Febrile Neutropenia

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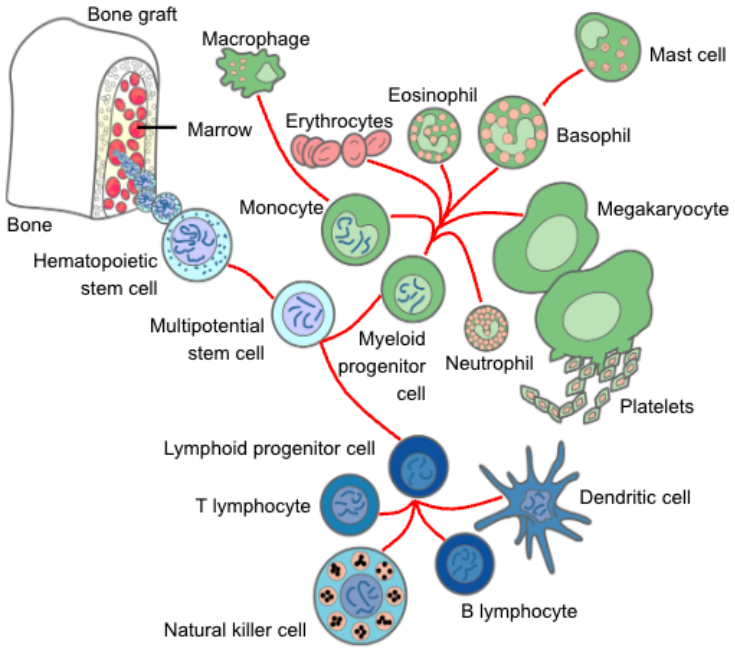
Background video: Neutrophil chasing *S. aureus*.

Objectives

- What are the most common infections associated with short versus prolonged neutropenia?
- How does the presentation of skin, mucocutaneous lesions, abdominal pain or pneumonia change the infection differential diagnosis?
- What are common empiric antimicrobial regimens used to treat patients while awaiting diagnostic results?

Normal hematopoiesis



- **Myeloid lineage (neutrophils / platelets)**
  - Homogeneous, terminally differentiated effector cells
  - Short-lived, post-mitotic
  - Continuous high-throughput production
  - Rapid quantitative recovery after chemotherapy (≈2–3 weeks)
- **Lymphoid lineage (T, B, NK cells)**
  - Highly heterogeneous populations
  - Mix of short-lived effector cells and long-lived memory cells

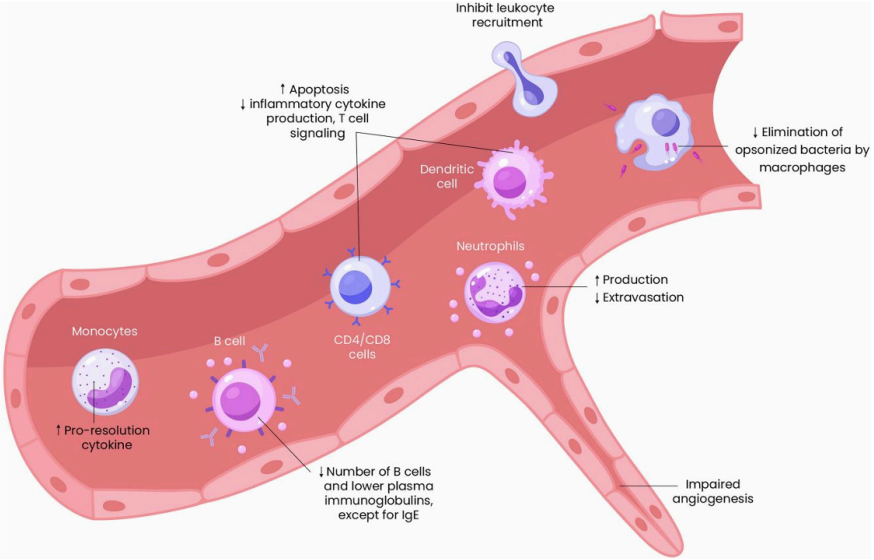
Chemotherapy-associated neutropenia

- **Antineoplastic chemotherapy impairs 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

Corticosteroids

Paradoxical effects:

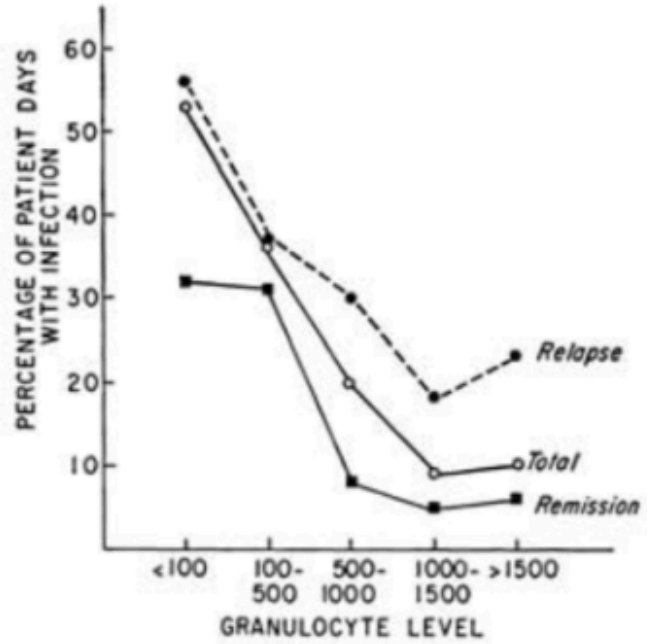
- ↑ Granulocytopoiesis (apparent benefit)
  - ↓ Accumulation at infection site
- ↓ Adherent capacity
- ↓ Chemotaxis
- ↓ Phagocytosis
- ↓ Intracellular killing



Immunity and innate immune cells

Cells	Molecules	Active against
PMNs • 1° granules • Specific granules	• Lysozyme, myeloperoxidase with (with H_2O_2) • Defensins, BPI, lactoferrin	Bacteria, fungi
Macrophages	• Similar to PMN but no myeloperoxidase • Nitric oxide • Arginase	Intracellular pathogens (depletes arginine)
Eosinophils	• Cationic proteins • Major basic protein • Peroxidase	Worms (extracellular)
Natural killer (NK) cells	• Perforins • Granzymes	Viral or bacterial infected cells

Quantitative relationship of neutropenia with infection risk



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

Absolute neutrophil count

$$\text{ANC} = \text{WBC} \times \frac{(\%\ \text{segmented neutrophils} + \%\ \text{banded neutrophils})}{100}$$

ANC (cells/μL)	Interpretation	Clinical relevance
1000–1500	Mild neutropenia	Usually low risk
500–1000	Moderate	Increased infection risk
<500	Severe neutropenia	High risk of serious infections
<100	Profound	Extremely high risk

Granulocytes (neutrophils)

