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Febrile Neutropenia

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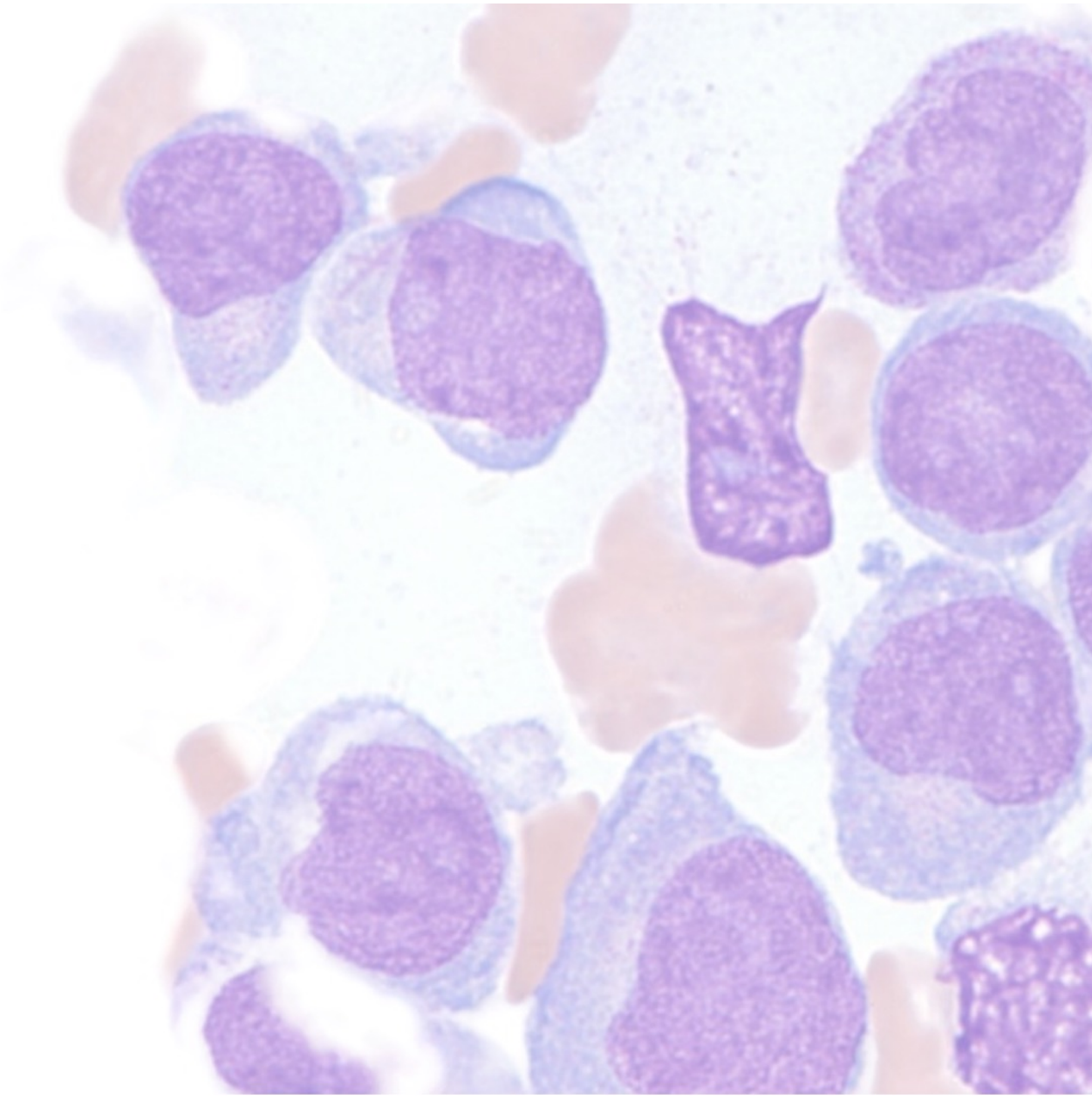
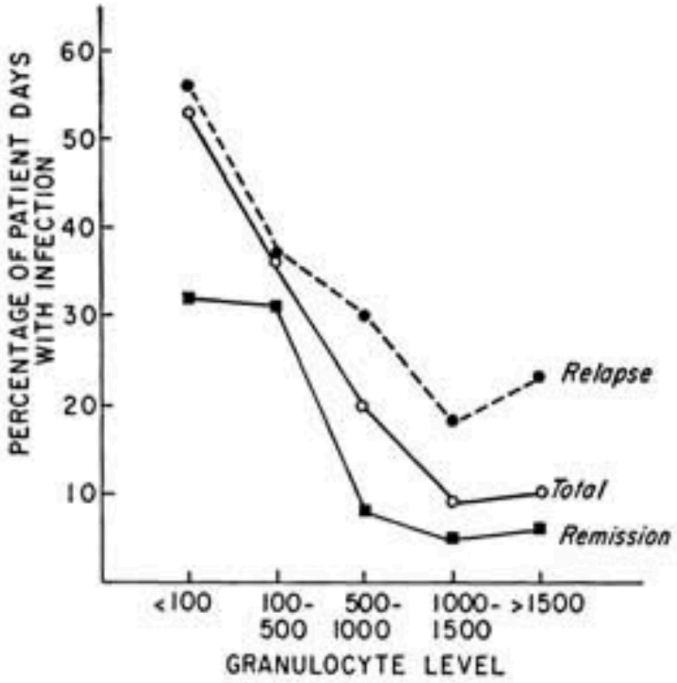
Objectives



Neutropenia with chemotherapy

- **Virtually all antineoplastic drugs in the treatment of malignant diseases have a deleterious effect on the proliferation of normal hematopoietic progenitor cells**
  - Obliteration of the mitotic pool
  - Depletion of the marrow reserve
- **Antineoplastic drugs, glucocorticoids and irradiation also interfere with the function of non-proliferating granulocytes, resulting in:**
  - Decreased chemotaxis
  - Diminished phagocytic capacity
  - Defective intracellular killing
- **Glucocorticoids seem to enhance granulocytopoiesis and mobilize the marginal and marrow pool reserve, *but***
  - reduce accumulation of granulocytes at site of infection (reduced adherence)
  - diminished chemotactic activity
  - decreased phagocytosis and intracellular killing

What is the risk of infection as neutrophils counts fall?



Granulocyte Level		Episodes	
Initial	Change	Total	Fatal
	/mm³	no.	%
<100	None	15	80
<1,000	None or fall	44	59
<1,000	Rise, but still <1,000	15	40
<1,000	Rise to >1,000	26	27
>1,000	Rise	44	32

Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med. 1966;64:328-340.

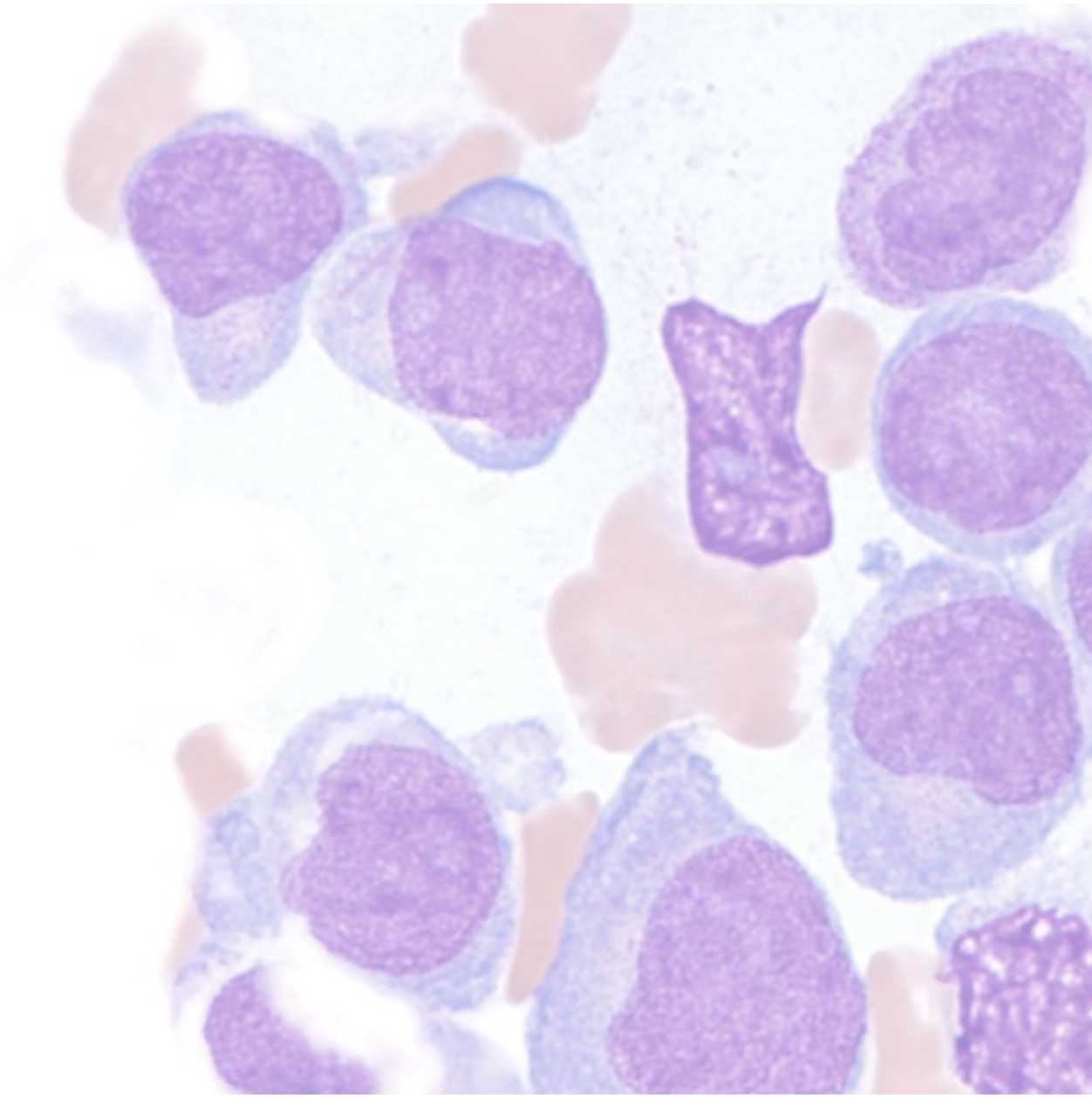
Febrile Neutropenia

- **Single oral temperature ≥ 38.3° or temperature ≥ 38.0 sustained over 1-hour**
- Absolute neutrophils count (ANC) = Total WBC x (% PMN + % banded neutrophils)
  - **Neutropenia**: Absolute neutrophil count < 1500 cells/μL
  - **Severe neutropenia**: 500 cells/μL, or an ANC expected to decrease to < 500 cells/μL in the next 48h
  - **Profound neutropenia**: ANC < 100 cells/μL
- **Frequency of fever episodes during hospital admission:**
  - Solid tumor patients: 5-10%
  - Non-leukemic, hematological malignancy 20-25%
  - Acute leukemia patients: 85-95%

Additional neutropenic fever definitions

- **Microbiologically documented infection**- Neutropenic fever with clinical focus of infection and associated pathogens
- **Clinically-documented infection**- Neutropenic fever with at clinical focus (e.g., cellulitis, pneumonia) but without isolation of an associated pathogen
- **Unexplained fever**- Neutropenic fever with neither a clinical focus of infection without an identified pathogen

Pathogenesis



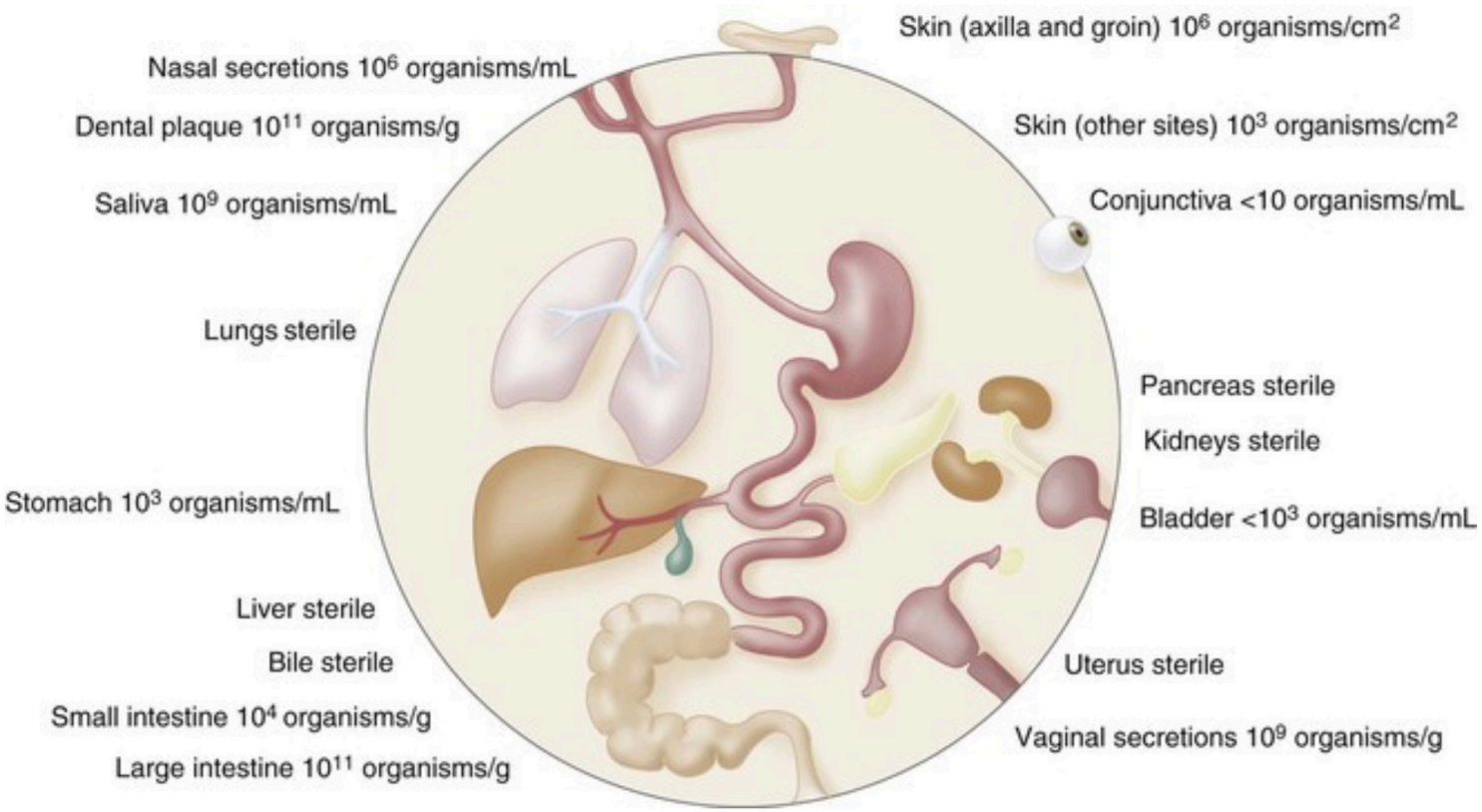
Innate immune cells

Source	Molecules	Active against
Polymorphonuclear leukocyte (PMN)		
(1) Primary granules	Lysozyme, Myeloperoxidase	Bacteria, Fungi (with H_2O_2)
(2) Specific granules	Defensins, BPI, lactoferrin	Bacteria, fungi
Macrophage	Similar to PMN but no myeloperoxidase Nitric oxide Arginase	Intracellular pathogens (depletes arginine)
Eosinophil	Cationic proteins Major basic protein Peroxidase	Worms (extracellular) Worms (extracellular) Worms (extracellular)
Natural killer cells	Perforins Granzymes Granulysin	Viral or bacterial-infected cells Bacteria, fungi

