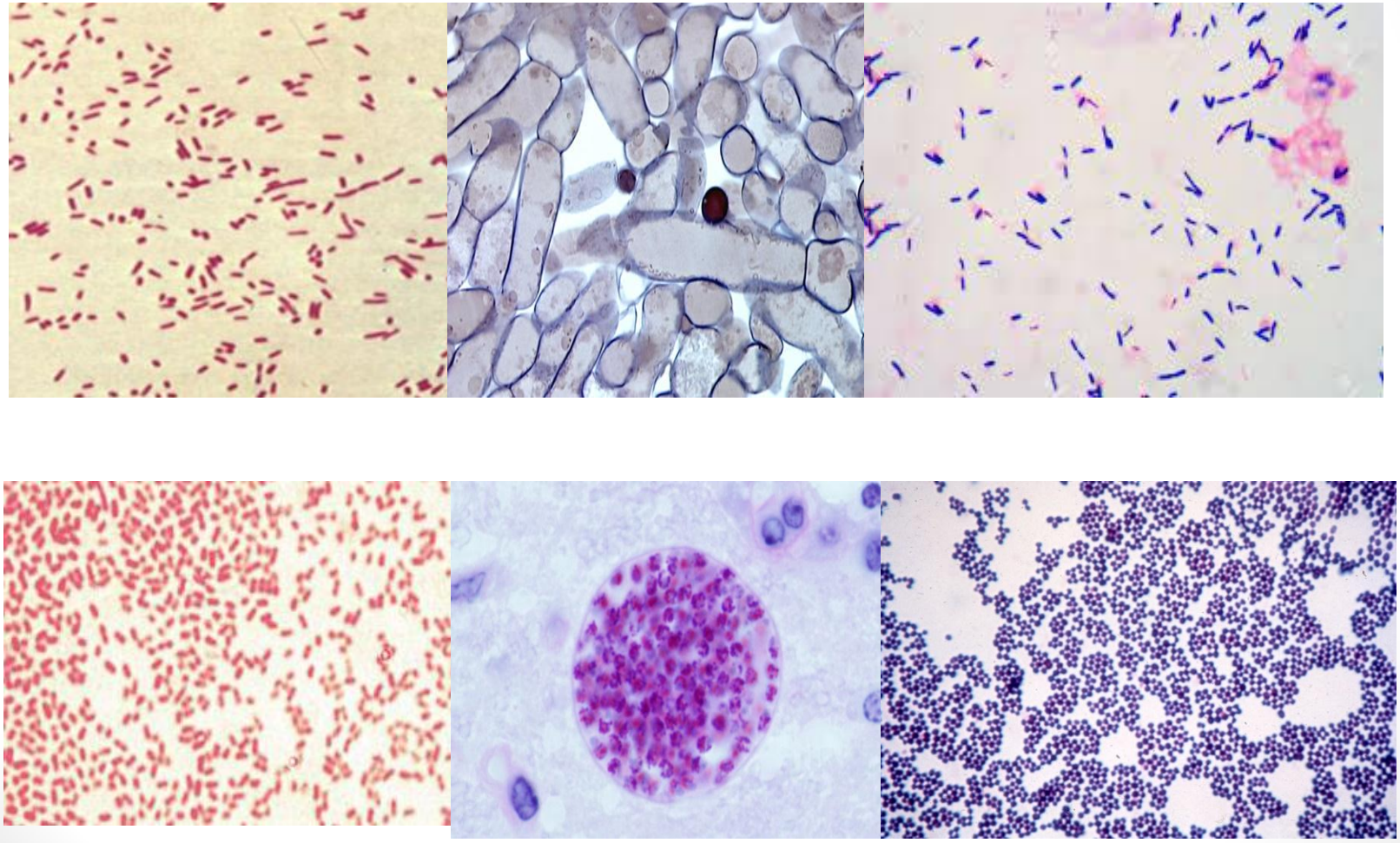
Neutropenic Fever Clinical Signs

Cellulitis	NO erythema, swelling, redness, or warmth
Pneumonia	NO symptom or pulmonary infiltrate on initial radiographs
Meningitis	NO or minimal pleocytosis
Urinary tract infection	NO pyuria.

Neutropenic Fever Clinical Signs

- Fever as their only presenting feature of infection.
- Pain at any site should heighten the suspicion of occult infection despite the absence of typical physical signs of infection.