- Chemotherapy & radiation → **neutropenia**
- Duration: Nadir 10-14 days, duration 3-4 weeks or longer
- **Primary risk factor for bacterial and fungal infections**
- Risk of infection increases with:
  - Depth of neutropenia
  - Duration of neutropenia
  - Concurrent organ dysfunction

Risk of infection by disease type

Disease	Risk Level
Acute myeloid leukemia	Highest
High-risk ALL, Relapsing leukemia	High
Low-risk ALL, CLL, Myeloma	Moderate
Non-Hodgkin lymphoma	Lower
Solid tumors	Lowest

ALL- acute lymphoblastic leukemia,

Clinical signs of infection are muted in neutropenic patients

% of patients who have a neutrophil count/mm^3 :

Signs and Symptoms	<100	101-1000	>1000
Fever	98	90	76
Fluctuance	6	36	52
Fissure or ulceration	21	42	54
Exudate	11	64	91
Purulent sputum	8	67	84
Pyuria	11	63	97

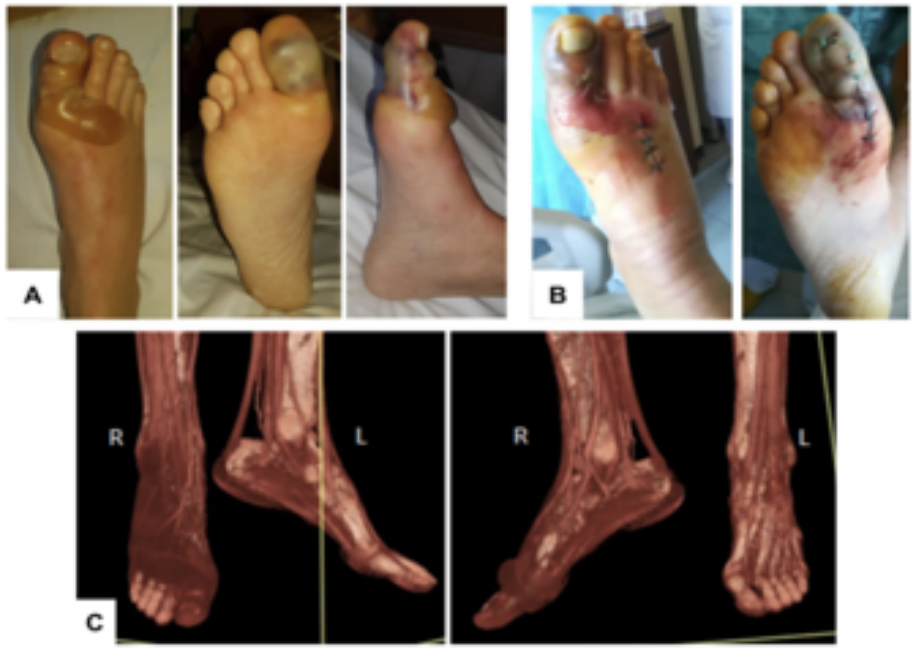
The integument (skin, mucus membranes)

Skin:

- Chemotherapy → hair loss, dryness
- Catheters → direct microbial access
- Broken skin → *S. aureus*, gram-negatives

Oropharynx:

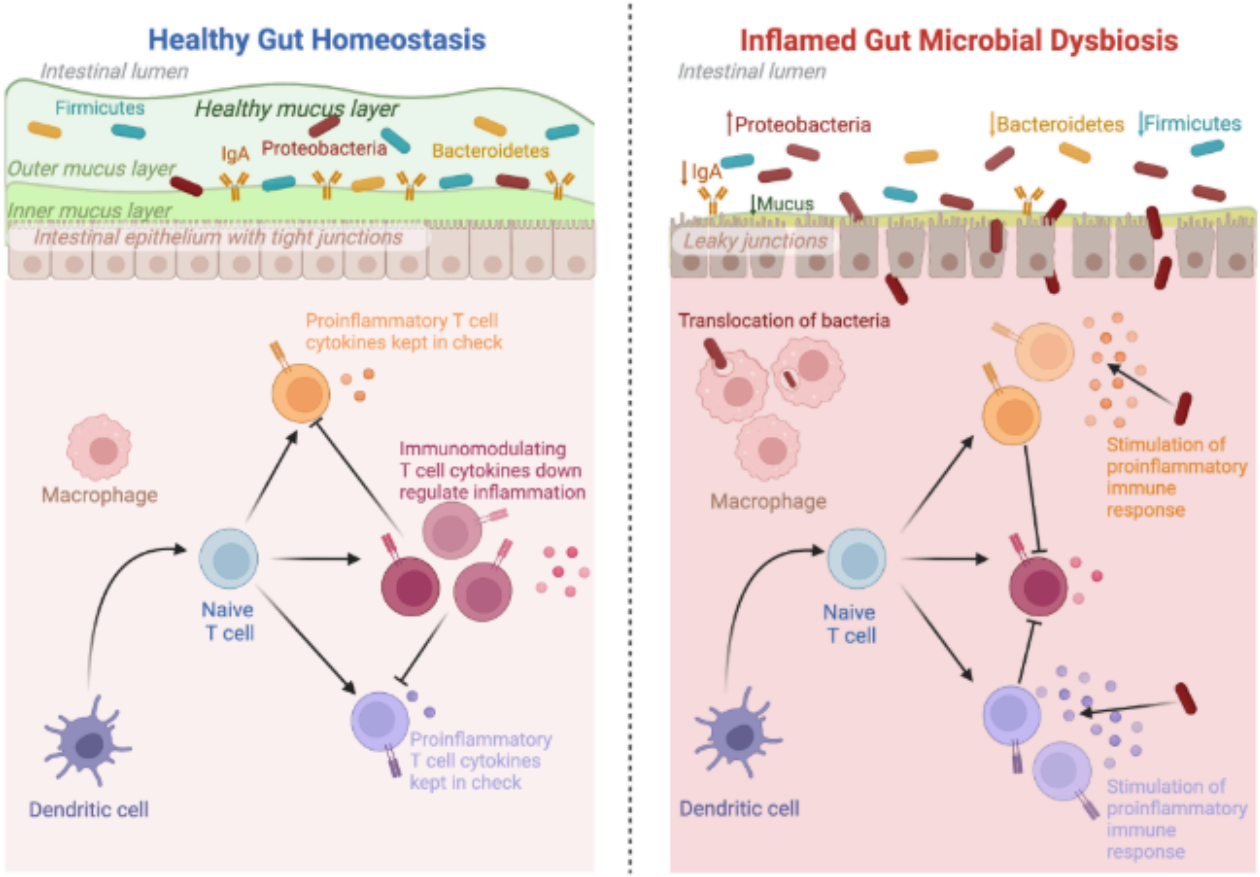
- Xerostomia + antibiotics → thrush, bacterial overgrowth