Contributory factors to the pathogenesis of neutropenic fever

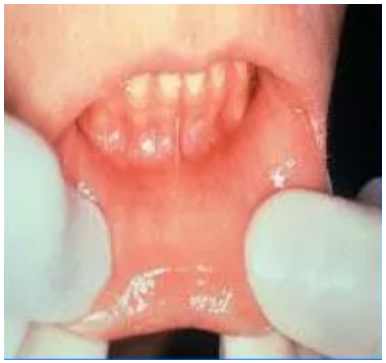
- Direct effects of chemotherapy on mucosal barriers and the immune system
- Breeches in host defenses related to the underlying malignancy

Bacterial flora

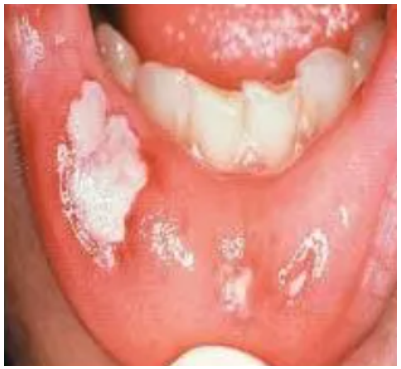


WHO oral toxicity scale (mucositis)

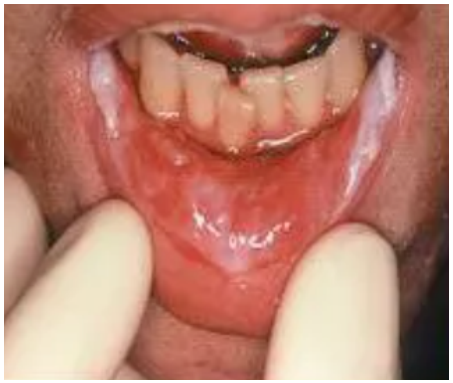
Grade 1:
Soreness and
Erythema



Grade 2:
Erythema and ulcers,
Patient can swallow food

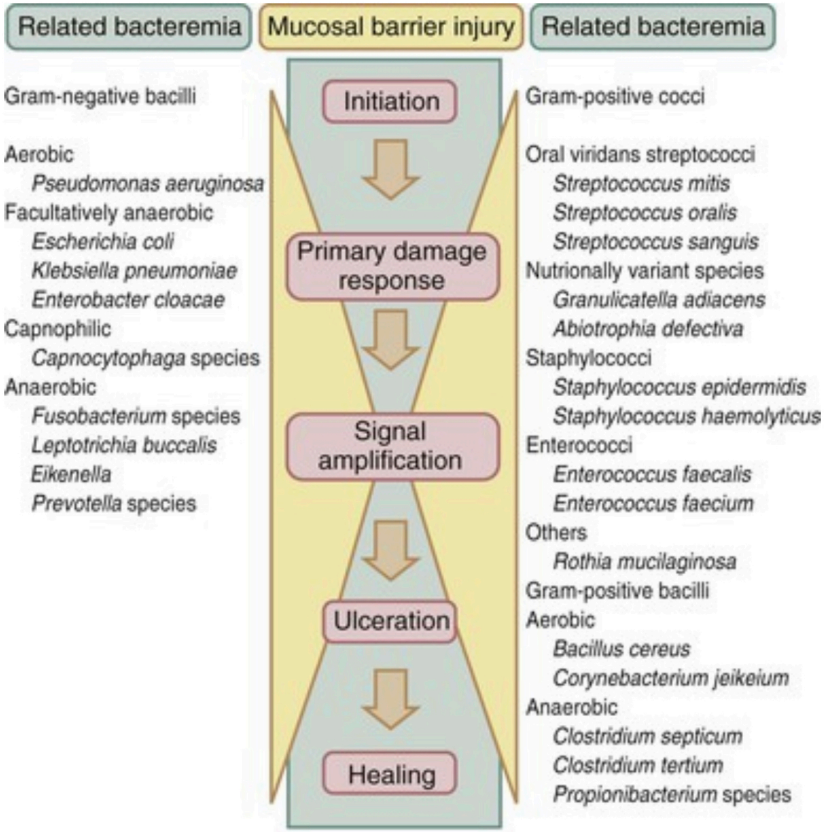


Grade 3
Ulcers with extensive
Erythema;
Cannot swallow food

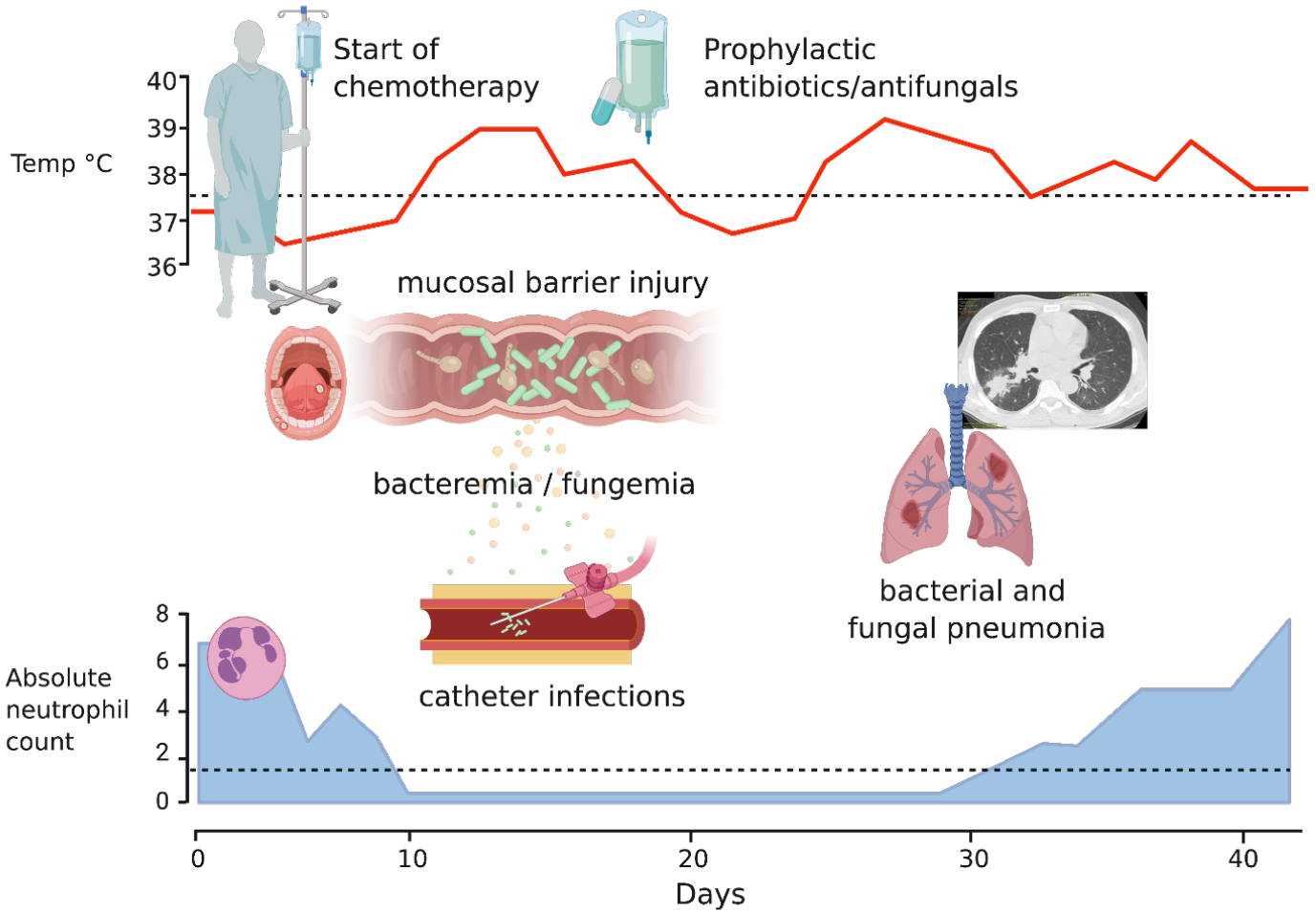


Grade 4
Alimentation is not
Possible

Mucosal barrier injury induced by cytostatic chemotherapy



Sequence of infection in febrile neutropenia



Most common bacterial pathogens

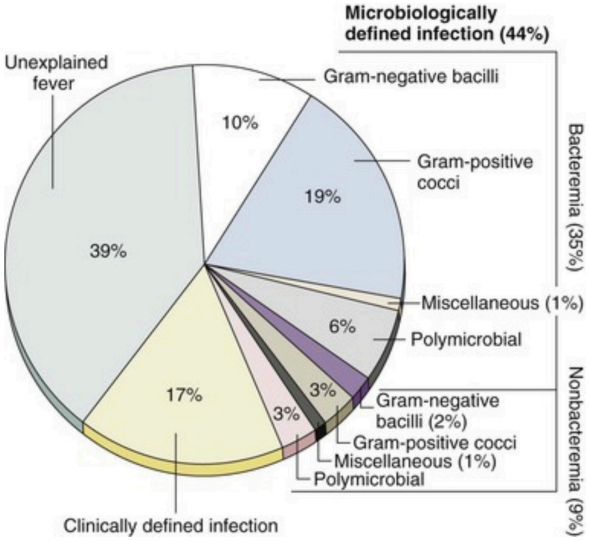
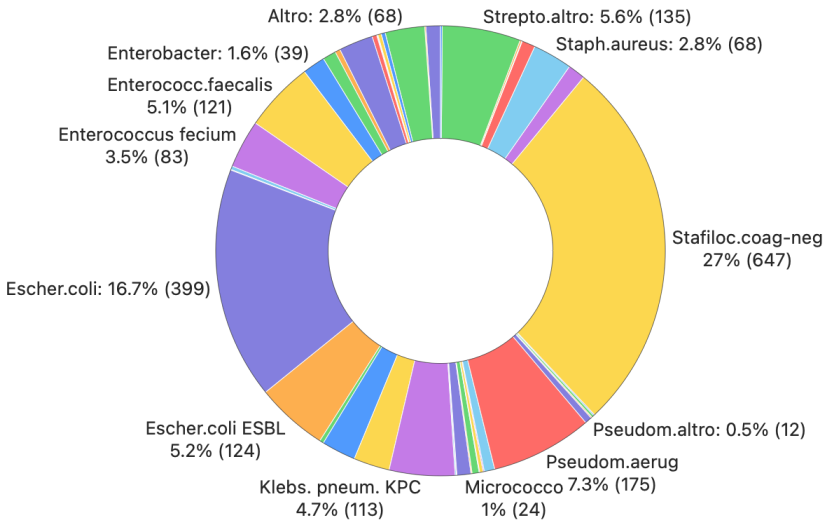


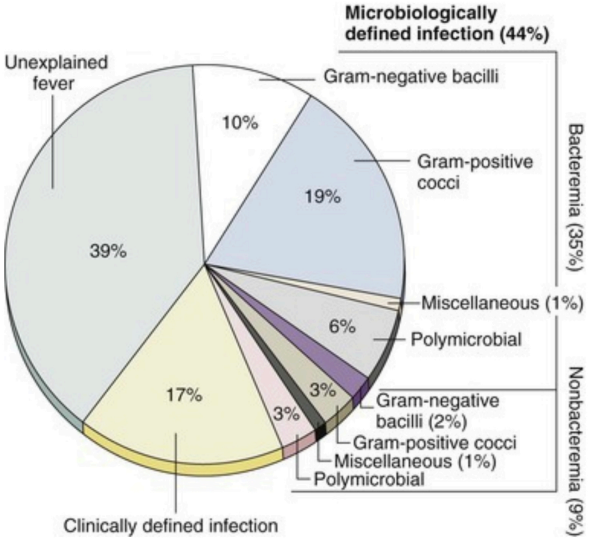
FIGURE 309-4 Causes of infection in 968 episodes of fever and neutropenia. (Un-

Seràgnoli Hematology Institute, Bologna



- **Neutropenic fever**
  - Infectious source documented in 20-30% of episodes
  - Bacteremia documented in 10-25% of patients
  - Aerobic Gram-positive and Gram-negative

Most common sites of infection



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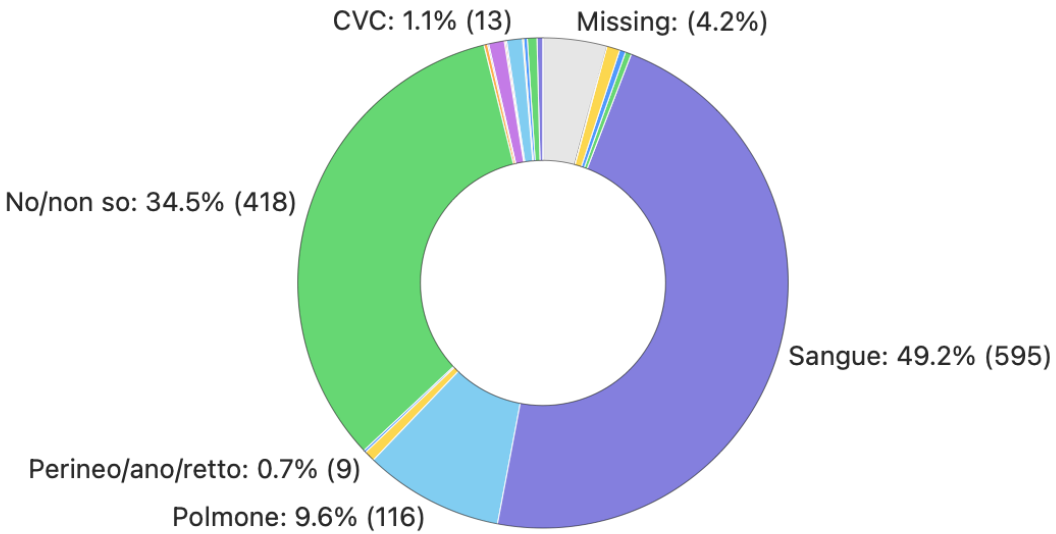
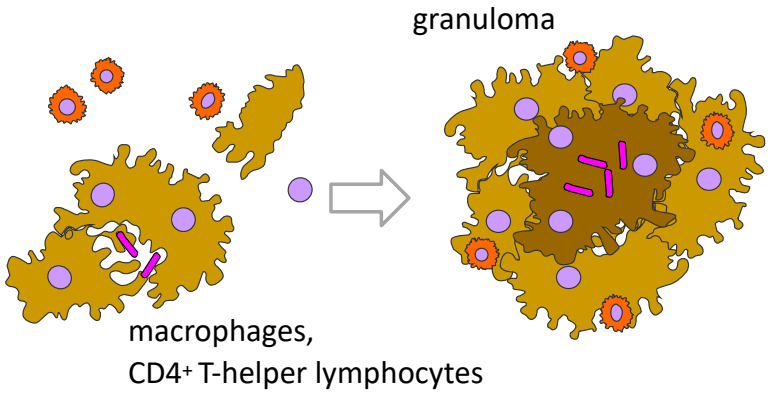


Risk of infection vs. duration of neutropenia

Phase I (1-10 days)		Phase II (10-27 days)		Phase III (≥ 27 days)
CoNS Staphylococcus Enterobacteriaceae Viridans streptococci Anaerobes Enterococcus C. difficile	+	MRSA VRE Resistant GNR S. maltophilia	+	Invasive moulds
Herpes simplex +/- Candida spp.		Herpes simplex Candida spp.		

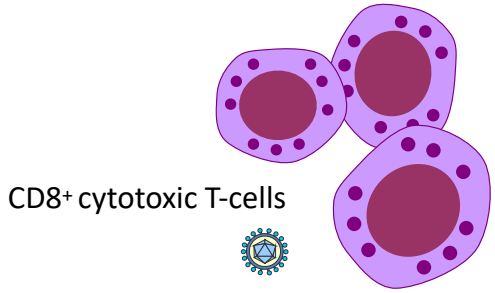
Caveat: Additional Pathogens of Concern in Patients with Suppressed Cell-Mediated Immunity



Intracellular bacteria...
Mycobacterium tuberculosis
Atypical mycobacterium
Legionella spp.
Listeria monocytogenes
Salmonella typhi
Nocardia spp.