Causing organism



Neutropenic Fever Management

- Door to needle time is an independent risk factor of mortality and morbidity.

Cohort Study of the Impact of Time to Antibiotic Administration on Mortality in Patients with Febrile Neutropenia

Regis G. Rosa, Luciano Z. Goldani

Infectious Diseases Division of Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

The time to antibiotic administration (TTA) has been proposed as a quality-of-care measure in febrile neutropenia (FN); however, few data regarding the impact of the TTA on the mortality of adult cancer patients with FN are available. The objective of this study was to determine whether the TTA is a predictor of mortality in adult cancer patients with FN. A prospective cohort study of all consecutive cases of FN, evaluated from October 2009 to August 2011, at a single tertiary referral hospital in southern Brazil was performed. The TTA was assessed as a predictive factor for mortality within 28 days of FN onset using the Cox proportional hazards model. Kaplan-Meier curves were used for an assessment of the mortality rates according to different TTAs; the log-rank test was used for between-group comparisons. In total, 307 cases of FN (169 subjects) were evaluated. During the study period, there were 29 deaths. In a Cox regression analysis, the TTA was independently associated with mortality within 28 days (hazard ratio [HR], 1.18; 95% confidence interval [CI], 1.10 to 1.26); each increase of 1 h in the TTA raised the risk of mortality within 28 days by 18%. Patients with FN episodes with a TTA of ≤30 min had lower 28-day mortality rates than those with a TTA of between 31 min and 60 min (3.0% versus 18.1%; log-rank $P = 0.0002$). Early antibiotic administration was associated with higher survival rates in the context of FN. Efforts should be made to ensure that FN patients receive effective antibiotic therapy as soon as possible. A target of 30 min to the TTA should be adopted for cancer patients with FN.

NF Antimicrobial Therapy

Cefepime 2 g IV q8h
Ceftazidime 2 gr q8h

Meropenem 1 g IV q8h
Imipenem 500 mg IV q6h
Doripenem 500 mg IV q8h

Piperacillin tazobactam
4.5 g IV q6h

Hypotension and pneumonia or antimicrobial resistance

+

Aminoglycoside
Gentamicin 2 mg/kg IV q8h
Amikacin 15 mg/kg/day
Tobramycin 2 mg/kg q8h

Vancomycin 15 mg/kg IV q12h

NCNN. Prevention and Treatment of Cancer-Related Infections. 2016 Guideline.

MASCC score (Multinational Association of Supportive Care in Cancer)

Category	**Weight** HOME IS SAFER THAN HOSPITAL
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or no previous invasive fungal infection	4
Outpatient status	3
Burden of disease: moderate symptoms	3
No dehydration	3
Aged <60 years	2

Klastersky J et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. 2000.
http://image.cdn.iha.com.tr/Contents/pool_file/2016/06/86484_20160214aw659265-01.jpg

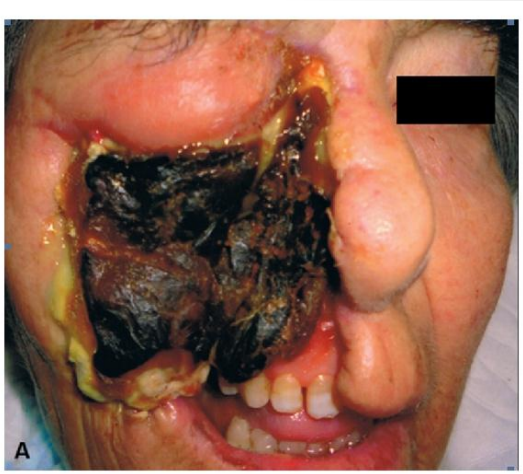
- Fever outside the hospital
- No comorbid conditions
- Neutropenia < 7 days
- Liver function tests in normal range
- Kidney function tests in normal range
- Solid tumors
- MASCC ≥ 21

Amoxicillin-clavulanete
875 mg PO every 12h
PLUS
Ciprofloxacin
500-750 mg PO every 12h

PPD 91%
NPV 36%
Sensitivity 71%
Specifity 68%

NCNN. Prevention and Treatment of Cancer-Related Infections. 2016 Guideline.

Mucormycosis



- Caused by the species Mucor and Rhizopus.
- Rhinocerebral mucormycosis involves infection of the sinuses with extension into surrounding structures (e.g., bones, orbits, brain, cavernous sinus, carotid artery, and jugular veins).
- Pulmonary mucormycosis is a rare, rapidly progressing type of pneumonia with a high mortality rate.