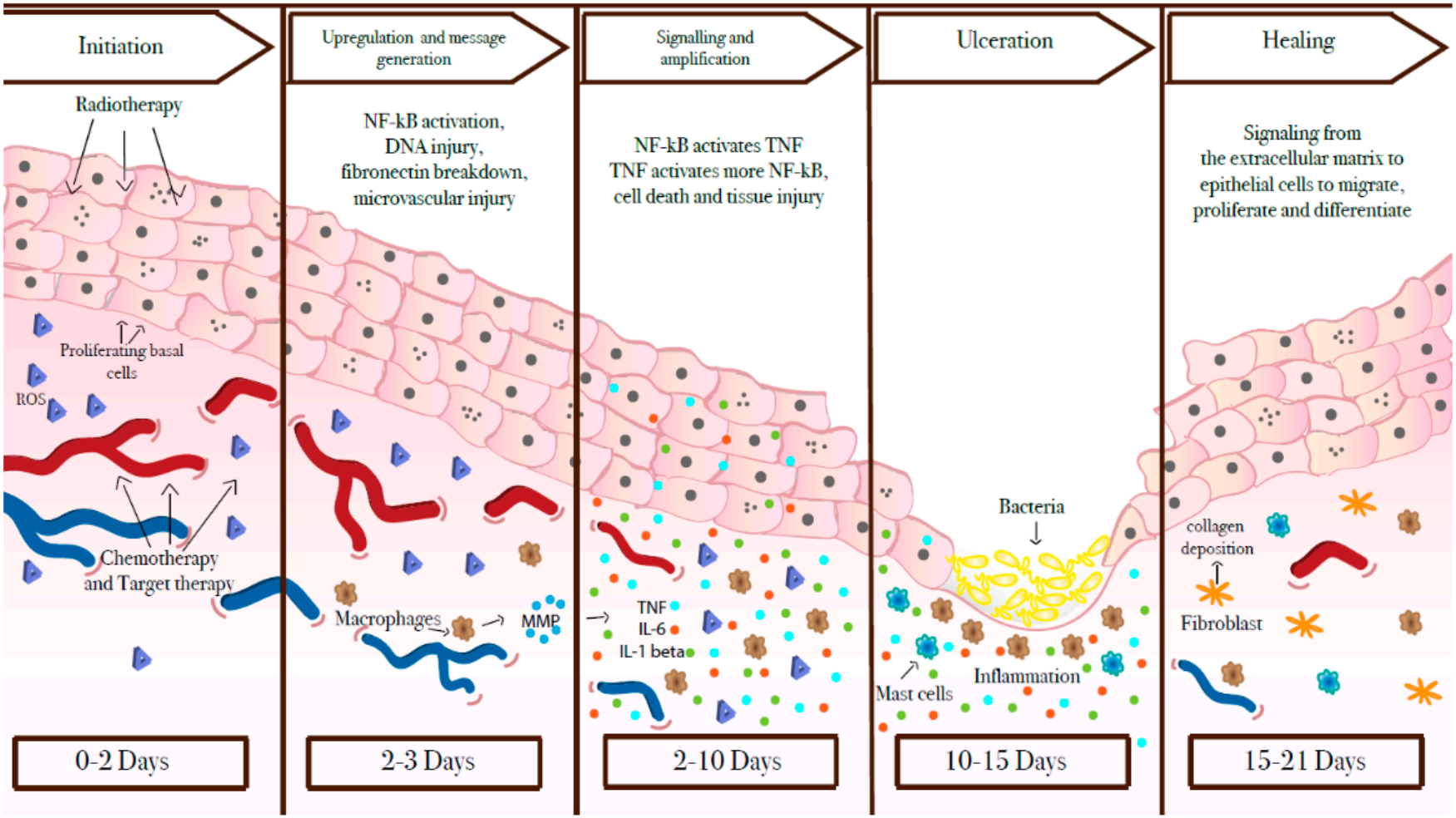
Alimentary Tract

- **Microbiome disruption** → *Clostridioides difficile*
- **Mucosal barrier injury** from chemotherapy
- Facilitates bacterial translocation
- Neutropenia allows progression to sepsis

Chemotherapy-associated dysbiosis



Model of mucosal barrier injury



Mucositis

WHO oral toxicity scale

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

Which pathogens translocate to the bloodstream?

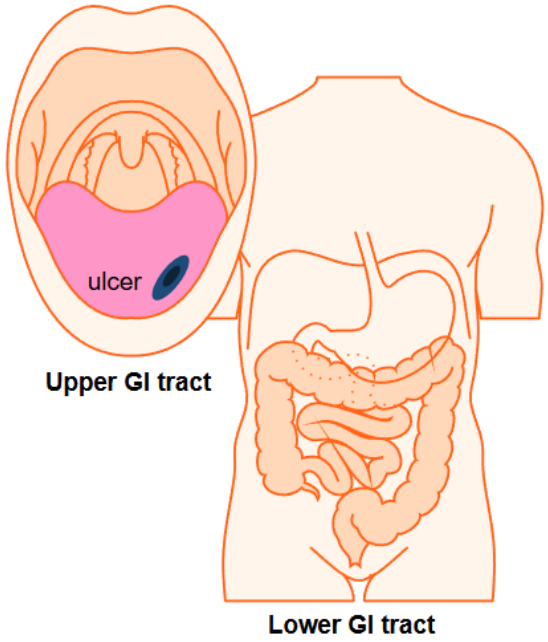
Gram-negative Bacilli

Aerobic
- *Pseudomonas aeruginosa*

Facultatively Anaerobic
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Enterobacter cloacae*

Capnophilic
- *Capnocytophaga species*

Anaerobic
- *Fusobacterium species*
- *Leptotrichia buccalis*
- *Prevotella species*



Gram-positive Cocci

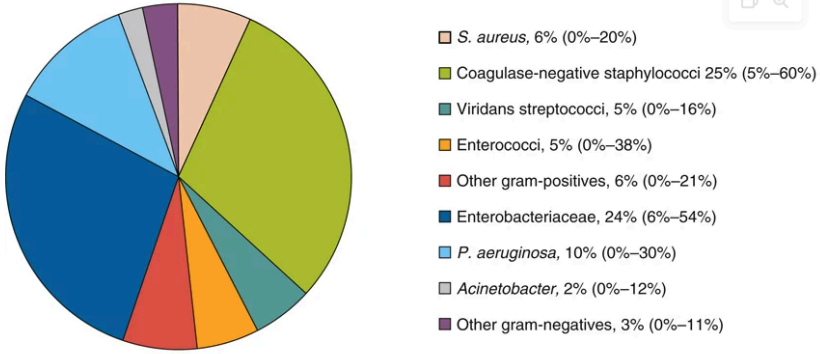
Oral viridans streptococci
- *Streptococcus mitis*
- *Streptococcus oralis*
- *Streptococcus sanguis*