Fungi...
Candida spp.
Endemic fungi
Cryptococcus neoformans
P. jiroveci

Parasites...
Toxoplasma gondii
Cryptosporidium
Leishmania



Viruses...
Herpes simplex
Varicella zoster
Cytomegalovirus
HHV-6
Epstein-Barr

Adenovirus
Polyomaviruses
Influenza
Parainfluenzae
RSV

Examples of common predisposing conditions-drugs: AIDS**,** allogeneic HSCT, high-dose corticosteroids, purine analogue chemotherapy (fludarabine), polyclonal and monoclonal T-cell depleting antibodies, temozolamide, T-cell depleting antibodies (alemtuzumab)

These pathogens are not covered by typical empiric regimens used for febrile neutropenia!

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ANTIMICROBIAL PROPHYLAXIS BASED ON OVERALL INFECTION RISK IN PATIENTS WITH CANCER

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Antimicrobial Prophylaxis[d]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 days	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation/maintenance • Alemtuzumab therapy • Moderate to severe GVHD • Anticipated neutropenia greater than 10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

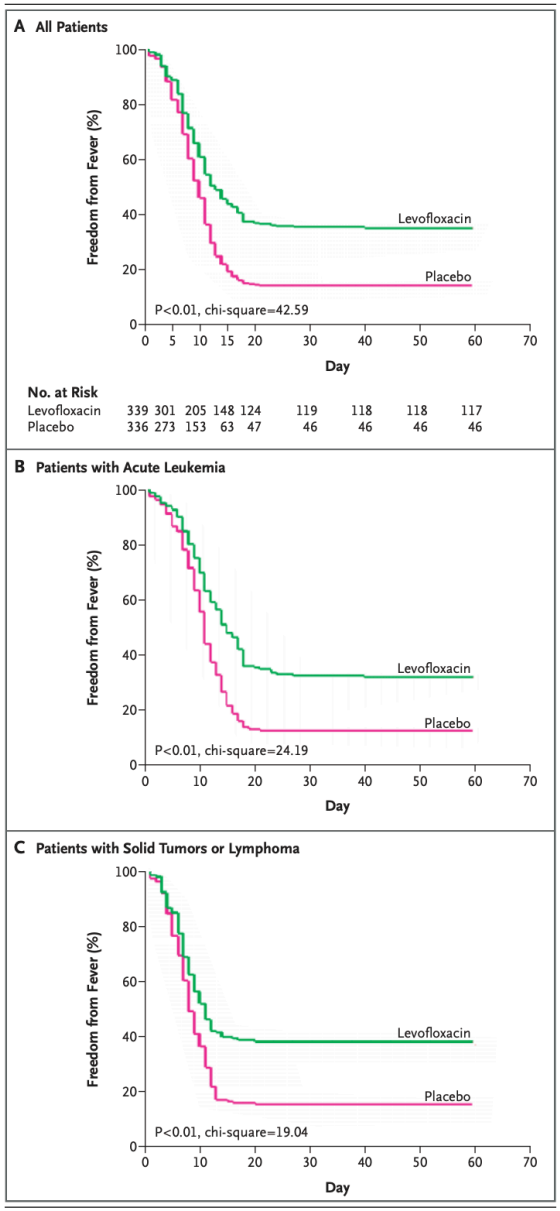


Table 3. Mortality Rates in the Treated Population.

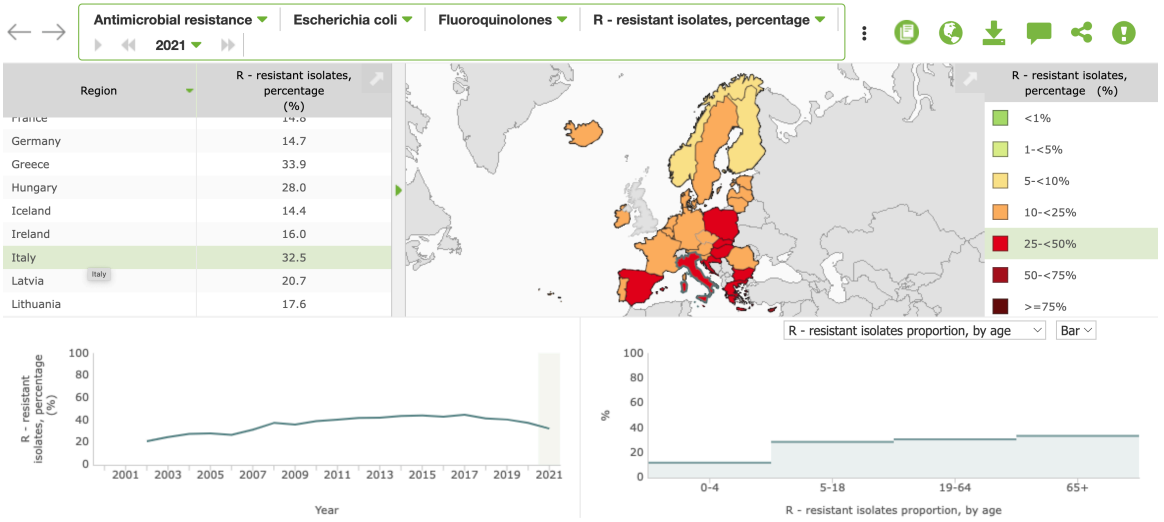
Variable	Levofloxacin (N=373)*	Placebo (N=363)	P Value
	no. of patients		
Death	10	18	0.15
Death due to infection	9	14	0.36
Microbiologically documented infection	4	7	0.25
Microbiologically documented infection with bacteremia	3	5	0.34
Single gram-positive isolate	2	2	
Single gram-negative isolate	0	2	
Polymicrobial (gram-positive and gram-negative) isolate	1	1	
Microbiologically documented infection without bacteremia	1	2	0.48
Single gram-positive isolate	0	1	
Single gram-negative isolate	1	1	
Clinically documented infection	2	4	0.33
Lung	1	2	
Other site	1	2	
Fever of unexplained origin	3	3	0.64
Death from noninfectious causes	1	4	0.17

* Two patients were lost to follow-up.

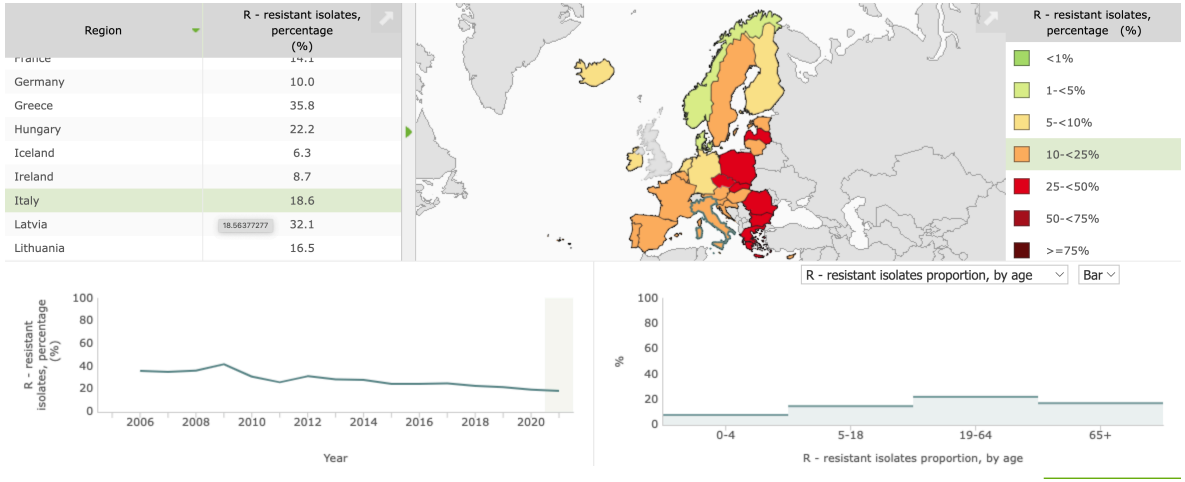
Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 2005; 353:977–987.

At what point of resistance does prophylaxis not work?

E. coli



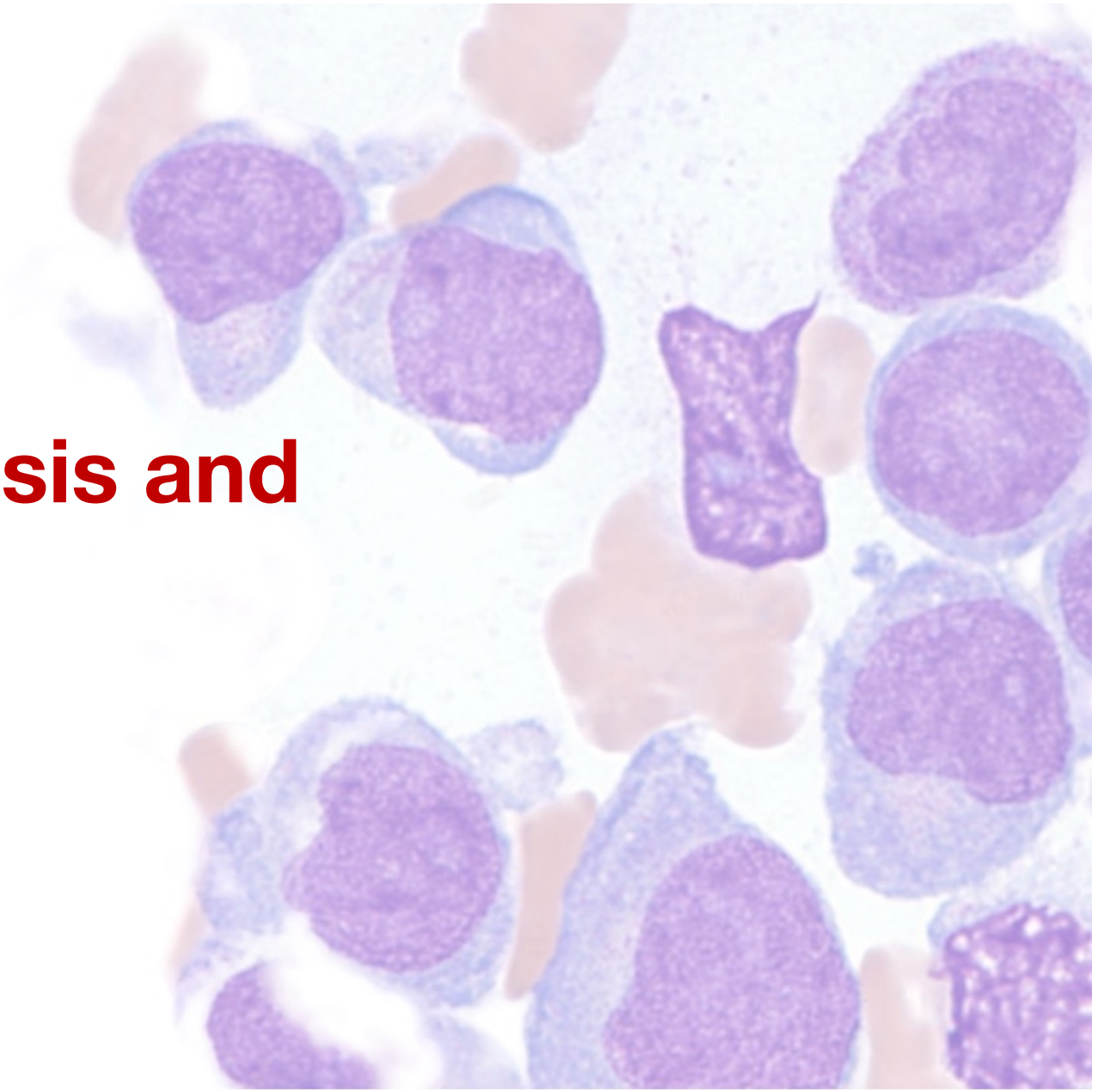
P. aeruginosa



Other potential problems with fluoroquinolone prophylaxis besides resistance

- Decreased sensitivity of culture
- Microbiome effects?
- Increased risk of *C. difficile* colitis?
- QTc interval prolongation
- SMP labeling warnings for increased risk of aortic dissection, tendon

Clinical diagnosis and management



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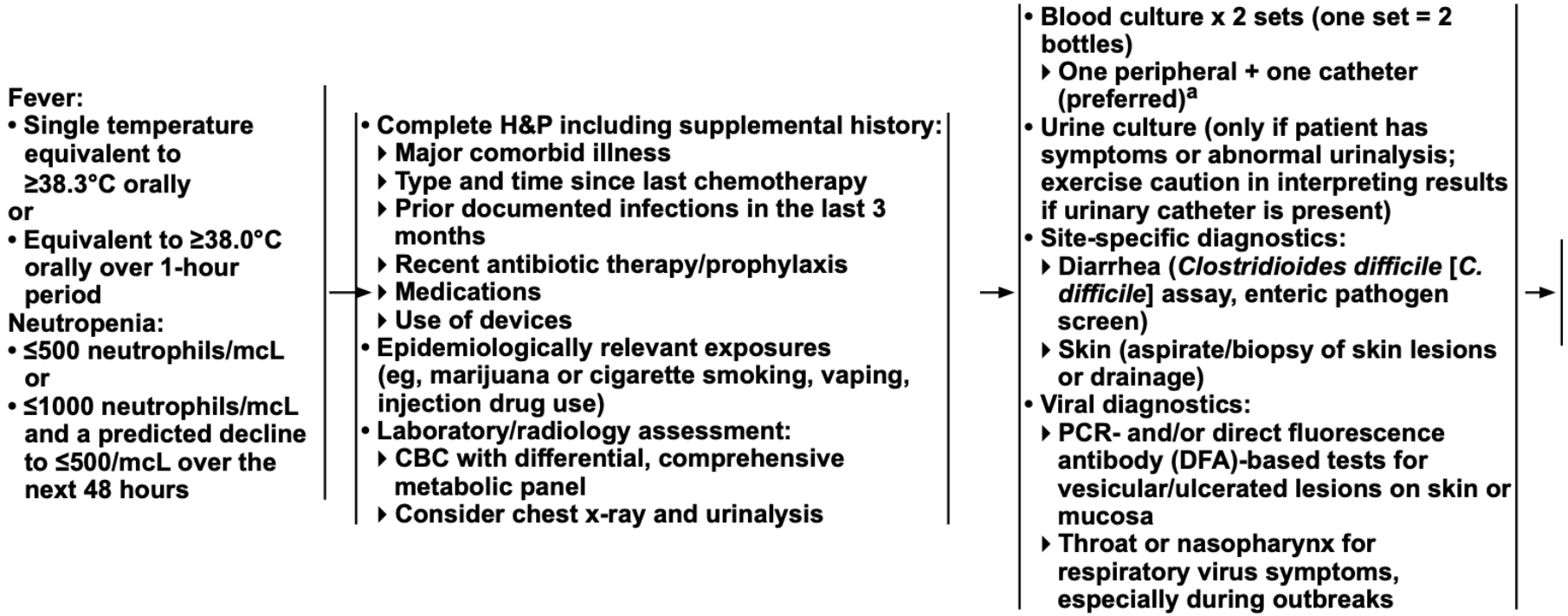
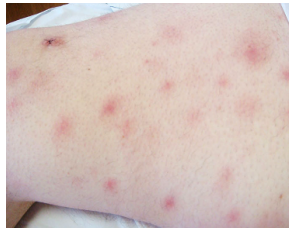
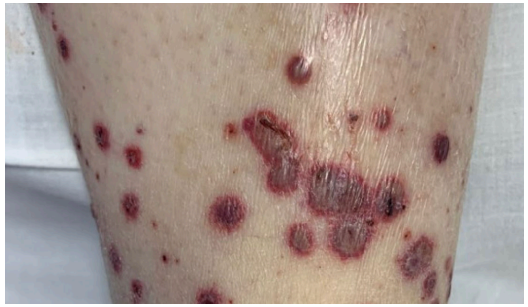
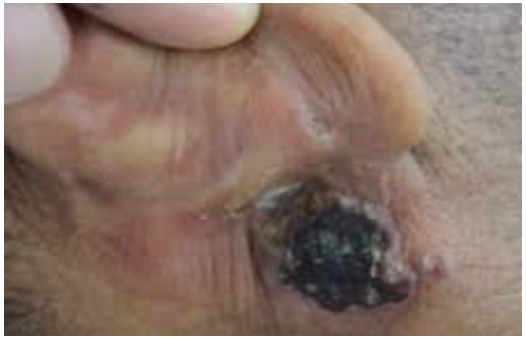