Paola DiCarlo et al. Multimodal Surgical and Medical Treatment for Extensive Rhinocerebral Mucormycosis in an Elderly Diabetic Patient: A Case Report and Literature Review , 2015.
https://mfalog.files.wordpress.com/2014/07/wpid-manusia-tanpa-wajah-mark-tatum.jpg?w=474

Rhinocerebral and pulmonary mucormycosis

- Aggressive resuscitation and
- Glycemic control
- Initiation of amphotericin B.

- Empiric broad-spectrum antimicrobial therapy for presumed bacterial infection or coinfection should be initiated.

Mucormycosis Treatment

Amphotericin B
5-10 mg/kg/d

Amphotericin B deoxycholate
1-1.5 mg/kg/d

Posaconazole
400 mg twice daily
Isavuconazole
200 mg thre times daily

Toxoplasmosis

- Toxoplasmosis is the most common parasitic central nervous system (CNS) opportunistic infection in AIDS patients
- More serious disease can develop due to *Toxoplasma* reactivation in AIDS, especially when the lymphocyte CD4 cell count drops below 100 cells / mm3
- Cerebral toxoplasmosis
- Chorioretinitis
- Cutaneus toxoplasmosis

Toxoplasmosis- Management

Pyrimethamine
100 mg loading dose
25-50 mg/day

+

Sulfadiazine
2-4 g/day divided 4 times daily

Trimethoprim
(10 mg/kg/day)
PLUS
sulfamethoxazole
(50 mg/kg/day)

Pneumocystis pneumonia (PCP)

- Most common opportunistic infection in persons with HIV infection.
- A cause of interstitial pneumonia.
- Complications
  - Pneumothorax
  - Respiratory failure
  - Death

Trimethoprim
(10 mg/kg/day)
PLUS
sulfamethoxazole
(50 mg/kg/day)

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children,2015.

Cytomegalovirus (CMV)

- CMV is a member of the herpesvirus family
- Found universally throughout all geographic locations and socioeconomic groups
- Infects between 50% and 85% of adults in the United States by 40 years of age
- Typically remains dormant within the body
- CMV is the leading infection and the greatest cause of transplant failure.
- CMV disease is present in 7.4% to 30% of all AIDS patient.

Jackson JB et al. Prevalence of cytomegalovirus antibody in hemophiliacs and homosexuals infected with human immunodeficiency virus type 1. Transfusion. 1988 Mar-Apr;28(2):187-9

Cytomegalovirus

Host	Presentation
Immunocompetent	**Heterophile negative mononucleosis syndrome**
Immunocompromised	**Retinitis** **Hepatitis** **Pneumonitis** **Gastritis** **Esophagitis** **Polyradiculopathy** **Myelitis**

CMV management

Ganciclovir i.v

5.0 mg/kg q12 hr

Intravenous immuno- globulin (IVIG)
400-500 mg/kg /d (5 days)

Valganciclovir oral

900 mg every 12 h

Kotton CN et al. Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013.

Pharmacotherapy. 2010 Jun;30(6):554-61. doi: 10.1592/phco.30.6.554.

Use of cytomegalovirus intravenous immune globulin for the adjunctive treatment of cytomegalovirus in hematopoietic stem cell transplant recipients.

Alexander BT[1], Hladnik LM, Augustin KM, Casabar E, McKinnon PS, Reichley RM, Ritchie DJ, Westervelt P, Dubberke ER.

⊕ Author information

Abstract

STUDY OBJECTIVE: To describe the characteristics and clinical outcomes of hematopoietic stem cell transplant (HSCT) recipients who received adjunctive cytomegalovirus intravenous immune globulin (CMV-IVIG) for probable or proven CMV disease.

DESIGN: Retrospective cohort study.

SETTING: Large, university-affiliated, tertiary-care medical center.

PATIENTS: Thirty-five adult HSCT recipients who received at least one dose of CMV-IVIG for adjunctive treatment of probable or proven CMV disease between January 1, 1999, and December 31, 2007.