Staphylococci
- *Staphylococcus epidermidis*

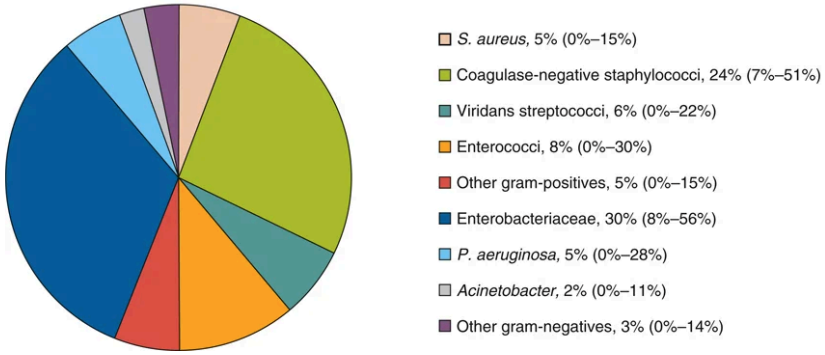
Others
- *Stomatococcus mucilaginosus*

Most common bacterial pathogens

REVIEW OF LITERATURE FROM YEARS 2005–2011



2011 ECIL–4 SURVEILLANCE STUDY

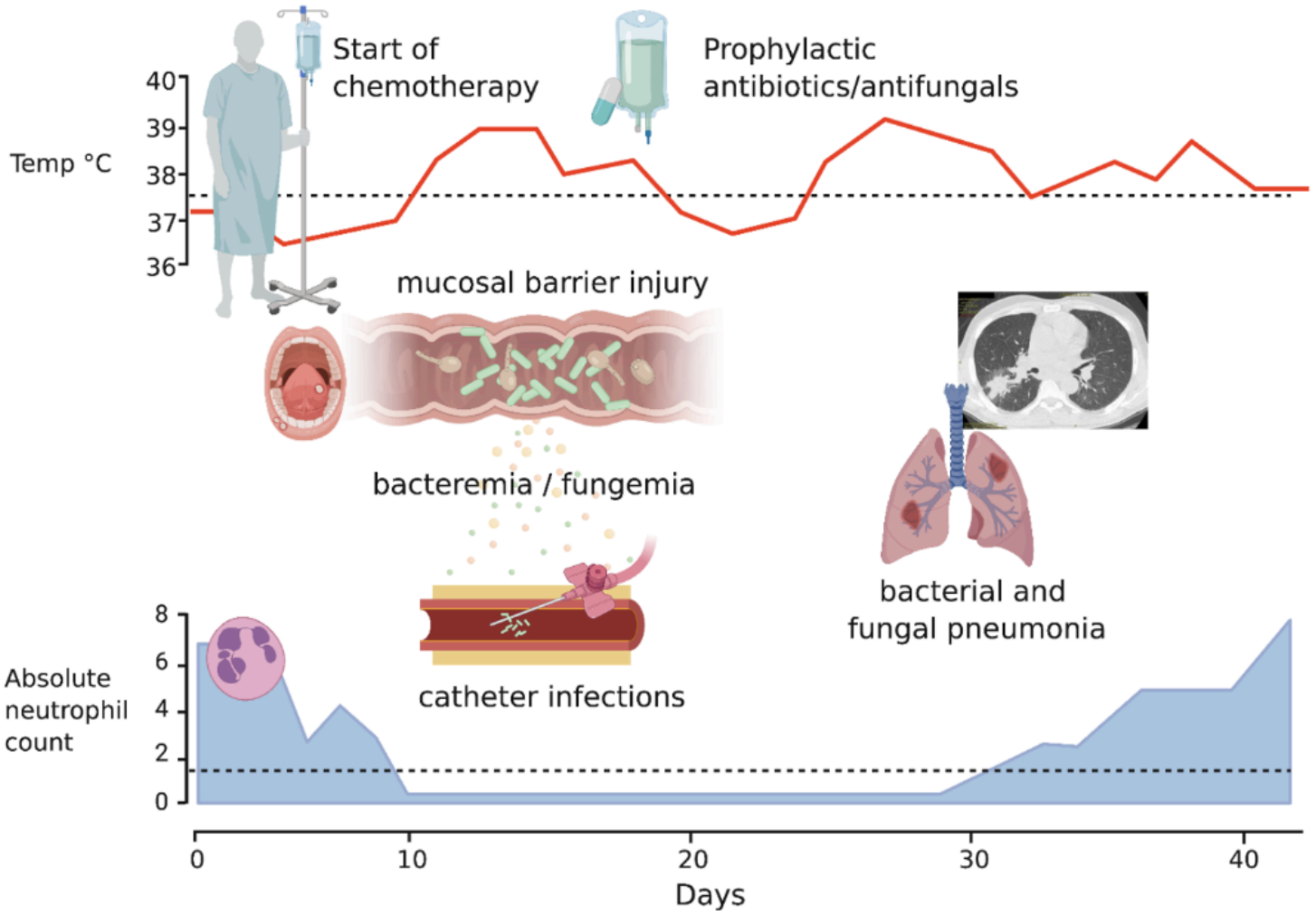


- Infectious source documented in only 20-30% of episodes
- Bacteremia documented in 10-25% of patients *with fever*
- Aerobic Gram-positive and Gram-negative

CVC-related infection rates

Catheter Type		Per 100 devices	Per 1000 catheter-days
Hickman/Broviac		22.5	1.6
Port-a-cath		3.5-4	0.1
PICC		3.1	1.1

Sequence of infection



Risk of infection vs. duration of neutropenia

Phase I (1-10 days)

- CONS - Staphylococcus spp.
- Enterobacterales
- Viridans streptococci
- Anaerobes
- Enterococcus
- Clostroides diffile

- Herpes simplex
- +/- Candida spp.

Phase II (10-27 days)