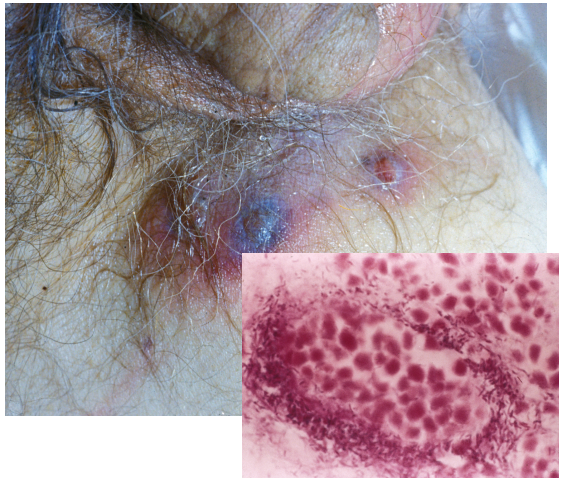
Skin lesions in neutropenic patients

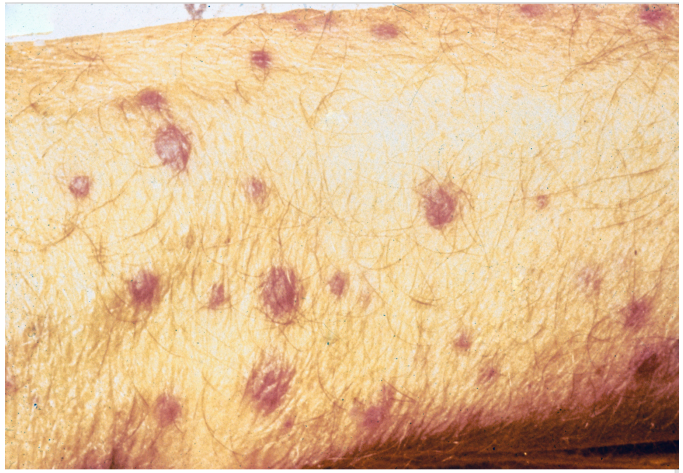




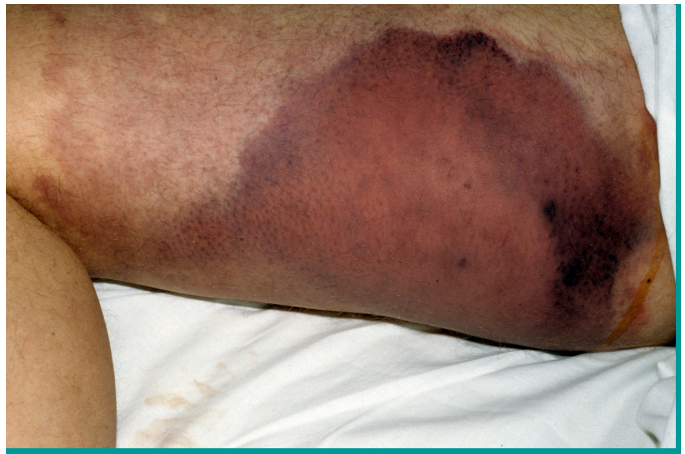


Ecythyma gangrenosum
Most common
(P. aeruginosa)
(Invasive molds-*Aspergillus, Fusarium)*





Skin Lesions in Disseminated Candidiasis



Leukemic Patient with *Clostridium perfringens*
Septicemia

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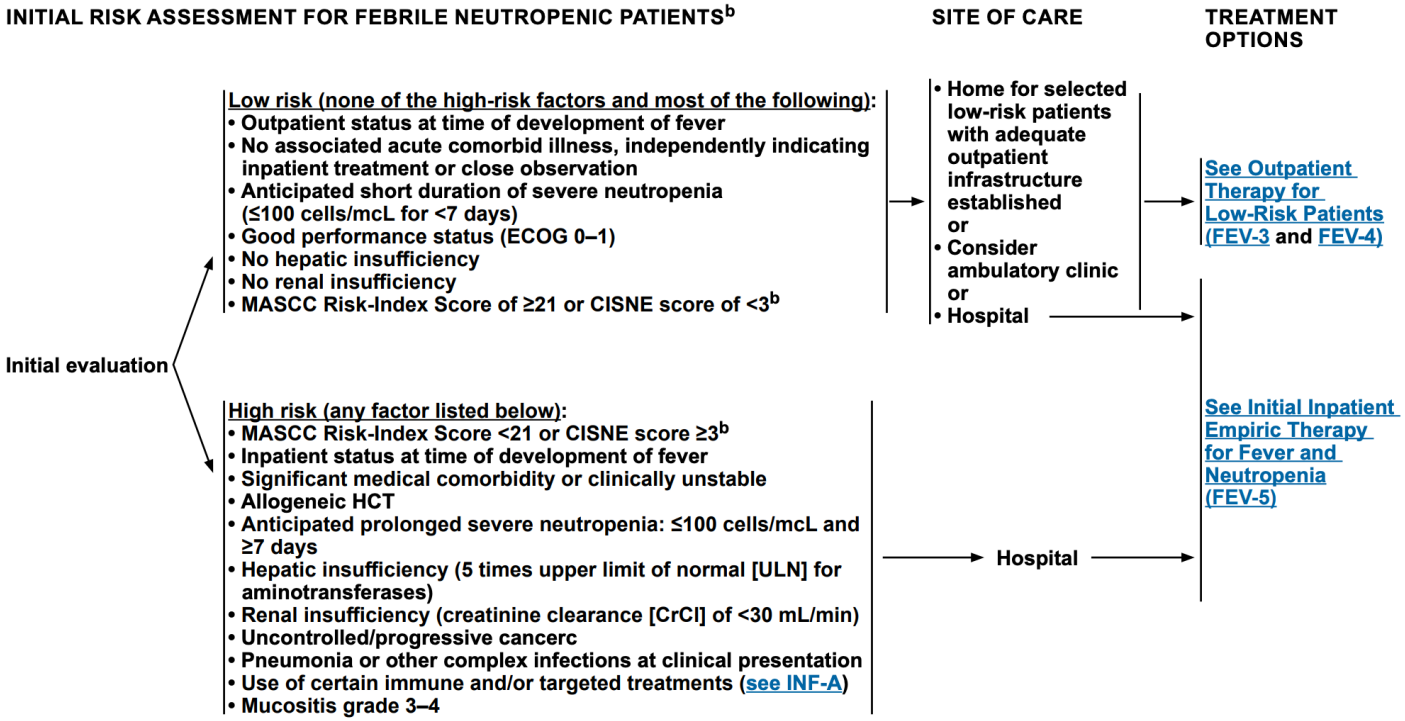
Risk assessment



[b] Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. Risk stratification is validated in adults; no generalizable, cross-validated, risk-stratified management exists for pediatric patients with febrile neutropenia. See Risk Assessment Resources (FEV-D).

[c] Uncontrolled/progressive cancer is defined as any patients with leukemia not in complete remission, or patients with other cancers and evidence of disease progression after more than 2 courses of chemotherapy.

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

What is my patient's risk of serious complications?

RISK ASSESSMENT RESOURCES

Using the MASCC Risk-Index Score

- **Using the visual analogue score, estimate the patient's burden of illness at the time of initial clinical evaluation. No signs or symptoms or mild signs or symptoms are scored as 5 points; moderate signs or symptoms are scored as 3 points. These are mutually exclusive. No points are scored for severe signs or symptoms or moribund.**
- **Based on the patient's age, past medical history, present clinical features, and site of care (input/output when febrile episode occurred), score the other factors in the model and total the sum.**

Burden of Illness

How sick is the patient at presentation?

No signs or symptoms	Mild signs or symptoms	Moderate signs or symptoms	Severe signs or symptoms	Moribund

Estimate the burden of illness considering all comorbid conditions

MASCC Risk-Index Score/Model[1,2]

Characteristic	Weight
• Burden of illness	
▸ No or mild symptoms	5
▸ Moderate 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 years	2

CISNE Score/Model[3]

Characteristic	Points
ECOG PS ≥2	2
Stress-induced hyperglycemia	2
COPD	1
Chronic cardiovascular disease	1
Mucositis NCI grade ≥2	1
Monocytes <200/μL	1

[1] The MASCC Risk-Index Score is for adults only. It does not apply to pediatric patients.

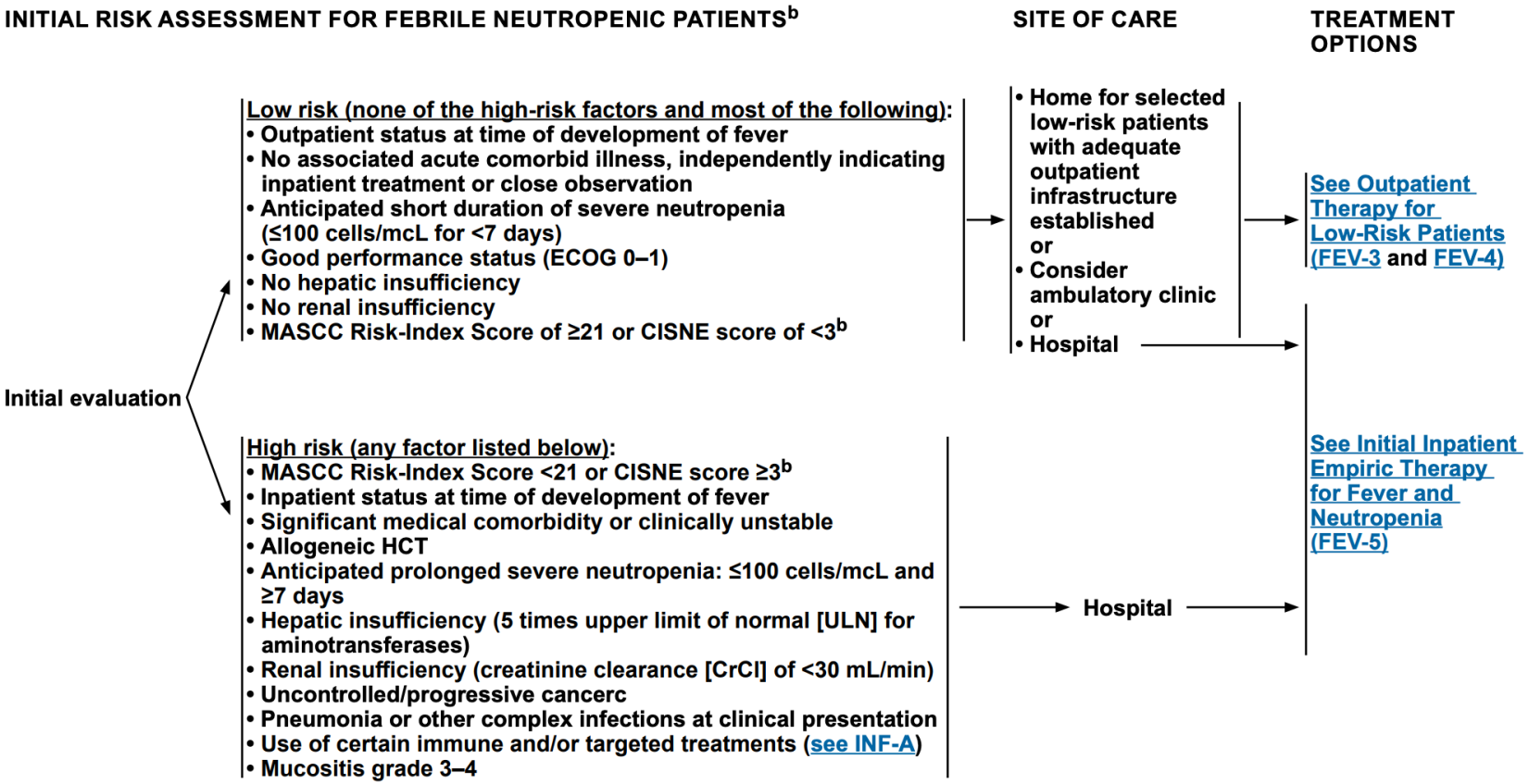
[2] Klastersky J, Paesmans M, Rubenstein EJ, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038-3051.

[3] Carmona-Bayonas A, Jimenez-Fonesca 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;33:465-471.

General risk groups

- **Low risk**
  - Severely neutropenic (ANC < 500 cells/μL) < 7 days
  - MASCC score > 21
  - No comorbidities or renal/hepatic dysfunction
  - Includes most patients receiving chemotherapy for solid tumors
- **High-risk**
  - Severely neutropenic (ANC < 500 cells/μL) > 7 days
  - MASCC score < 21
  - Ongoing comorbidities or other risk factors

Risk stratification



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Outpatient management: Low risk

OUTPATIENT THERAPY FOR LOW-RISK PATIENTS

TREATMENT OPTIONS

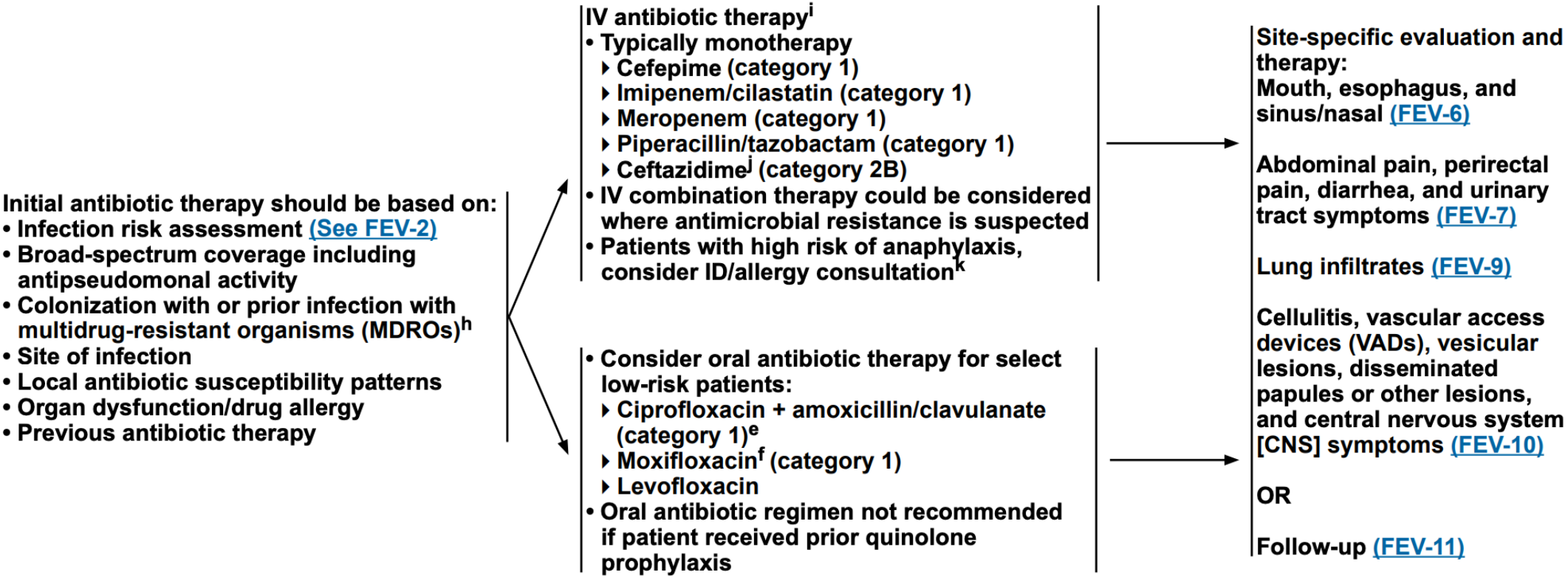
- Intravenous (IV) antibiotics at home
- Daily long-acting IV agent ± oral therapy
  - Home or office
- Oral therapy only[d]:
  - Ciprofloxacin plus amoxicillin/clavulanate[e] (category 1)
  - Levofloxacin
  - Moxifloxacin[f] (category 1)