MEASUREMENTS AND MAIN RESULTS: All-cause mortality at hospital discharge was the primary outcome. All patients received an allogeneic HSCT. Twenty-six patients (74%) had pneumonitis, nine (26%) had enteritis, and 29 (83%) had CMV viremia. All patients received concomitant antiviral therapy; 31 (89%) received ganciclovir, and 14 (40%) received foscarnet. All-cause mortality at hospital discharge was 49% (17 patients). Patient characteristics associated with mortality included requiring intubation for CMV pneumonia (11 [79%] of 14 nonsurvivors vs 3 (25%) of 12 survivors, $p=0.016$) and earlier disease onset after HSCT (median 48 days for nonsurvivors vs 106 days for survivors, $p<0.001$). In the multivariate analysis, only requiring intubation for CMV pneumonia remained a significant risk factor for increased mortality. A low rate of adverse events was attributed to CMV-IVIG, with mild hypertension (two patients [6%]) and erythema and chills (one patient [3%]) being the most common.

CONCLUSION: The mortality rate in our study population was similar to previous reports in the literature and may be somewhat lower than rates reported with antiviral monotherapy. Our analysis suggests that factors associated with mortality include the need for intubation and, possibly, earlier onset of CMV disease after HSCT. Treatment with CMV-IVIG appears to be well tolerated in HSCT recipients. These findings support further trials of CMV-IVIG efficacy in this setting.

Take Home Message

Should All be Treated the Same Way?

- Early resusscitation
- Early antibiotic therapy (Door to needle time)
- Early antifungal therapy (Dependent on impression)
- Risk assesment and disposition of immunocompromised patient.

Thanks for your attention

Lower Risk in Neutropenic Fever

- Absolute neutrophil and monocyte counts 100 cells/mm^3 or higher
- Age between 16-60
- Cancer in partial or complete remission
- Mild or no symptoms
- Outpatient status at the time of fever onset
- Fever lower than 39 C°
- Normal findings on chest radiographs
- Absence of hypotension
- Respiratory rate up to 24 breaths per minute
- Absence of chronic pulmonary diseases and diabetes mellitus
- Absence of confusion
- Absence of dehydration
- No history of fungal infection during the 6 months

NF Antimicrobial Therapy

- MRSA: Consider early addition of vancomycin, linezolid, or daptomycin(B-III).
- VRE: Consider early addition of linezolid or daptomycin(B-III).
- ESBLs: Consider early use of a carbapenem(B-III).
- KPCs: Consider early use of polymyxin-colistin or tigecycline(C-III).

NF Antimicrobial Therapy

- Most penicillin-allergic patients tolerate cephalosporins,
- but those with a history of an immediate-type hypersensitivity reaction should be treated with a combination that avoidsb-lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin
- (A-II).

Toxoplazma tedavi alternatif

- Pyrimethamine (100-mg loading dose orally followed by 25-50 mg/day) plus clindamycin (300 mg orally 4 times daily)

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ANTIBACTERIAL AGENTS: EMPIRIC GRAM-POSITIVE ACTIVITY

Gram-positive Agents[a]	DOSE	SPECTRUM[a]	COMMENTS/PRECAUTIONS
Vancomycin	15 mg/kg IV every 12 h[b] For *C. difficile*: 125 mg PO every 6 h	Gram-positive organisms, with exception of VRE and a number of rare Gram-positive organisms	IV Formulation • Should not be considered as routine therapy for neutrope and fever unless certain risk factors present (See FEV-D) • Dosing individualized with monitoring of levels • Loading dose may be considered
Daptomycin	6 mg/kg/d IV[b]	• Gram-positive organisms • Has in vitro activity against VRE but is not FDA-approved for this indication	• Weekly CPK to monitor for rhabdomyolysis • Not indicated for pneumonia due to inactivation by pulmo surfactant • Consider an ID consult if using daptomycin above 6 mg/k
Linezolid	600 mg PO/IV every 12 h	Gram-positive organisms, including VRE	• Hematologic toxicity (typically with prolonged cases, >2 w occur, thrombocytopenia most common (0.3%–10%) • Serotonin syndrome is rare, use cautiously with SSRIs[1] • Not routinely used in fever and neutropenia, although ma neutrophil and platelet recovery for extended use • Treatment option for VRE and MRSA • Peripheral/optic neuropathy with long-term use

[a] These drugs are not recommended as monotherapy for fever in the setting of neutropenia and should only be added for documented infection with resistant Gram-positive organisms or if certain risk factors are present. (See FEV-D)
[b] Requires dose adjustment in patients with renal insufficiency. Dosing variations exist.