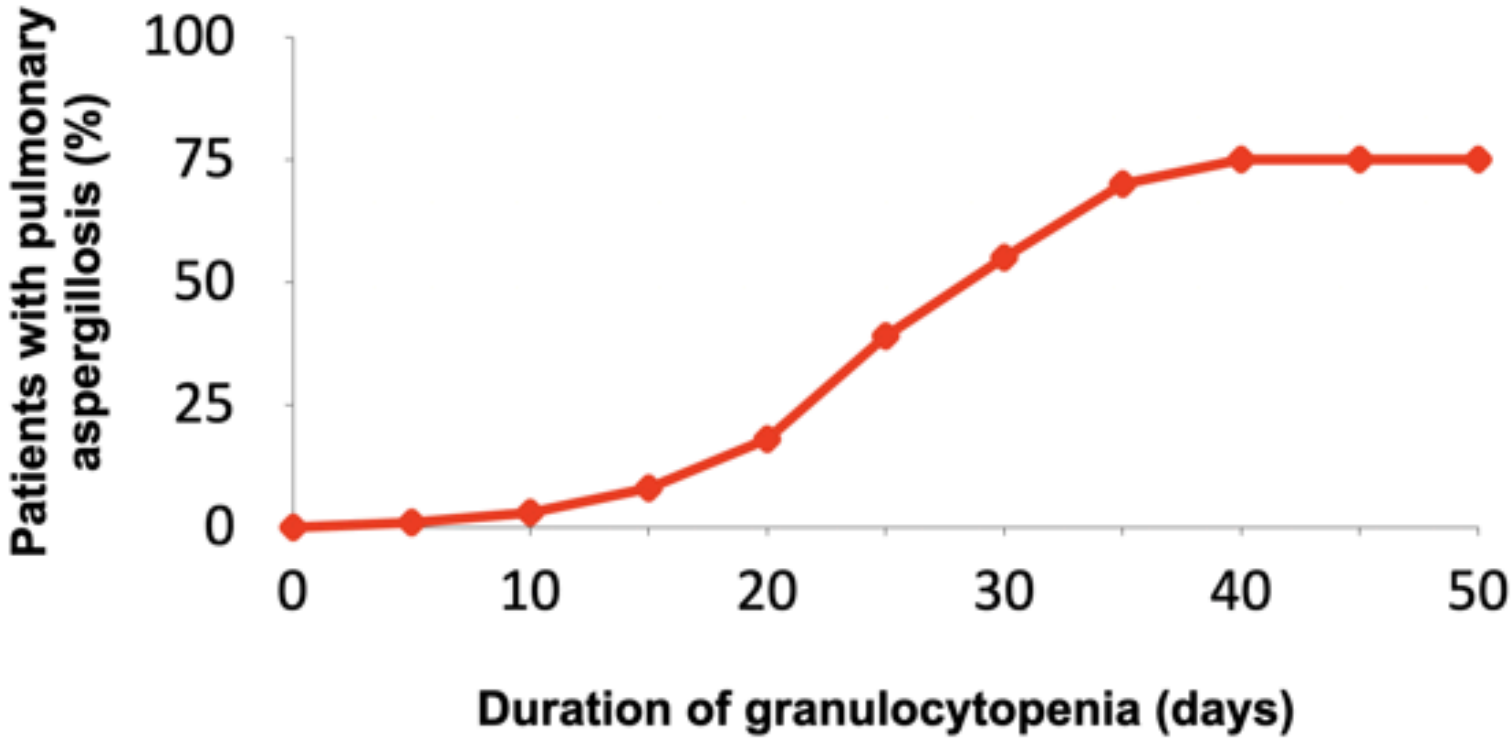
- **Phase I pathogens *plus***
- Methicillin-resistant S. aures (MRSA)
- Vancomycin-resistant Enterococcus (VRE)
- Resistant gram-negative bacteria
- *Stenotrophomonas maltophilia*

- Herpes simplex
- +/- Candida spp.

Phase III (> 27 days)

- **Phase I&II pathogens, *plus***
  + Invasive molds

Invasive pulmonary aspergillosis risk vs. neutropenia



Non-neutropenic risk factors

- Mucositis - Barrier disruption, translocation
- Central venous catheters - Entry point for pathogens
- Microbiome alterations - Chemotherapy-induced dysbiosis
- **Immunosuppressive drugs** - T-cell depletion
- **Biologic agents** - Targeted immune effects

Novel targeted therapies: immune sequelae

Novel targeted therapies: immune sequelae

Target	Agents	B-Cell Depletion	T-Cell Depletion	HGG[1]	Neutropenia
	Rituximab	+++	-	+	++[2]
CD20	Ofatumumab	+++	-	+	
	Obinutuzumab				
CD52	Alemtuzumab	++	+++	+	+[3]
CD38	Daratumumab	+	+		
SLAMF7	Elotuzumab	-			-
CD19/CD3	Blinatumomab	+++	+	++	++
	Ibrutinib				
BTK	Acalabrutinib	++			+
	Zanubrutinib				
	Idelalisib				
PI3K	Copanlisib	++			+
	Duvelisib				
JAK	Ruxolitinib	-			
BCL-2	Venetoclax	-			++

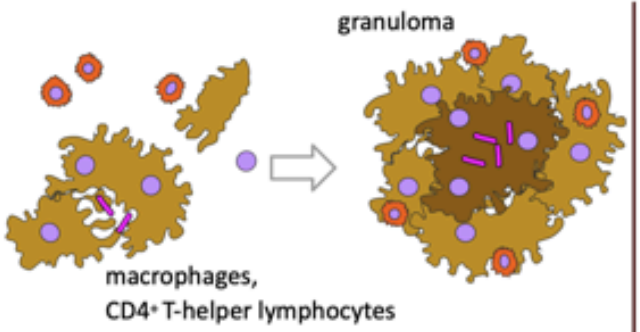
Plus signs indicate relative effect (mild, moderate, significant). [1] Hypogammaglobulinemia. [2] Late neutropenia may occur (median time 175 days, Dunleavy et al.). [3] Neutropenia typically resolves in 2–

Example biologic agents and infection risk

Agent	Key Infections
Rituximab (anti-CD20- Bcell depletion)	HBV reactivation, PML
Brentuximab (anti-CD30 +lymphoma cells)	PCP, PML
Bortezomib (26s proteasome inhibitor-Mantel cell lymphoma, myeloma)	VZV reactivation
Ruxolitinib (JAK1/2 kinase inhibitor)	VZV, TB
Idelalisib (P13K-delta-Bcell receptor inhibitor)	HSV, CMV, PCP
Ibrutinib (Bruton's tyrosine kinase-B cell receptor)	IFD (with steroids)

Pneumocystis (carinii) jirovecii pneumonia (PCP); VZV varicella zooster; TB tuberculosis; HSV-herpes simplex virus; CMV- cytomegalovirus;

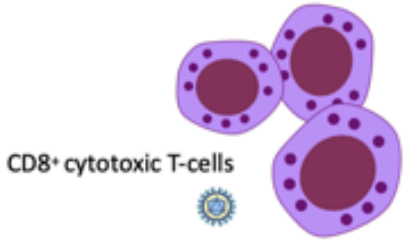
Impaired cell-mediated immunity increases the spectrum of possible pathogens



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)

Summary-Key infection epidemiology

Changing bacterial epidemiology

Historical trend:

- 1980s-2000s: Gram-positive predominance
- Recent: Gram-negative resurgence

Current ratio (ECIL-4 surveillance):

- Gram-positive: 55%
- Gram-negative: 45%

Resistant pathogens of concern

Gram-negative:

- ESBL-producing Enterobacterales
- Carbapenem-resistant Enterobacterales (CRE)
- *Stenotrophomonas maltophilia* (carbapenem-resistant)
- MDR *Pseudomonas aeruginosa*

Gram-positive:

- MRSA
- Vancomycin-resistant enterococci (VRE)

Risk factors for resistant infections

1. Previous infection/colonization with MDR organism
2. Prior broad-spectrum antibiotic exposure
3. Healthcare-associated infection
4. Prolonged hospitalization
5. Urinary catheter
6. Older age
7. ICU admission