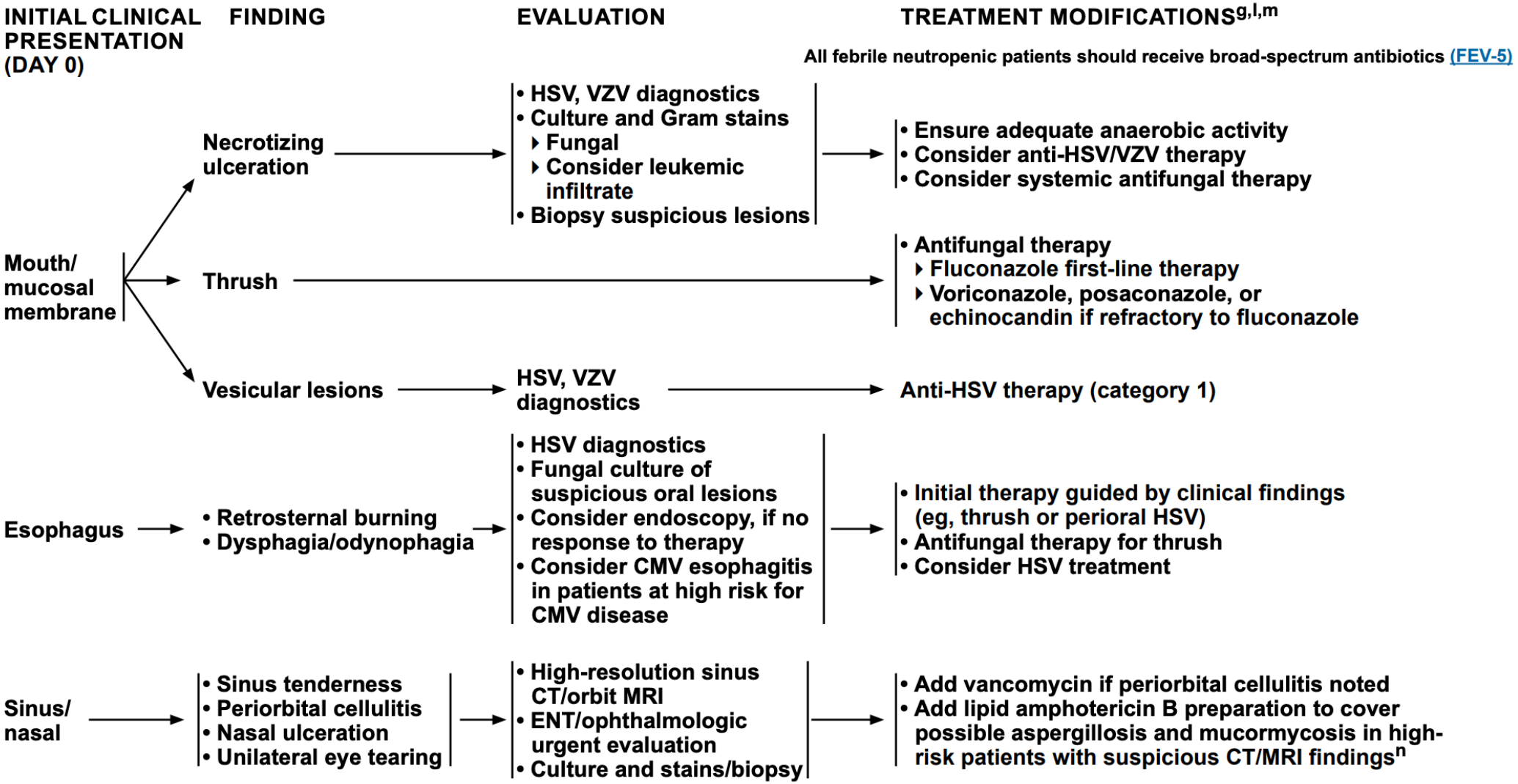
→

FOLLOW-UP

- Patient should be monitored daily
- Daily assessment (clinic or home visit) for the first 72 hours to assess response, toxicity, and compliance; if responding, then telephone follow-up daily thereafter.
- Specific reasons to return to clinic:
  - Any positive culture from blood or other sterile source
  - New signs/symptoms reported by the patient
  - Persistent or recurrent fever at 3–5 days
  - Inability to continue prescribed antibiotic regimen (ie, oral intolerance)
  - Office visit for infusion of IV antibiotics

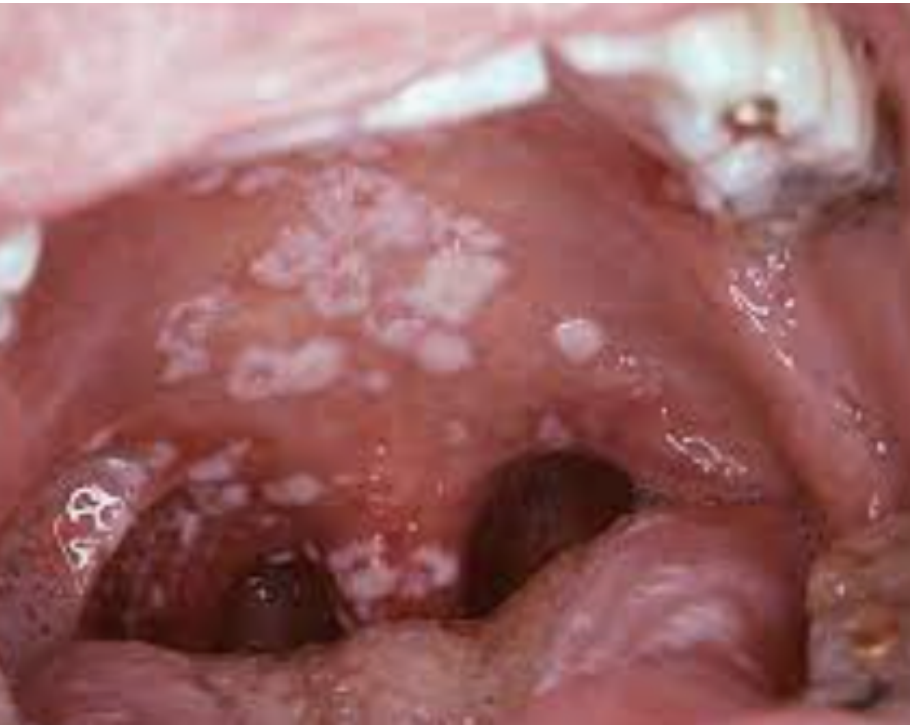
INITIAL INPATIENT EMPIRIC THERAPY FOR FEVER AND NEUTROPENIA[g]

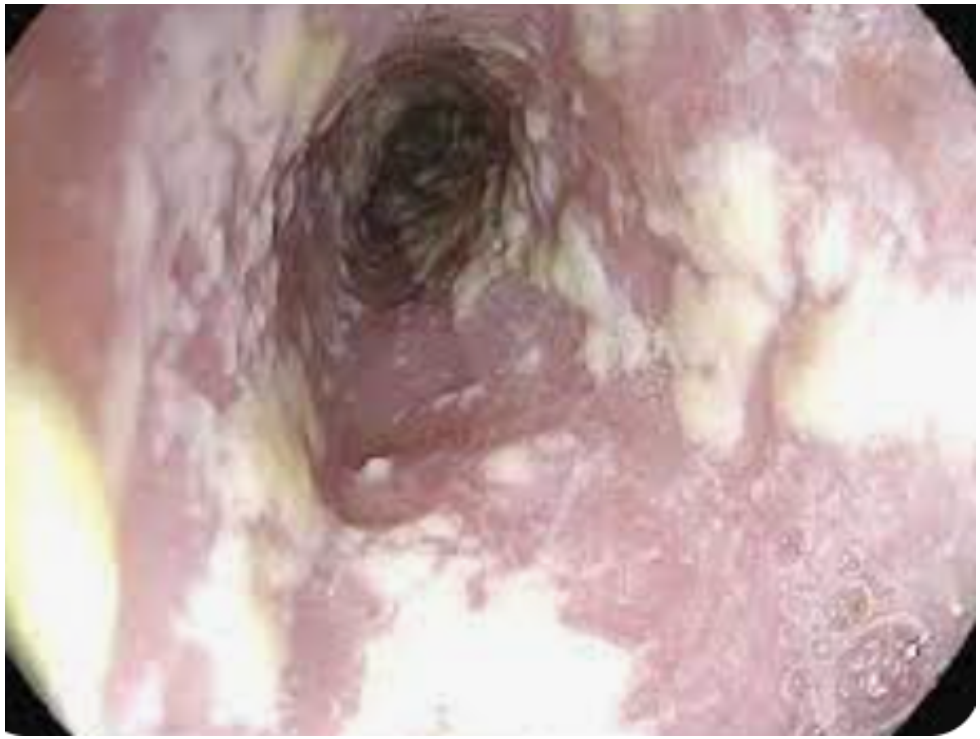




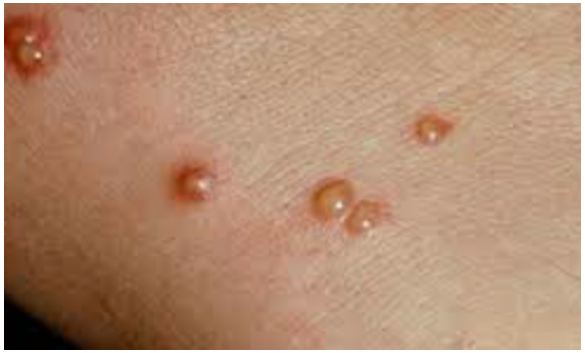
[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions.
[n] Posaconazole or isavuconazonium sulfate can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B formulations. Posaconazole is not approved by the FDA as primary therapy or secondary therapy for refractory invasive fungal infections.

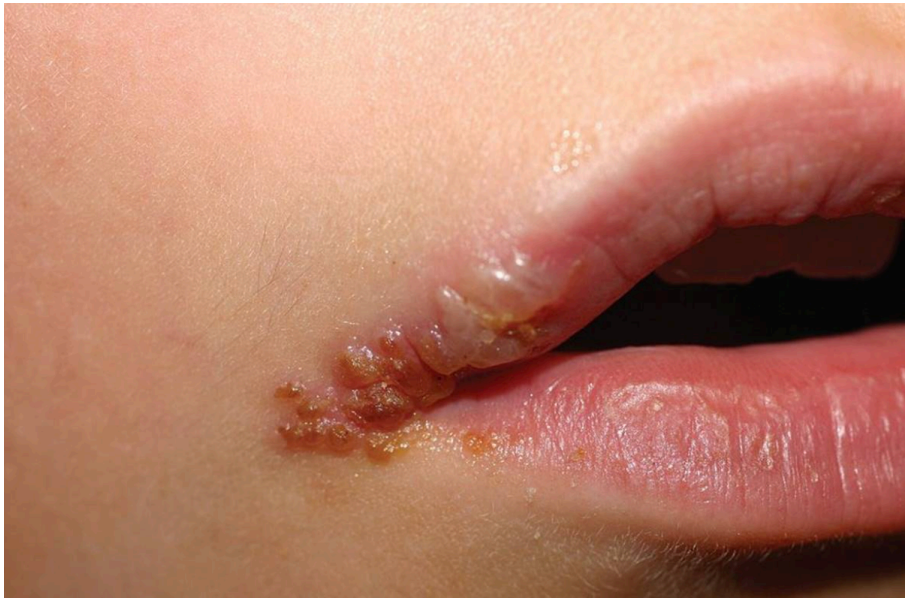
Follow-up (FEV-11)