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ANTIBACTERIAL AGENTS: OTHER

OTHER ANTIBACTERIAL AGENTS	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Aminoglycosides ▪ Amikacin ▪ Gentamicin ▪ Tobramycin	Consider single loading dose in critically ill patients with individualized monitoring of levels[b]	Activity primarily against Gram-negative organisms	Often used as empiric therapy in seriously ill or hemodynamically unstable patients
Ciprofloxacin[f] in combination with Amoxicillin/clavulanate	500–750 mg PO every 12 hours or 400 mg IV every 8–12 h[b] 875 mg PO every 12 h[g]	▪ Good activity against Gram-negative and atypical (eg, *Legionella spp.*) organisms ▪ Less active than "respiratory" fluoroquinolones against Gram-positive organisms ▪ Ciprofloxacin alone has no activity against anaerobes	▪ Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis ▪ Increasing Gram-negative resistance in many centers ▪ Oral antibiotic combination therapy in low-risk patients
Levofloxacin	500–750 mg oral or IV daily[b]	▪ Good activity against Gram-negative and atypical (eg, *Legionella spp.*) organisms ▪ Improved Gram-positive activity compared to ciprofloxacin ▪ Levofloxacin no activity against anaerobes ▪ Moxifloxacin has limited activity against Pseudomonas	▪ Prophylaxis may increase bacterial resistance and superinfection[5] ▪ Limited studies as empirical therapy in patients with fever and neutropenia ▪ Prophylaxis in neutropenic patients[3,4]
Moxifloxacin	400 mg oral or IV daily		
Metronidazole	500 mg infused every 6 h or 500 mg PO every 6–8 h	Good activity against anaerobic organisms	
Trimethoprim/sulfamethoxazole (TMP/SMX)	Prophylaxis: Single or double strength daily or Double strength 3 times per wk[b] Therapy: 15 mg/kg daily in divided doses	Activity against *P. jirovecii*	▪ Highly effective as prophylaxis against *P. jirovecii* in high-risk patients (See INF-6) ▪ Monitor for myelosuppression, hepatotoxicity, and hyperkalemia

[b] Requires dose adjustment in patients with renal insufficiency.
[f] Consider adding a second agent in cases of severe infection based on local susceptibility pattern.
[g] Although study data list 500 mg every 8 h, common practice uses amoxicillin/clavulanate 875 every 12 h.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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ANTIVIRAL AGENTS

AGENT	COMMON INDICATION	SPECTRUM	COMMENTS/CAUTIONS
Intravenous immuno-globulin (IVIG)	Doses of IVIG vary among different studies and different viral illnesses. A dose of 400–500 mg/kg administered daily for 5 days is common for parvovirus B19-associated disease.[10] For CMV pneumonia and RSV disease, adjunctive IVIG (400 mg/kg) every other day for 3–5 doses is commonly administered; the optimal dosing schedule is undefined.	RSV, Parvovirus B19, CMV	▪ Pathogen-specific immunoglobulin or monoclonal antibodies may be considered ▪ CMV-specific IVIG is not more efficacious than standard IVIG
Ribavirin (category 3)	Consider for treatment of RSV disease[h]: 6 gm administered by continuous inhalation via SPAG-2 nebulizer every 12–18 h daily or 2 g over 2 h TID; or 600–800 mg PO BID; may be paired with IVIG (400–500 mg/kg every other day)[11,12]	RSV	▪ Experience in immunocompromised adults with RSV disease is limited, but should be considered given potential morbidity and mortality associated with RSV infection ▪ Ribavirin is teratogenic; precautions are required during administration (see package insert)
Entecavir	0.5 mg PO every day (nucleoside-treatment-naïve with compensated liver disease); or 1 mg PO every day (lamivudine-refractory or known lamivudine resistance mutations or decompensated liver disease)	**HBV**	▪ Potential for HBV resistance: ▸ Lamivudine: high (especially as monotherapy) ▸ Tenofovir: none reported to date ▸ Entecavir: low ▪ Dose adjustment recommended for renal impairment ▪ Lactic acidosis and severe hepatomegaly with steatosis reported with nucleoside analogues ▪ Tenofovir potential for nephrotoxicity; monitor for renal function Entecavir and tenofovir monotherapy are generally preferred. Choice of agent is heavily influenced by the overall condition of the patient, renal insuffiency, and the type of chemotherapy planned. Combination therapy is not generally recommended unless viral load is significantly elevated.
Lamivudine	100 mg PO every day		
Tenofovir DF	300 mg PO every day		

[h]Inhaled ribavirin is only FDA approved for hospitalized infants and young children with severe lower respiratory tract RSV disease.