Fungal pathogens

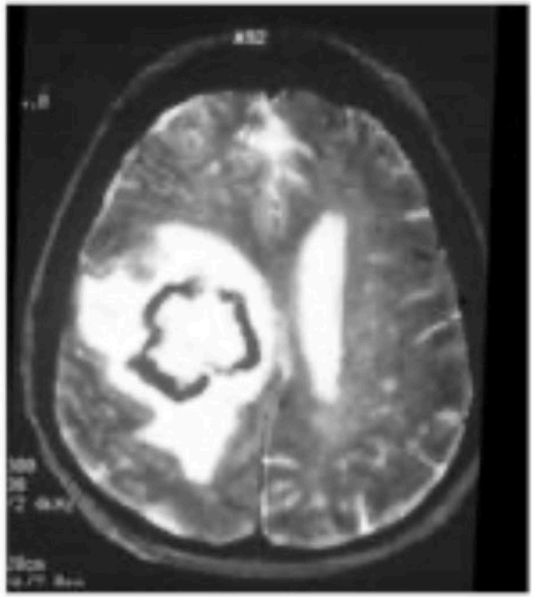
Most Common:

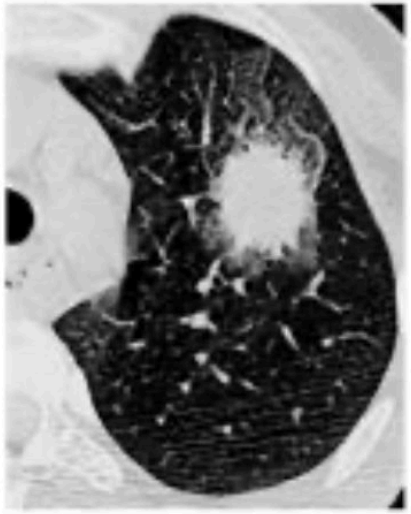
- *Aspergillus* species > *Candida* in hematology due to fluconazole prophylaxis that covers yeast but not molds
- *Candida* species (increasing non-albicans)

Emerging concerns:

- *Candida auris* - MDR, biofilm-forming
- Azole-resistant *Aspergillus fumigatus*
- *Mucorales* (increasing in some centers)

Breakthrough fungal infections on antifungal prophylaxis





Invasive aspergillosis risk

Population	Incidence
Acute myelogenous leukemia (induction)	7.9%
Acute lymphocytic leukemia (adults)	4.3-11.7%
Chronic myelogenous leukemia	2.3%
Chronic lymphocytic leukemia, lymphoma, myeloma	<1%
Autologous HSCT	0.3-2%
Allogeneic HSCT	8-15%

Viral infections

Herpes viruses:

- Herpes simplex 1&2 (HHV 1&2) reactivation: reactivation in up to 60% of seropositive patients with mucositis, profound neutropenia, impaired T-cell function, or high-dose corticosteroid exposure
- Varicella zoster (HHV3) : Increased with bortezomib, ruxolitinib
- Epsein-barr virus (HHV4): Increased with T-cell suppression, post-transplant lymphoproliferative disorder (PTLD)
- Cytomegalovirus (HHV5): T-cell suppressing regimens- pneumonitis, colitis, hepatitis
- HHV-6: Encephalitis in transplant patients
- HHV-7:Roseola-like illness
- HHV8: Kaposi’s sarcoma

Respiratory viruses:

- Influenza, RSV, parainfluenza
- SARS-CoV-2: High morbidity/mortality in cancer patients

Prophylaxis strategies

Antibacterial prophylaxis

Fluoroquinolone (ciprofloxacin, levofloxacin) prophylaxis:

Pros	Cons
Reduces febrile episodes	Increasing resistance, especially selection of ESBL
Reduces BSI	No consistent mortality benefit (recent data) reduction in febrile episodes
Oral administration	Drug interactions
	QT prolongation, tendinopathy

Current status: Controversial; some guidelines no longer recommend especially in centeres with high levels of resistance

The benefit of FQ prophylaxis may no longer translate to mortality reduction because most prevented infections can be effectively treated

Antifungal prophylaxis - Key points

When to use mold-active prophylaxis:

- Anticipated IFD incidence in population of >8%
- AML/MDS induction chemotherapy
- High-risk ALL
- Relapsing leukemia

Posaconazole:

- Number needed to treat (NNT) to prevent 1 IFD: 16
- Number needed to treat (NNT) to prevent 1 death: 27

Antifungal prophylaxis

Agent	Dose	Indication	
Fluconazole	400 mg daily	Candidiasis risk only	
		Posaconazole tablets	300 mg BID day 1, then 300 mg daily | AML/MDS/ BMT
Voriconazole	200 mg BID	Alternative (TDM needed)	
Isavuconazole	200 mg daily (after loading)	Alternative, not “approved” for prophylaxis indication	

Problem: Drug interactions with agents metabolized through CYP3A4. Interactions are less severe with fluconazole and isavuconazole (weak CYP3A4 inhibitors) vs. posaconazole and voriconazole (strong CYP3A4 inhibitors)

Pneumocystis jirovecii prophylaxis

Patients at risk- Indications:

- Acute lymphocytic leukemia (all ages)
- Fludarabine, alemtuzumab, idelalisib therapy (T-cell suppressing chemotherapy)
- Corticosteroids ≥10-20 mg/day × 4 weeks
- CD4 <200/μL

First-line: TMP-SMX 160/800 mg 3×/week

Alternatives: Dapsone, atovaquone, aerosolized pentamidine

Antiviral prophylaxis

HSV/VZV:

- Acyclovir 800 mg BID or valacyclovir 500 mg BID
- For all seropositive patients with acute leukemia
- Required with bortezomib, alemtuzumab, idelalisib

HBV:

- Screen all patients before chemotherapy
- Entecavir or tenofovir for HBsAg-positive
- Continue 6-18 months post-chemotherapy

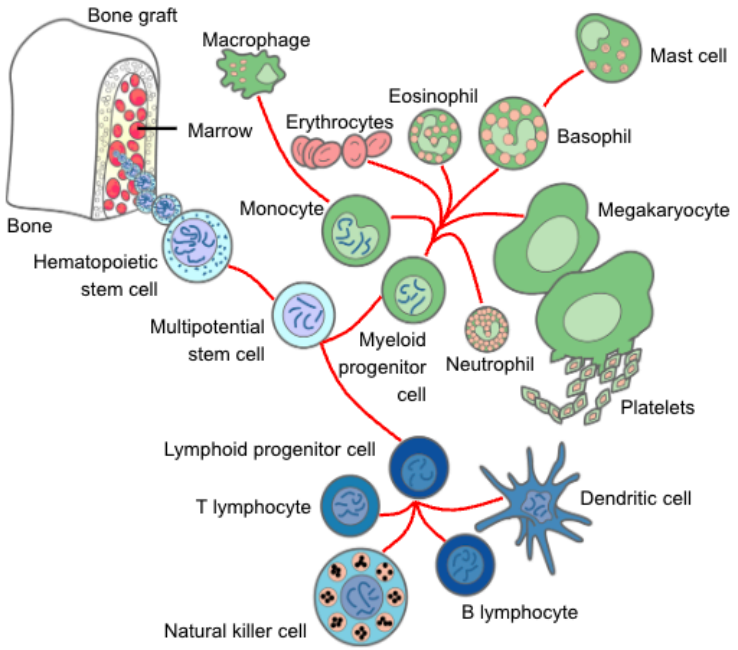
Granulocyte-colony stimulating factor (G-CSF)