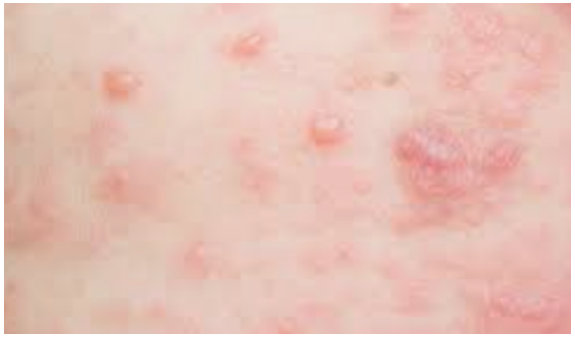


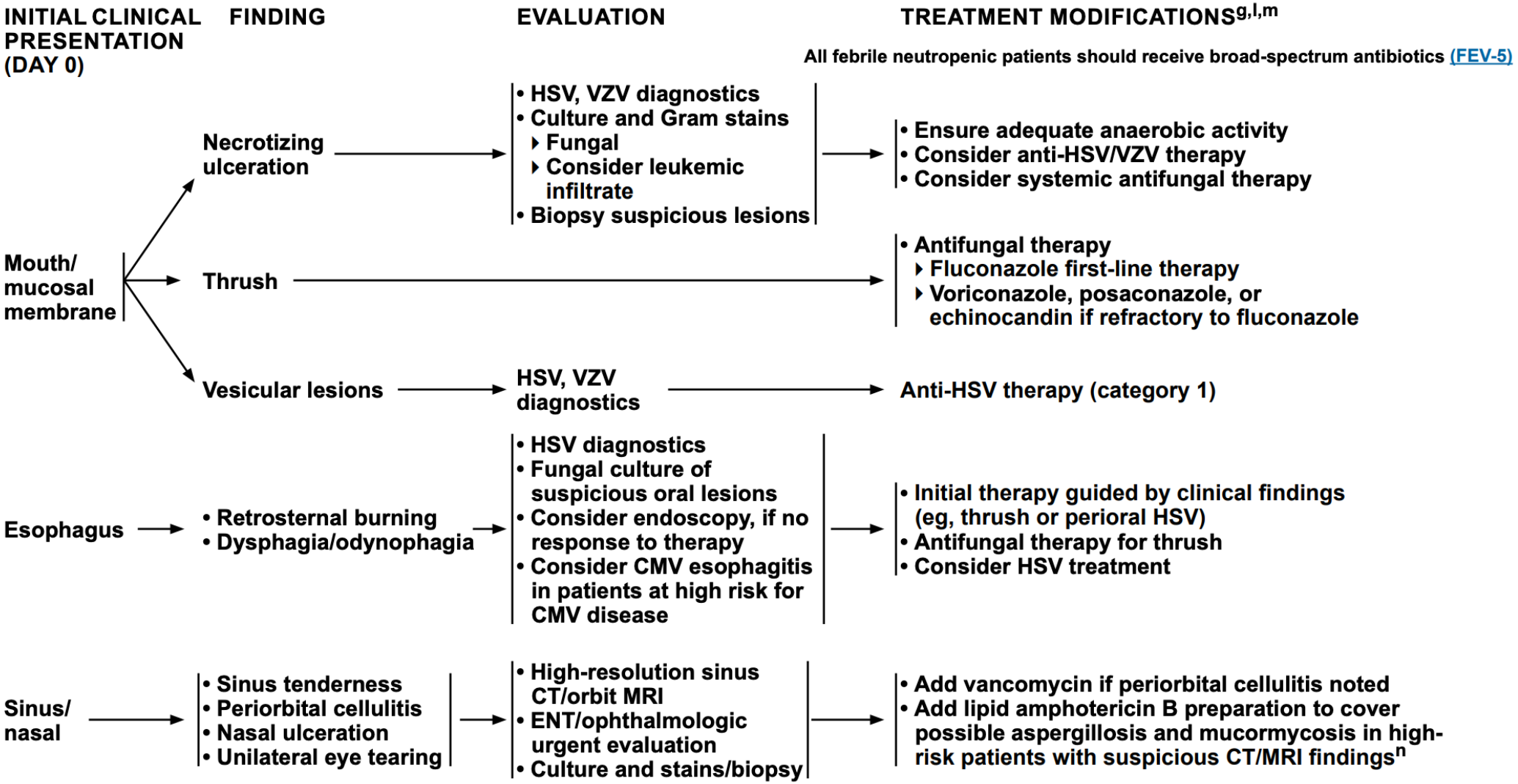


Vesicular lesions





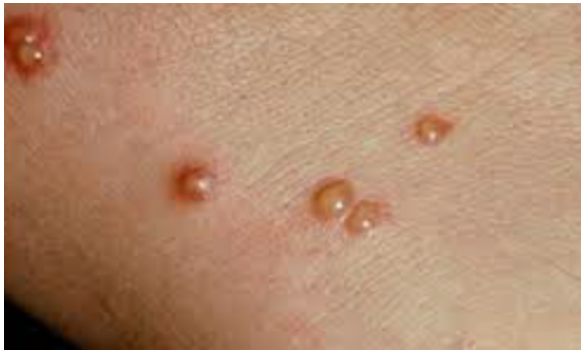


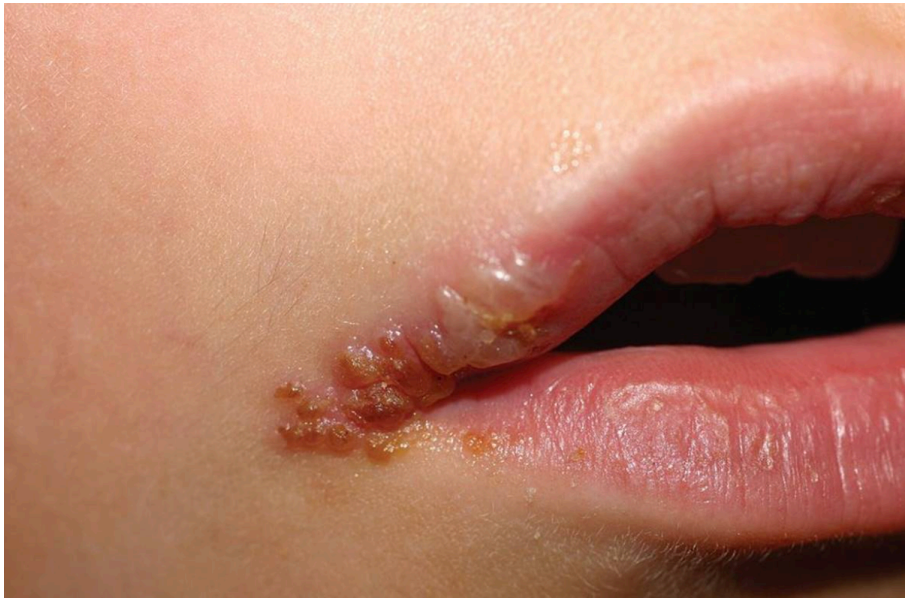


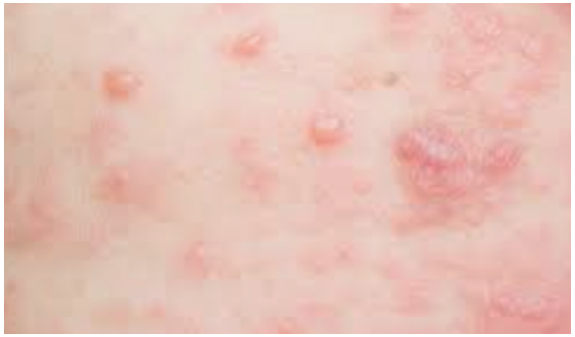
[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions.
[n] Posaconazole or isavuconazonium sulfate can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B formulations. Posaconazole is not approved by the FDA as primary therapy or secondary therapy for refractory invasive fungal infections.

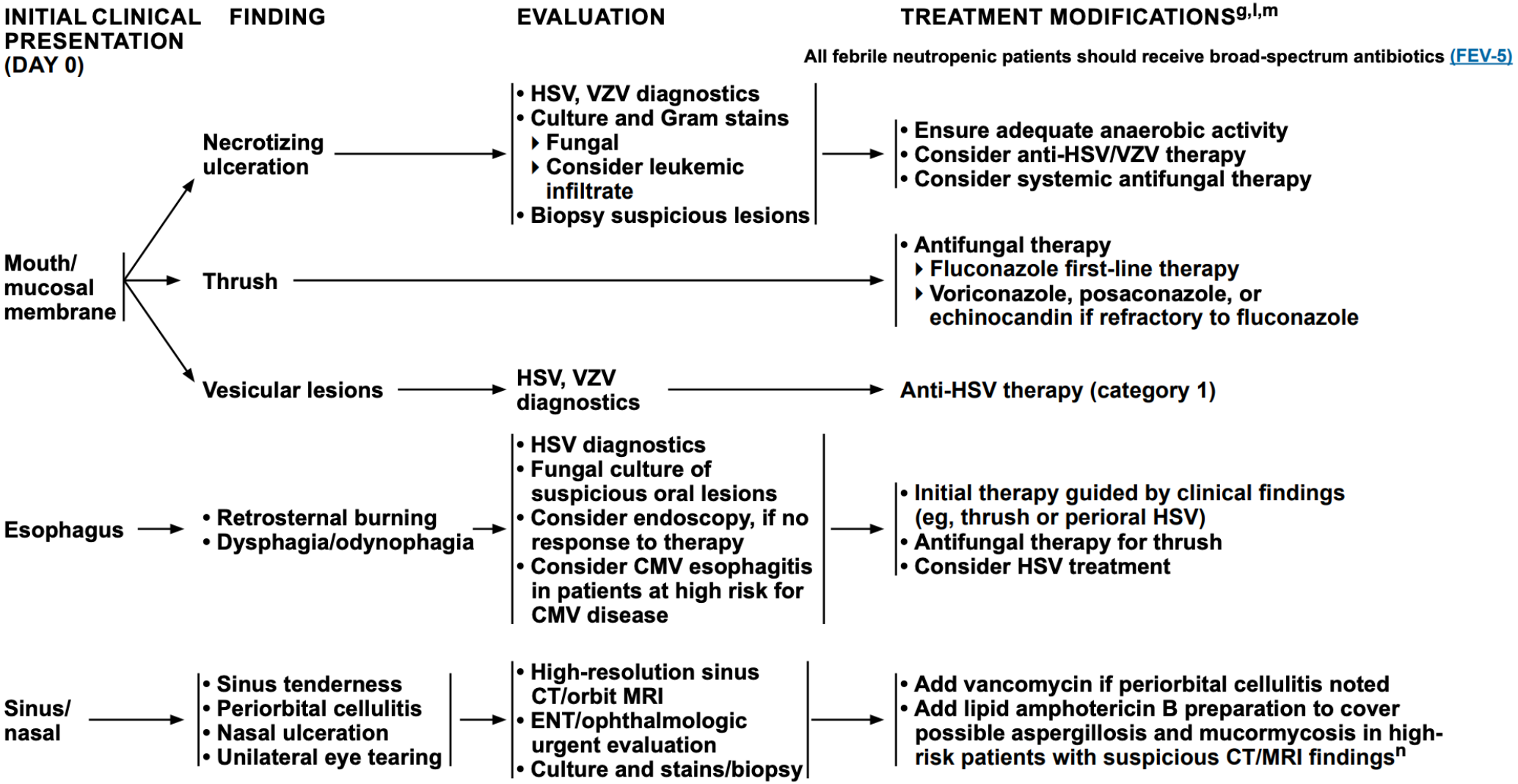
Follow-up (FEV-11)

Vesicular lesions









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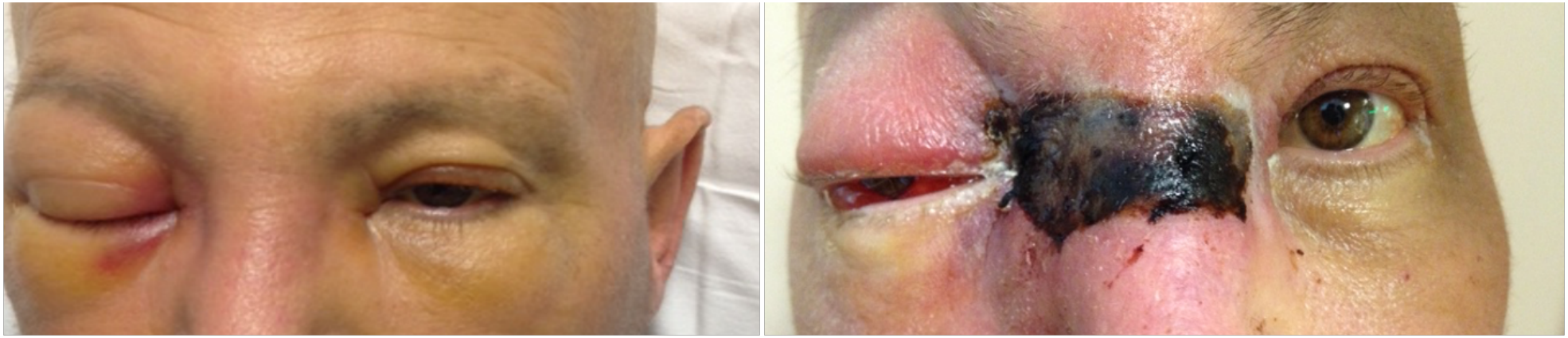
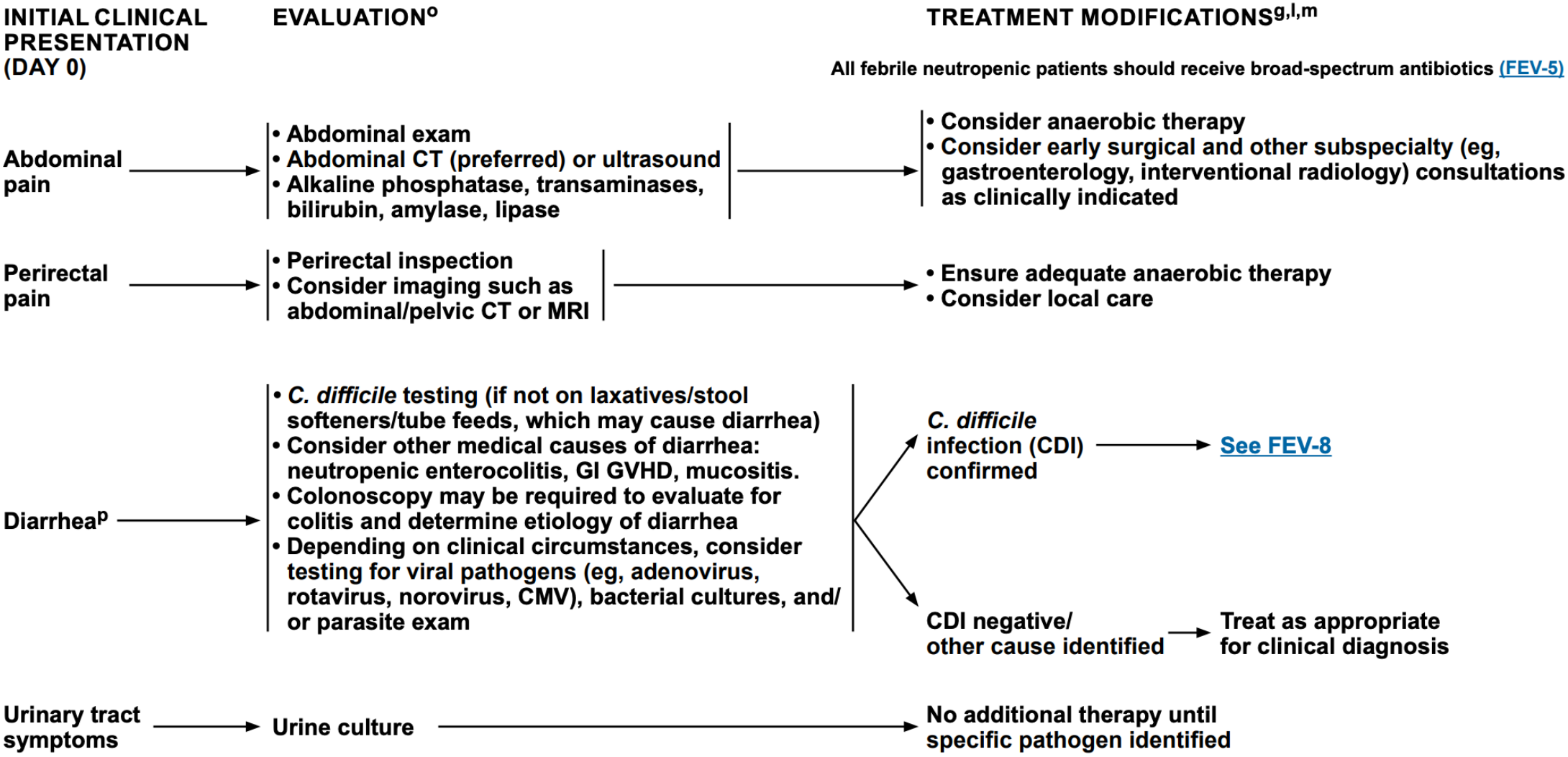
Follow-up (FEV-11)

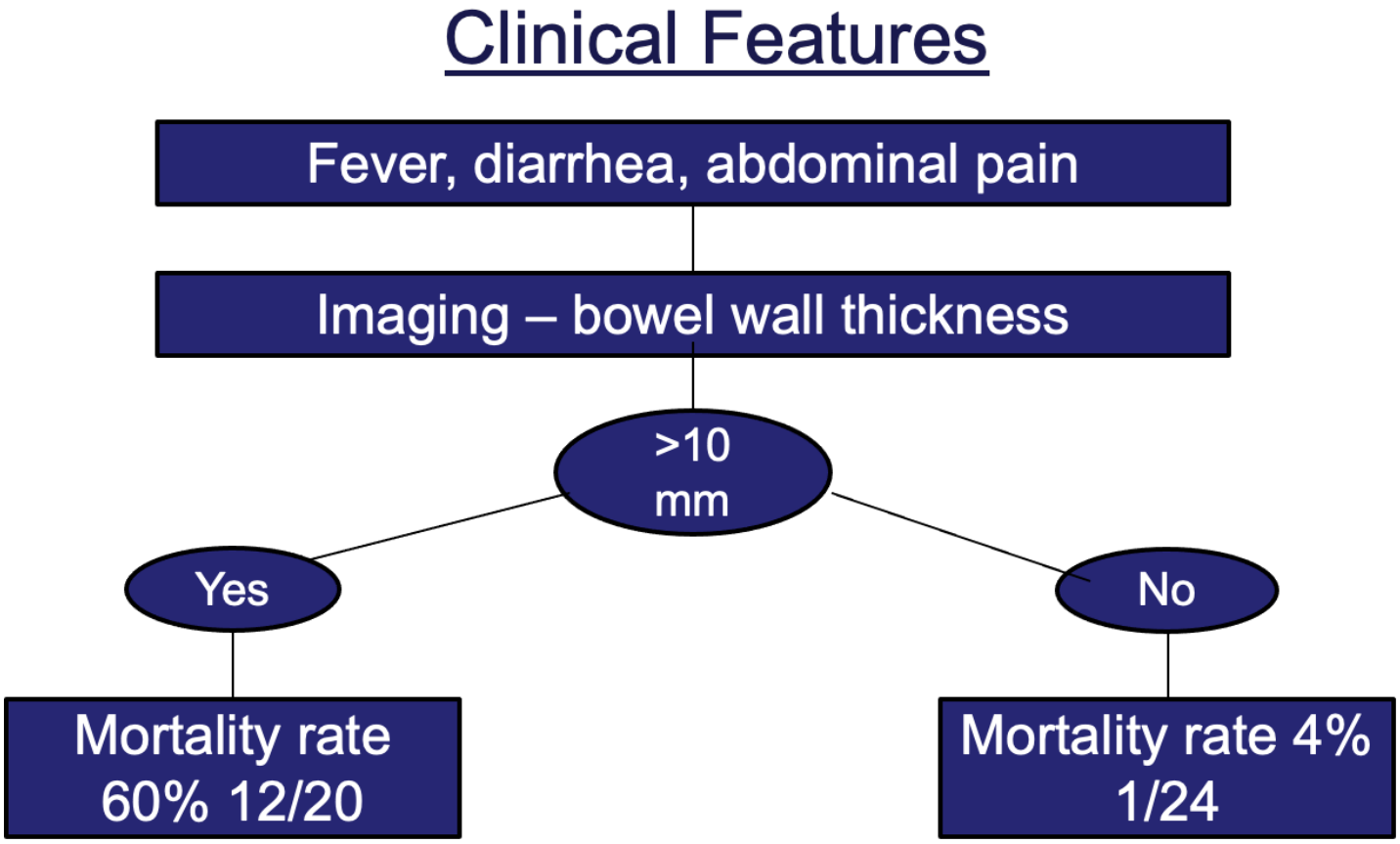
Periorbital swelling → aggressive fungal disease