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ANTIVIRAL AGENTS[a]

AGENT	COMMON INDICATION	SPECTRUM	COMMENTS/CAUTIONS
Cidofovir[e]	Treatment: Cidofovir 5 mg/kg IV every wk for 2 wks, followed by cidofovir 5 mg/kg every 2 wks with probenecid 2 gm PO 3 h before the dose, followed by 1 gm PO 2 h after the dose and 1 gm PO 8 h after the dose and IV hydration	CMV, HZV, VZV, adenovirus	Ocular toxicity, bone marrow toxicity, hydration, and probenecid required to reduce nephrotoxicity Third-line for CMV
Foscarnet	Prophylaxis for CMV: 60 mg/kg IV every 8–12 h for 7 d, followed by 90–120 mg/kg IV daily until day 100 after HCT[d,7,8] Preemptive therapy for CMV: Induction for 2 wks, either 60 mg/kg IV every 8 h or 90 mg/kg IV every 12 h. Therapy: Acyclovir-resistant HSV (40 mg/kg every 8 h for 7–10 days); CMV disease (90 mg/kg every 12 h for 2 wks followed by 120 mg/kg daily for at least an additional 2–4 wks and resolution of all symptoms). Add IVIG for CMV pneumonia.	HSV, VZV, CMV, HHV-6	Drug of choice for acyclovir-resistant HSV and VZV and ganciclovir-resistant CMV; nephrotoxic; monitor electrolytes
Oseltamivir[f]	Prophylaxis: 75 mg PO daily[g,9] Treatment: 75 mg BID	Influenza A & B	May cause nausea (improved when taken with food)
Zanamivir[f]	Prophylaxis: 2 oral inhalations (5 mg/inhalation) daily Treatment: 2 oral inhalations (5 mg/inhalation) BID	Influenza A & B	Duration influenced by nature of exposure (ongoing vs. time limited); may cause bronchospasm

[a]Requires dose adjustment in patients with renal insufficiency.
[d]In general, the strategy of CMV surveillance testing by PCR followed by preemptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HCT patients.
[e]A dose of 1 mg/kg administered three times a week is common for less severe adenovirus infections.
[f]Consider peramivir for patients who cannot have oral oseltamivir or inhaled zanamivir.
[g]Prophylaxis among highly immunocompromised persons during community and nosocomial outbreaks of influenza A should be considered.

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ANTIVIRAL AGENTS[a]

AGENT	COMMON INDICATION	SPECTRUM	COMMENTS/CAUTIONS
Acyclovir	• Prophylaxis[b]: HSV (400–800 mg PO BID); VZV in allogeneic HCT recipients (800 mg PO BID)[1]; CMV in allogeneic HCT recipients (800 mg PO QID)[2,c] for patients unable to tolerate oral therapy, 250 mg/m^2 IV every 12 h • Post-VZV exposure prophylaxis: 800 mg PO 5 times daily • Treatment: significant mucocutaneous HSV (5 mg/kg IV every 8 h for 7–10 days); single dermatomal VZV (800 mg PO 5 times daily or 10 mg/kg IV every 8 h for 7–10 days); disseminated HSV or VZV including viral encephalitis (10 mg/kg IV every 8 h)[3]	**HSV, VZV**	• Hydration to avoid crystal nephropathy with high dose • Dosing based upon ideal body weight
Famciclovir	Prophylaxis: HSV or VZV (250 mg PO BID) Treatment: HSV (250 mg PO TID) or VZV (500 mg PO TID)[5,6]	**HSV, VZV**	No data for oncologic related prophylaxis
Ganciclovir	• Preemptive therapy for CMV: 5 mg/kg every 12 h for 2 weeks; if CMV remains detectable, further ID evaluation may be required • Treatment: CMV disease (5 mg/kg every 12 h for 2 weeks followed by 5–6 mg/kg daily for at least an additional 2–4 weeks and resolution of all symptoms). Consider adding IVIG for CMV pneumonia. Formulations and dosages of IVIG vary in different series"	**CMV, HSV, VZV, HHV-6**	May cause bone marrow suppression
Valacyclovir	• Prophylaxis[b]: HSV or VZV (500 mg PO BID or TID) CMV in allogeneic HCT recipients (2 gm PO QID)[c,4] • Treatment: HSV or VZV (Valacyclovir 1 gm PO TID)[3]	**HSV, VZV**	
Valganciclovir	• Prophylaxis: CMV (900 mg daily)[d] • Preemptive therapy for CMV: Induction with 900 mg PO BID for at least 2 weeks and until negative test; consider additional 900 mg PO daily for at least 7 days after a negative test for maintenance	**CMV HSV, VZV, HHV-6**	May cause bone marrow suppression