Primary prophylaxis:

- When febrile neutropenia risk >20%
- Based on age, comorbidities, regimen

Secondary prophylaxis:

- After prior neutropenic complication
- When dose reduction would compromise outcomes



G-CSF acts at multiple levels of neutrophil production: it promotes proliferation and differentiation of myeloid progenitor cells committed to the granulocytic lineage, accelerates maturation through the promyelocyte → myelocyte → metamyelocyte → band → mature neutrophil stages, and shortens the transit time through the bone marrow.

Vaccination recommendations

Vaccine	Timing	Notes
Influenza	Annual	Avoid during intensive chemo
Pneumococcal (PCV)	Before chemo if possible	Better response than PPSV23
SARS-CoV-2	3-dose primary + boosters	All patients and contacts
Herpes zoster (RZV)	VZV seropositive	Inactivated vaccine

Management of febrile neutropenia

Standard diagnostic approach: Initial workup

Every episode of febrile neutropenia — obtain immediately:

Microbiology

- Blood cultures × 2 sets (peripheral + each CVC lumen)
- Urine culture (if symptoms or urinary catheter)
- Culture from any accessible suspected site (wound, skin lesion, sputum)

Laboratory

- CBC with differential, CRP, procalcitonin
- Comprehensive metabolic panel (LFTs, creatinine)
- Galactomannan (serum) if prolonged neutropenia or mold risk
- β-D-glucan if invasive fungal disease suspected

Imaging

- Chest CT (preferred over X-ray if any respiratory symptoms)
- Additional CT/ultrasound guided by symptoms

Standard diagnostic approach: Targeted investigations

Clinical Presentation	Key Additional Workup
Respiratory symptoms / hypoxia	Computed tomography (CT)of chest; BAL if stable (GM, cultures, PCR panel)
Abdominal pain / diarrhea	CT abdomen/pelvis; *C. difficile* toxin PCR; stool culture
Skin/soft tissue lesion	Skin biopsy (histopathology + bacterial, fungal, mycobacterial cultures)
Neurological signs	CT/MRI brain; LP if safe (CSF cell count, cultures, cryptococcal Ag)
CVC site inflammation	CVC-drawn vs. peripheral differential time-to-positivity
Persistent fever ≥4–7 days	Repeat CT chest/sinuses; serum GM ± BDG; consider bronchoscopy

Diagnostic yield is limited (positive cultures in ~20–30% of episodes), but targeted workup guides de-escalation and avoids unnecessary

Definition of fever

Trigger for starting empirical antibiotics:

- **Single temperature** ≥38.5°C (oral/axillary), OR
- **Two measurements** ≥38.0°C separated by ≥1 hour

Also treat infection suspected with:

- Hypothermia (<35.5°C)
- Altered mental status
- Hypotension
- Skin/mucosal lesions

Classification of episodes

1. **Microbiologically documented with bacteremia** - Positive blood culture
2. **Microbiologically documented without bacteremia** - Other site culture positive
3. **Clinically documented** - Signs/symptoms without microbiologic proof
4. **Fever of unknown origin (FUO)** - No clinical or microbiologic documentation

Risk stratification: MASCC score

Variable	Points
Burden of illness: none/mild	5
Burden of illness: moderate	3
No hypotension	5
No COPD	4
Solid tumor/no prior fungal infection	4
Outpatient status	3
No dehydration	3
Age <60 years	2

Score >21: Low risk

Risk stratification: CISNE score

Variable	Points
ECOG PS ≥2	2
Hyperglycemia stress	2
COPD	1
Cardiovascular disease	1
Mucositis grade ≥2	1
Monocytes <200/μL	1

Score ≥3: High risk (for solid tumor patients)

Treatment strategies

Two main approaches:

Escalation:

- Start narrow, broaden if needed
- For stable patients without risk of MDR pathogens

De-escalation:

- Start broad, narrow when microbiology results available
- For unstable patients or MDR colonization

Escalation strategy

Day 0:

- Anti-*Pseudomonas* β-lactam monotherapy
- Piperacillin-tazobactam, cefepime, or ceftazidime

Day 2-4 (if needed):

- Add vancomycin if skin/catheter infection
- Change to anti-pseudomonal carbapenem if septic
- Some clinicians may just add aminoglycoside (I do not recommended)
- Add antifungal if persistent fever

De-escalation strategy

Day 0:

- Carbapenem (meropenem) ± aminoglycoside
- Or targeted therapy based on colonization

Day 2-4:

- De-escalate based on cultures
- Stop aminoglycoside if not needed
- Narrow spectrum if pathogen identified

Key antibiotics for empiric treatment

Drug	Adult Dose	Administration	When
Piperacillin-tazobactam	4.5 g q6-8h	Extended/continuous infusion	Low risk of ESBL
Cefepime	2 g q8h	Extended infusion	Low risk of ESBL- active at lower inoculum
Meropenem	1-2 g q8h	Extended infusion (3-6h)	Higher risk of ESBL
Ceftazidime-avibactam	2.5 g q8h	2-hour infusion	Higher risk of KPC carbapenemase
Ceftolozane-tazobactam	1.5-3 g q8h	1-hour infusion	Higher risk of MDR *P. aeruginosa*

Glycopeptide use (to cover MRSA)

Add vancomycin or alternative (daptomycin) for:

- Suspected catheter-related infection
- Skin/soft tissue infection
- Known MRSA colonization
- Severe sepsis with hypotension
- Pneumonia (or linezolid but not daptomycin)
- Prior MRSA infection

Stop after 48-72h if no gram-positive pathogen identified

Duration of therapy

For FUO:

- If afebrile 48-72h + clinically stable: consider stopping
- Short courses (72h) shown safe in selected patients

For documented infection:

- Guided by pathogen, site, and response
- Generally until neutrophil recovery and clinical cure

Antifungal therapy

Empirical vs diagnostic-driven approach

Empirical:

- Start antifungal after 4-7 days persistent fever
  - Rationale: INnthe past, up to one-third of patients with prolonged neutropenia had evidence of fungal infections at autopsy- not diagnosed antemortem
- Traditional approach; high antifungal exposure-overtreatment of patients

Diagnostic-driven:

- Use biomarkers (GM, BDG) + CT imaging
- Reduces unnecessary antifungal use
- Requires good diagnostic infrastructure