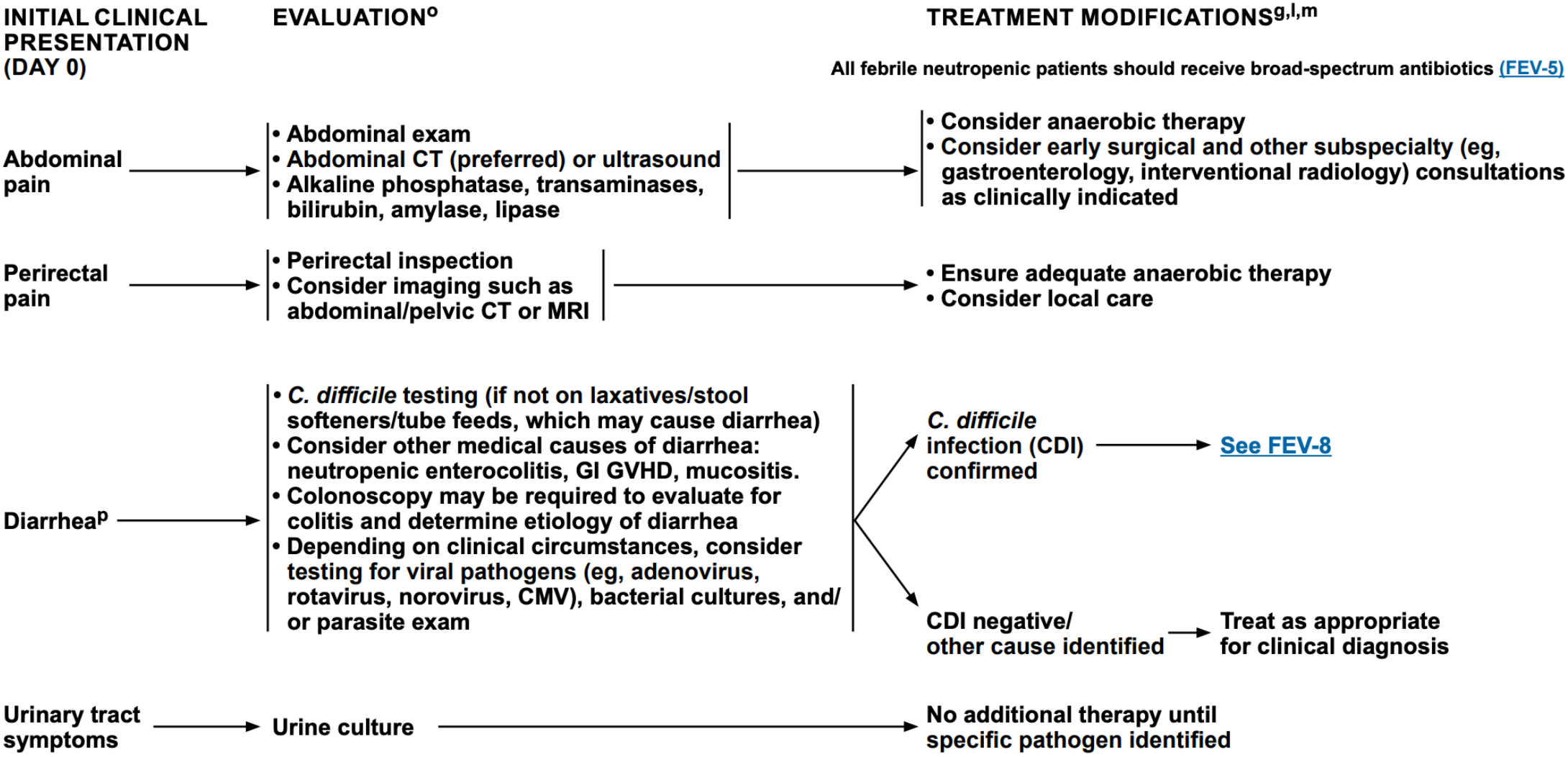


Rhinocerebral mucormycosis evolution over 24 hours in a neutropenic patient

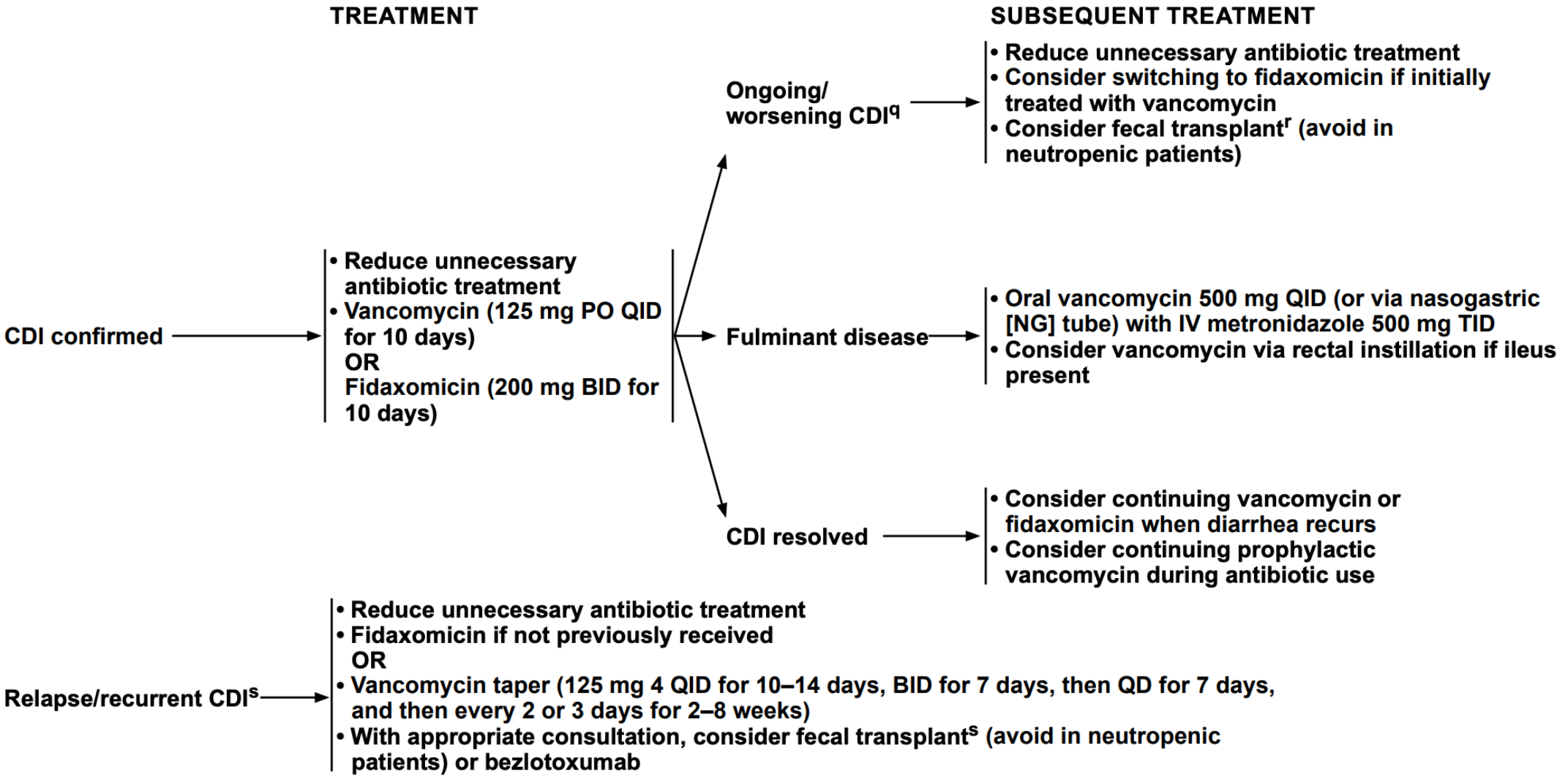

INITIAL CLINICAL PRESENTATION (DAY 0)
EVALUATION[o]
TREATMENT MODIFICATIONS[g,l,m]
All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-5)
Abdominal pain
• Abdominal exam
• Abdominal CT (preferred) or ultrasound
• Alkaline phosphatase, transaminases, bilirubin, amylase, lipase
• Consider anaerobic therapy
• Consider early surgical and other subspecialty (eg, gastroenterology, interventional radiology) consultations as clinically indicated
Perirectal pain
• Perirectal inspection
• Consider imaging such as abdominal/pelvic CT or MRI
• Ensure adequate anaerobic therapy
• Consider local care
Diarrhea[p]
• C. difficile testing (if not on laxatives/stool softeners/tube feeds, which may cause diarrhea)
• Consider other medical causes of diarrhea: neutropenic enterocolitis, GI GVHD, mucositis.
• Colonoscopy may be required to evaluate for colitis and determine etiology of diarrhea
• Depending on clinical circumstances, consider testing for viral pathogens (eg, adenovirus, rotavirus, norovirus, CMV), bacterial cultures, and/or parasite exam
C. difficile infection (CDI) confirmed
See FEV-8
CDI negative/ other cause identified
Treat as appropriate for clinical diagnosis
Urinary tract symptoms
Urine culture
No additional therapy until specific pathogen identified

Neutropenic enterocolitis (typhlitis)




INITIAL CLINICAL PRESENTATION (DAY 0)
EVALUATION[o]
TREATMENT MODIFICATIONS[g,l,m]
All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-5)
Abdominal pain
• Abdominal exam
• Abdominal CT (preferred) or ultrasound
• Alkaline phosphatase, transaminases, bilirubin, amylase, lipase
• Consider anaerobic therapy
• Consider early surgical and other subspecialty (eg, gastroenterology, interventional radiology) consultations as clinically indicated
Perirectal pain
• Perirectal inspection
• Consider imaging such as abdominal/pelvic CT or MRI
• Ensure adequate anaerobic therapy
• Consider local care
Diarrhea[p]
• C. difficile testing (if not on laxatives/stool softeners/tube feeds, which may cause diarrhea)
• Consider other medical causes of diarrhea: neutropenic enterocolitis, GI GVHD, mucositis.
• Colonoscopy may be required to evaluate for colitis and determine etiology of diarrhea
• Depending on clinical circumstances, consider testing for viral pathogens (eg, adenovirus, rotavirus, norovirus, CMV), bacterial cultures, and/or parasite exam
C. difficile infection (CDI) confirmed
See FEV-8
CDI negative/ other cause identified
Treat as appropriate for clinical diagnosis
Urinary tract symptoms
Urine culture
No additional therapy until specific pathogen identified

TREATMENT OF *CLOSTRIDIOIDES DIFFICILE* INFECTIONS (CDI) IN PATIENTS WITH CANCER



INITIAL CLINICAL PRESENTATION (DAY 0)

EVALUATION[t,u]

TREATMENT MODIFICATIONS[g,l,m]

All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-5)

Lung infiltrates →

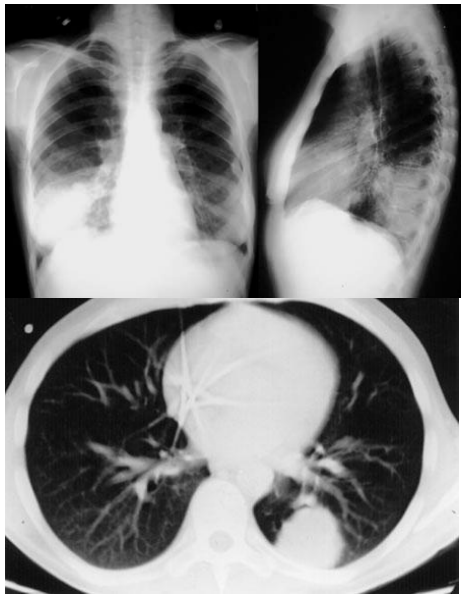
- **Blood and sputum cultures**
- **Consider depending on risk:**
  - **Nasopharyngeal swab for respiratory viruses, rapid tests[v] including SARS-CoV-2**
  - **Legionella urine antigen test**
  - **Serum galactomannan in patients at risk for mold infections [See Intermediate to High-Risk Patients on (INF-1)]**
  - **CT of chest to better define infiltrates**
  - **Bronchoalveolar lavage (BAL), including galactomannan and special stains or molecular techniques for identification of additional viral, protozoal, fungal, mycobacterial, and bacterial pathogens, particularly if no response to initial therapy or if diffuse infiltrates present**
  - **Consider diagnostic lung biopsy**
  - **β-glucan test for PJP**

→

- **Consider adding coverage for atypical bacteria (azithromycin, doxycycline, or fluoroquinolone)**
- **Consider adding:**
  - **Mold-active antifungal agent [See Intermediate to High-Risk Patients on (INF-1)]**
  - **Antiviral therapy during influenza season in local area[w]**
  - **TMP/SMX if possible *Pneumocystis jirovecii* etiology**
  - **Vancomycin or linezolid if MRSA suspected**
- **Re-evaluate for ability to de-escalate**

Pre-engraftment infections: pneumonia

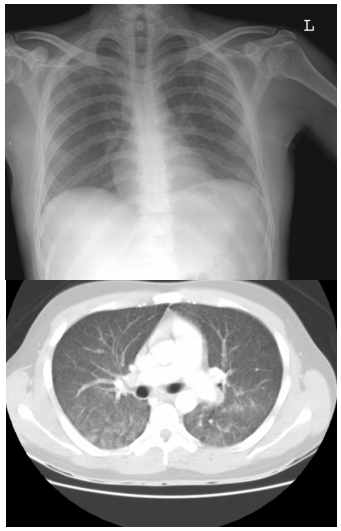
Consolidation



Acute
Bacterial
Thromboembolic
Hemorrhage

Sub-acute
Bacterial (resistant)
Fungal
Nocardia
Tuberculosis
Tumor
(Late PCP, radiation, Drug-induced)
BOOP

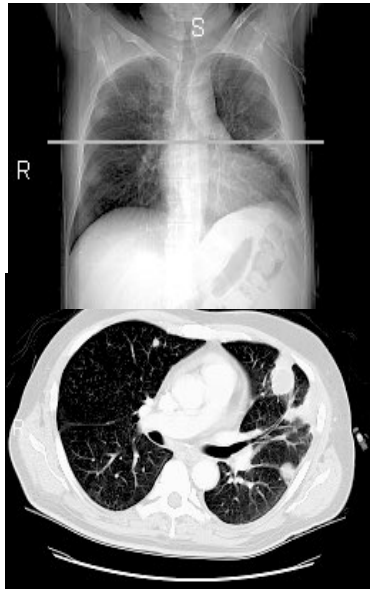
Peribronchovascular infiltrates



Acute
Pulmonary edema
Leukagglutination rxns
Engraftment rxns
DAH

Sub-acute
Viral
PCP
Radiation
Drug-induced

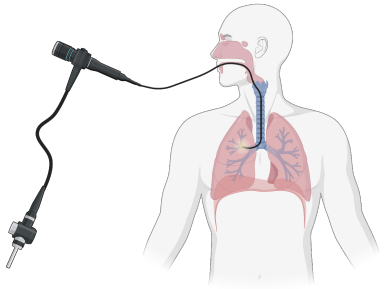
Nodular infiltrates



Acute
Bacterial
(Pseudomonas, S. aureus)