[a]Requires dose adjustment in patients with renal insufficiency.
[b]Antiviral prophylaxis should be targeted to specific high-risk patients (see INF-3). In non-transplant high-risk patients, prophylaxis should be administered to patients seropositive for HSV or VZV (or with a history of chicken pox). In HCT recipients, prophylaxis is only indicated if either the donor or recipient is seropositive for the virus in question. The indicated doses for antiviral agents are for adults with normal renal function; consult package insert for dose modification in pediatric patients and in patients with renal impairment. Prophylactic antiviral doses may be higher than those routinely used in immunocompetent persons (for example, for recurrent cold sores); there is substantial variability in the prophylactic doses of acyclovir used in different clinical trials in patients with hematologic malignancies and in HCT recipients.
[c]High-dose acyclovir and valacyclovir have been used as prophylaxis for CMV. Because these agents have weak activity against CMV, a strategy of CMV surveillance and preemptive therapy with ganciclovir, valganciclovir, or foscarnet is required among patients at high risk for CMV disease.
[d]In general, the strategy of CMV surveillance testing by PCR followed by preemptive anti-CMV therapy for a positive result is favored over universal long-term prophylaxis in allogeneic HCT patients.

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ANTIFUNGAL AGENTS: EMPIRIC AMPHOTERICIN B FORMULATIONS[d]

AMPHOTERICIN B FORMULATIONS[e]	DOSE	SPECTRUM	COMMENTS/CAUTIONS[g]
Amphotericin B deoxycholate (AmB-D)	Varies by indication, generally 0.5–1.5 mg/kg/d	Broad spectrum of antifungal activity including *Candida* *Aspergillus* sp., (excluding *Aspergillus terreus*) Zygomycetes, rarer molds, *Cryptococcus neoformans*, and dimorphic fungi	• Substantial infusional and renal toxicity including electrolyte wasting • Saline loading may reduce nephrotoxicity • Infusional toxicity may be managed with anti-pyretics, an anti-histamine, and meperidine (for rigors)
Amphotericin B lipid complex (ABLC)	5 mg/kg/d IV for invasive mold infections		Reduced infusional and renal toxicity compared to AmB-D
Liposomal amphotericin B (L-AMB)	3–5 mg/kg/d IV[f,f]		Reduced infusional and renal toxicity compared to AmB-D

[d] Can be considered for prophylaxis with ID consult for appropriate dosing recommendations.
[e] Broad spectrum of antifungal activity. Significant infusional and renal toxicity, less so with lipid formulations.
[f] The vast majority of subjects in this trial had invasive aspergillosis; optimal dosing of L-AMB for other mold infections (such as mucormycosis with 3 mg/kg/d IV) was as effective but less toxic than 10 mg/kg/d as initial therapy for invasive mold infections.
[g] Slowing the rate of infusion is an additional way to manage amphotericin infusion reactions.

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ANTIFUNGAL AGENTS: ECHINOCANDINS

ECHINOCANDINS[6,h]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Anidulafungin	200 mg IV x 1 dose, then 100 mg/d IV	Active against Candida and *Aspergillus sp.* Not reliable or effective against other fungal pathogens.	• Empiric therapy for candidemia and invasive candidiasis (category 1), pending susceptibility data • Efficacy established compared to fluconazole as primary therapy for candidemia and invasive candidiasis[12] • Excellent safety profile
Caspofungin	• 70 mg IV x 1 dose, then 50 mg IV daily; (35 mg IV daily for patients with moderate liver disease) • Some investigators use 70 mg IV daily as therapy for aspergillosis in salvage cases		• Primary therapy for candidemia and invasive candidiasis (category 1)[8] • Treatment for invasive, refractory aspergillosis. Similar efficacy compared to AmB-D as primary therapy for candidemia and invasive candidiasis but significantly less toxic[8] • 45% success rate as therapy for invasive, refractory aspergillosis[9] • Similar efficacy, but less toxic compared with L-AMB as empirical therapy for persistent neutropenic fever[3] • Excellent safety profile
Micafungin	• 100 mg/d IV for candidemia and 50–100 mg/d IV as prophylaxis • 150 mg/d IV used at some centers for *Aspergillus sp.* infection in salvage cases		• Primary therapy for candidemia and invasive candidiasis (category 1) • Similar efficacy compared to caspofungin[10] and compared to L-AMB[11] as primary therapy for candidemia and invasive candidiasis • Excellent safety profile