Sub-acute
Fungal
Nocardia
Tuberculosis
(PCP)
Tumor

Bronchoscopy: Timing is critical



501 consecutive allo HSCT patients

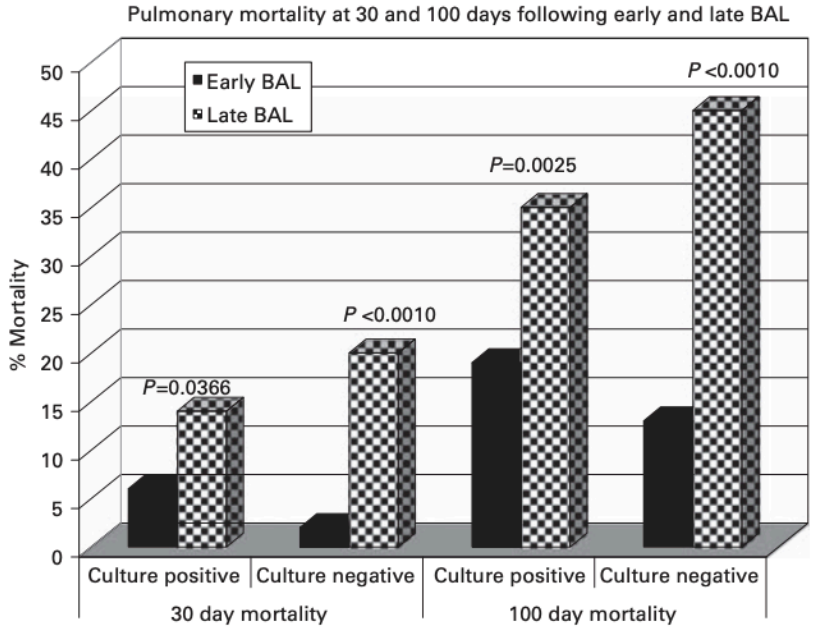


Figure 1 Pulmonary mortality at 30 and 100 days following early and late bronchoalveolar lavage (BAL). Significantly lower mortality rates were observed when a diagnosis of infection was confirmed by early fiberoptic bronchoscopy (FOB; black bars) compared to late examinations (checkered bars). Early culture-negative FOBs were also associated with lower mortality rates compared to late culture-negative exams. These findings were true for both 30- and 100-day mortality rates.

Shannon VR et al. Bone Marrow Transplant 2010; 45:647–655.

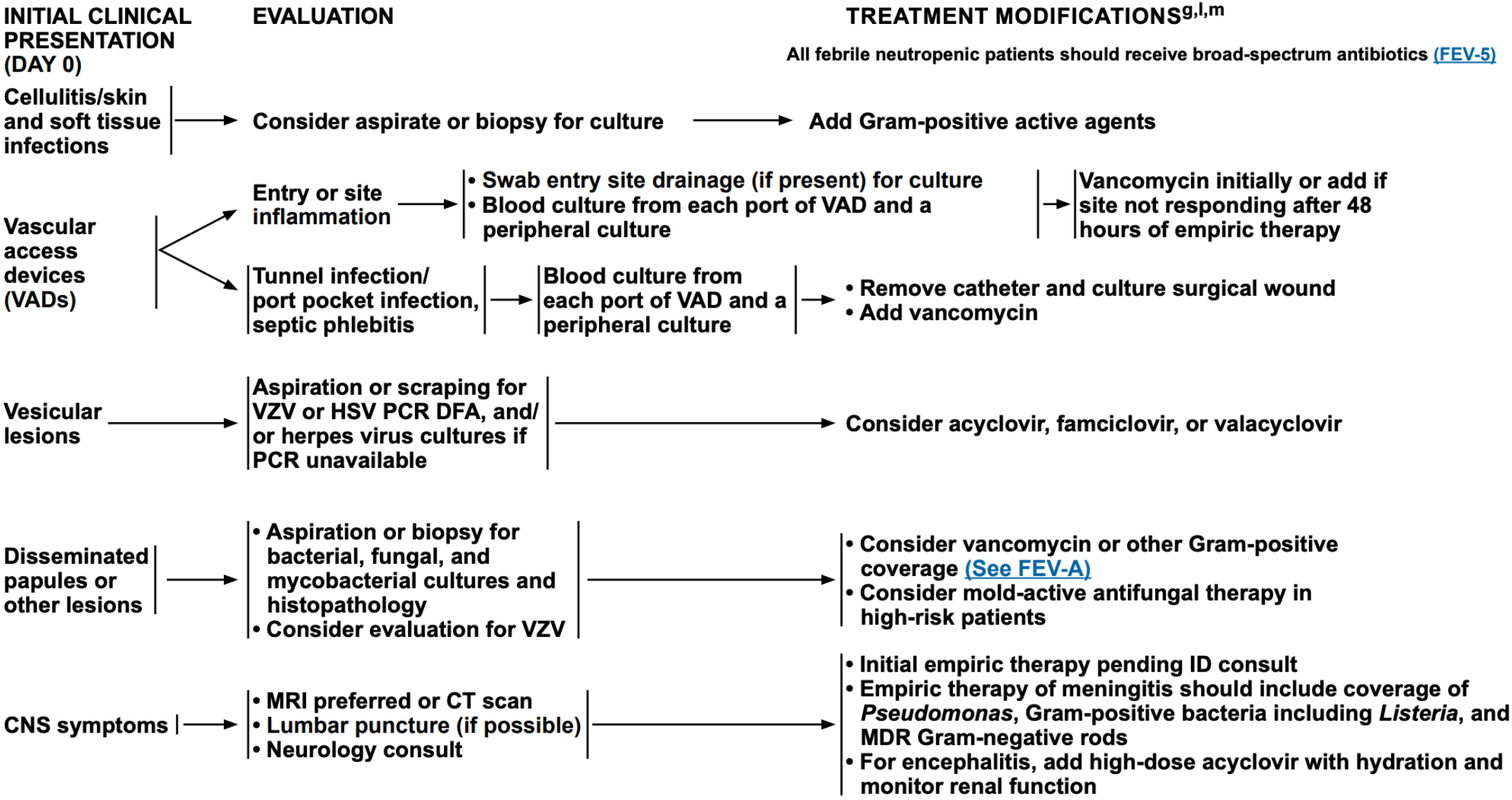
- **Identifying uncommon pathogens and unsuspected pathogens requiring unique therapy**
- **Administering correct therapy**
- **Discontinuing inappropriate therapy**
- **Determining duration of therapy**
- **Modifying intensity of therapy (dose, combination)**
- **Preventing spread of MDR pathogens to other patients**

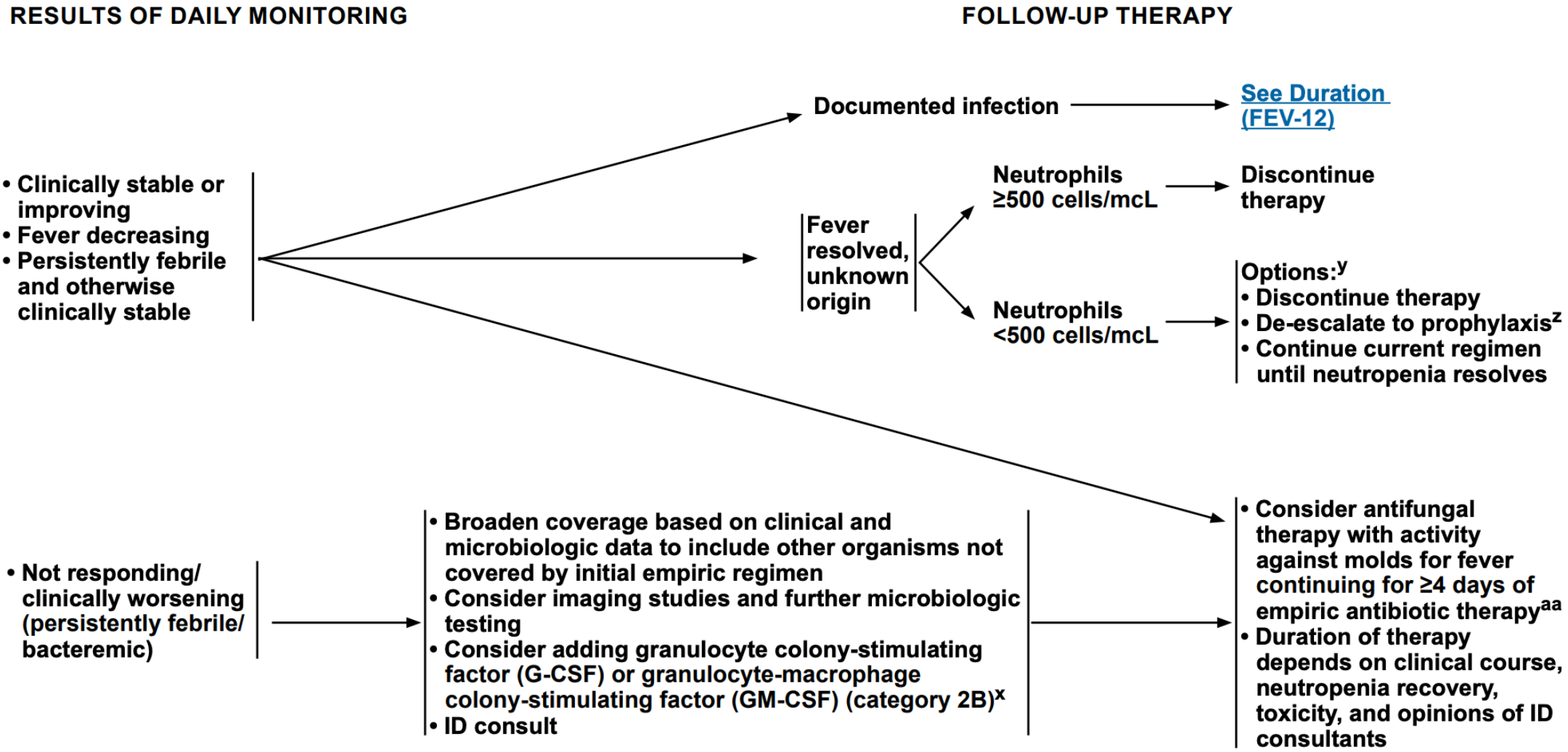
Early= within 4 days
Late > 4 days.

Highest yield in first 24h

Community respiratory viruses

- **Influenza, parainfluenza, RSV, human meta-pneumovirus, SARS.CoV-2**
  - Nasopharyngeal wash for respiratory viral panel
  - Sinus/chest CT
  - Respiratory isolation
  - Virus-specific management, delay chemotherapy if possible


INITIAL CLINICAL PRESENTATION (DAY 0)
EVALUATION
TREATMENT MODIFICATIONS[g,l,m]
All febrile neutropenic patients should receive broad-spectrum antibiotics (FEV-5)
Cellulitis/skin and soft tissue infections
Consider aspirate or biopsy for culture
Add Gram-positive active agents
Vascular access devices (VADs)
Entry or site inflammation
• Swab entry site drainage (if present) for culture
• Blood culture from each port of VAD and a peripheral culture
Vancomycin initially or add if site not responding after 48 hours of empiric therapy
Tunnel infection/ port pocket infection, septic phlebitis
Blood culture from each port of VAD and a peripheral culture
• Remove catheter and culture surgical wound
• Add vancomycin
Vesicular lesions
Aspiration or scraping for VZV or HSV PCR DFA, and/ or herpes virus cultures if PCR unavailable
Consider acyclovir, famciclovir, or valacyclovir
Disseminated papules or other lesions
• Aspiration or biopsy for bacterial, fungal, and mycobacterial cultures and histopathology
• Consider evaluation for VZV
• Consider vancomycin or other Gram-positive coverage (See FEV-A)
• Consider mold-active antifungal therapy in high-risk patients
CNS symptoms
• MRI preferred or CT scan
• Lumbar puncture (if possible)
• Neurology consult
• Initial empiric therapy pending ID consult
• Empiric therapy of meningitis should include coverage of Pseudomonas, Gram-positive bacteria including Listeria, and MDR Gram-negative rods
• For encephalitis, add high-dose acyclovir with hydration and monitor renal function


RESULTS OF DAILY MONITORING
FOLLOW-UP THERAPY
• Clinically stable or improving
• Fever decreasing
• Persistently febrile and otherwise clinically stable
Documented infection
See Duration (FEV-12)
Fever resolved, unknown origin
Neutrophils ≥500 cells/mcL
Discontinue therapy
Neutrophils <500 cells/mcL
Options:y
• Discontinue therapy
• De-escalate to prophylaxisz
• Continue current regimen until neutropenia resolves
• Not responding/ clinically worsening (persistently febrile/ bacteremic)
• Broaden coverage based on clinical and microbiologic data to include other organisms not covered by initial empiric regimen
• Consider imaging studies and further microbiologic testing
• Consider adding granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) (category 2B)x
• ID consult
• Consider antifungal therapy with activity against molds for fever continuing for ≥4 days of empiric antibiotic therapyaa
• Duration of therapy depends on clinical course, neutropenia recovery, toxicity, and opinions of ID consultants

FOLLOW-UP THERAPY FOR RESPONDING DISEASE

SUGGESTED MINIMUM DURATION OF THERAPY FOR DOCUMENTED INFECTION[g,l,m]

These are general guidelines for patients with uncomplicated disease and may need to be revised for individual patients. Treatment duration can be modified depending on infection severity and patient factors.

Documented infection →

- **Targeted treatment of documented infections should be done**
- **Reassessment of empiric broad-spectrum therapy**
- **De-escalation and duration of antimicrobial therapy may be individualized based on:**
  - **Neutrophil recovery**
  - **Rapidity of defervescence**
  - **Specific site of infection**
  - **Infecting pathogen**
  - **Patient's underlying illness**
- **Catheter removal for septic phlebitis, tunnel infection, or port pocket infection**

→

- **Skin/soft tissue: 5–14 days**
- **Bloodstream infection**
  - **Gram-negative: 7–14 days**
  - **Gram-positive: 7–14 days**
  - ***S. aureus*: typically requires 4 weeks after first negative blood culture; ID consult advised**
  - **Yeast: ≥2 weeks after first negative blood culture**
  - **Catheter removal favored for bloodstream infections with *Candida* or other yeasts, *S. aureus*, *Pseudomonas aeruginosa*, *Corynebacterium jeikeium*, *Acinetobacter* spp., *Bacillus* spp., atypical mycobacteria, molds, vancomycin-resistant enterococci (VRE), *Stenotrophomonas maltophilia*, and other MDROs**
- **Bacterial sinusitis: 7–14 days**
- **Bacterial pneumonia: 5–14 days**
- **Fungal (mold and yeast):**
  - ***Candida*: minimum of 2 weeks after first negative blood culture**
  - **Mold (eg, *Aspergillus*): minimum of 12 weeks**
- **Viral:**
  - **HSV/VZV: 7–10 days (category 1); acyclovir, valacyclovir, or famciclovir (uncomplicated, localized disease to the skin)**
  - **Influenza: a minimum 5-day course of oseltamivir[bb]**

[g] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.
[l] See Antifungal Agents (FEV-B) for dosing, spectrum, and specific comments/cautions.
[m] See Antiviral Agents (FEV-C) for dosing, spectrum, and specific comments/cautions. The antivirals are not equal in terms of efficacy, side effects, and resistance.
[bb] A minimum 5-day course is standard based on data from ambulatory and otherwise healthy individuals with intact immune systems; some centers consider longer courses or higher doses (eg, 150 mg) for the highly immunocompromised, but there is no proven benefit to prolonged therapy.

Persistent neutropenic fever