[h] A number of centers use combination voriconazole and an echinocandin for invasive aspergillosis based on clinical data. Evidence for combination therapy remains limited.

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ANTIFUNGAL AGENTS: AZOLES

AZOLES[a]	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Fluconazole	In adults with normal renal function: 400 mg IV/PO daily	• Active against *Candida* • Active against coccidioidomycosis and *C. neoformans*	• *Candida glabrata* is associated with variable resistance in vitro and *Candida krusei* is always resistant • Inactive against molds (eg, *Aspergillus* sp., Zygomycetes)
Isavuconazole	372 mg every 8 h x 6 doses IV/PO; then 372 mg every day IV/PO	Data are emerging for clinical activity for patients with invasive aspergillosis and mucormycosis	• Can be considered in patients intolerant or refractory to first-line anti-mold therapy
Itraconazole[b]	Oral 400 mg daily (aim for trough of >0.25 mcg/mL after 7 d of therapy)	• Active against *Candida*, *Aspergillus* sp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans*	• Itraconazole has negative inotropic properties and is contraindicated in patients with significant cardiac systolic dysfunction
Posaconazole[b]	• Prophylaxis: ▸ Oral tablet 300 mg BID on day 1 and then 300 mg PO every day[c] ▸ IV 300 mg every 12 h on day1 and then 300 mg IV every day after ▸ 200 mg TID oral solution	• Effective as prophylaxis in neutropenic patients with myelodysplastic syndrome and acute myelogenous leukemia[4], and in HCT recipients with significant GVHD[5] • Active against *Candida*, *Aspergillus* sp., some Zygomycetes sp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans*	• Evaluated as treatment of refractory infection (but not FDA-approved) in several invasive fungal diseases • Data on posaconazole as primary therapy for invasive fungal infections are limited • Liquid formulation should be administered with a full meal or liquid nutritional supplement or an acidic carbonated beverage. New formulation is better absorbed, though it should be taken with food. • For patients who cannot eat a full meal or tolerate an oral nutritional supplement alternative antifungal therapy should be considered • Proton pump inhibitors decrease posaconazole plasma concentration with oral solution
Voriconazole[b]	• IV 6 mg/kg every 12 h x 2 doses, then 4 mg/kg every 12 h; oral 200 mg PO BID (for invasive aspergillosis);[1] • IV 6 mg/kg every 12 h x 2, then 3 mg/kg every 12 h for non-neutropenic patients with candidemia[2]	• Active against *Candida*, *Aspergillus* sp., and some of the rarer molds • Active against dimorphic fungi and *C. neoformans* • Standard of care as primary therapy for invasive aspergillosis (category 1)[1,3] • Effective in candidemia in non-neutropenic patients[2]	• Poor activity against Zygomycetes • Long-term complications resulting from metabolic irregularities may include increased risk for squamous cell carcinoma and hyperphosphatemia • Fluorosis may occur with prolonged use and is associated with bone/muscle pain • Evidence for combination therapy remains limited[6] • IV formulation should be used with caution in patients with significant pre-existing renal dysfunction

[a]Azoles inhibit fungal cell membrane synthesis and inhibit cytochrome P450 isoenzymes that may lead to impaired clearance of other drugs metabolized by this pathway. Fluconazole is a less potent inhibitor of cytochrome P450 isoenzymes than the mold-active azoles. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details). Reversible liver enzyme abnormalities are observed. QT prolongation and interactions have been reported.
[b]Therapeutic drug monitoring (TDM) is an ongoing area of research; TDM should be considered in consultation with ID specialists. (See Discussion).
[c]Liquid formulation may be used as needed.

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