GM -galactomannan ELISA test, BDG- β-D-glucan

Diagnostic tools

Test	Target	Specimen
Galactomannan (GM)	*Aspergillus*	Serum, BAL
β-D-glucan (BDG)	Broad fungi (not Mucorales)	Serum
PCR	Species-specific	Blood, BAL
CT imaging	Structural changes	Chest/sinuses

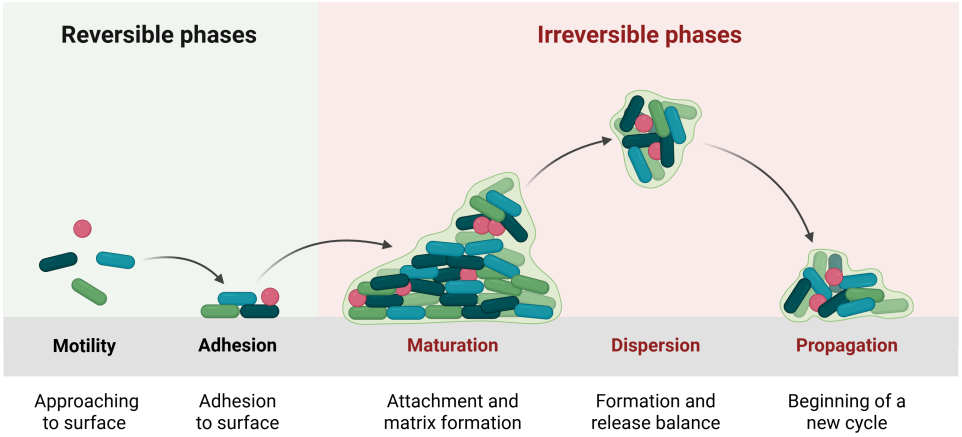
Mucormycosis

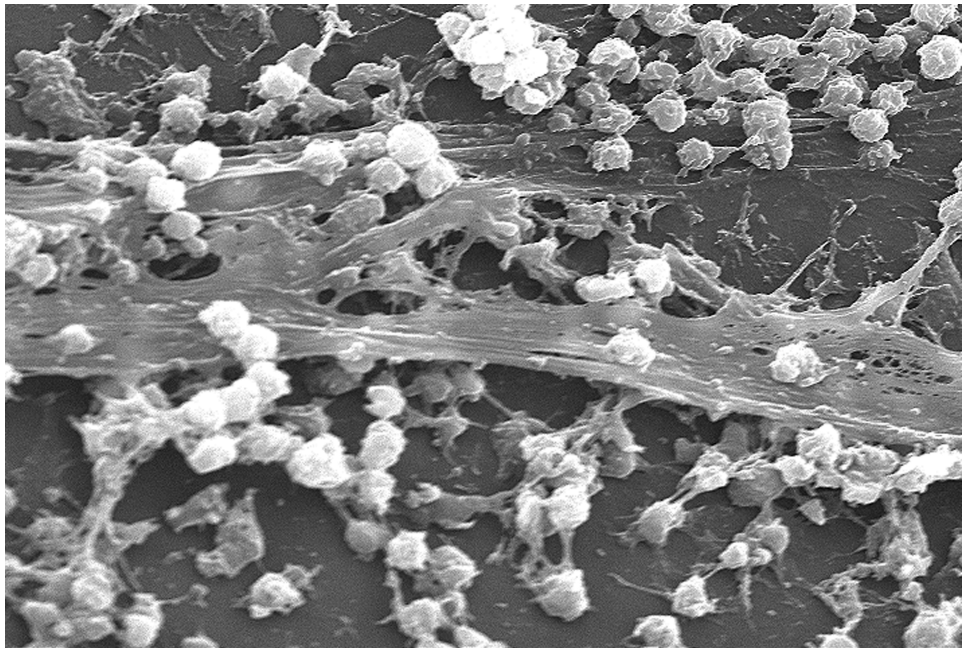
Antifungal Selection

Indication	First-line
Invasive aspergillosis	Voriconazole or isavuconazole
Mucormycosis	Liposomal amphotericin B
Candidemia	Echinocandin
Empirical therapy	Liposomal amphotericin B or caspofungin

Specific clinical infections

Central venous catheter (CVC) infections





Central venous catheter (CVC) infections

Management depends on:

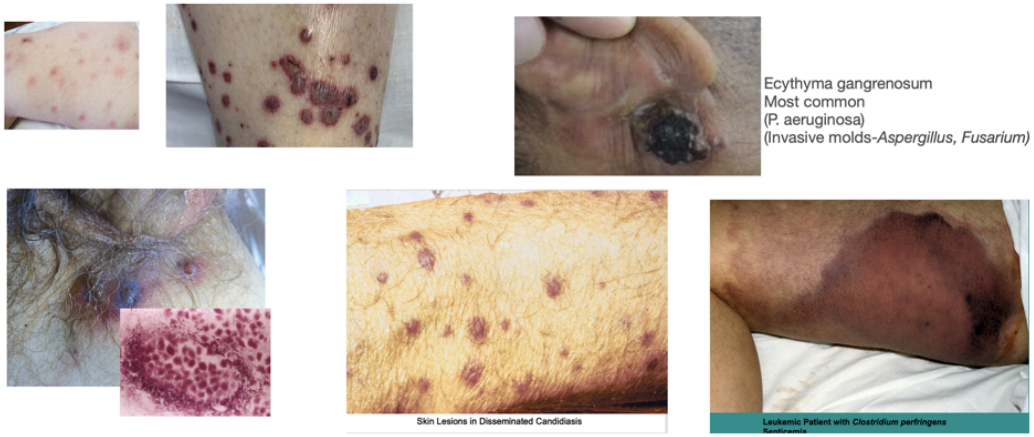
- Organism (CoNS vs *S. aureus* vs gram-negatives)
- Presence of tunnel/pocket infection
- Clinical stability

Catheter removal indicated for:

- *S. aureus*, *Candida*, *Pseudomonas* bacteremia
- Tunnel infection
- Persistent bacteremia despite antibiotic therapy

Skin lesions

Evidence of disseminated infection (hematogenous spread)



Common presentations:

- **Ecthyma gangrenosum** — necrotic ulcer with black eschar; classic for *P. aeruginosa* or invasive molds (*Aspergillus*, *Fusarium*)
- **Disseminated papules/nodules** — *Candida*, *Fusarium*, or *Aspergillus* septate emboli
- **Leukemia cutis** — infiltration by circulating blasts
- **Intravascular hemolysis** — rapidly spreading crepitant necrosis from *Clostridium perfringens* septicemia

Ecthyma gangrenosum

Clinical features:

- Begins as erythematous macule → hemorrhagic bullae → **necrotic ulcer** with black eschar and erythematous halo
- Usually found on buttocks, perineum, axillae, and extremities
- May appear **without** bacteremia (direct skin inoculation)

Most common pathogens:

- *Pseudomonas aeruginosa* (bacteremia or local invasion)
- Invasive molds: *Aspergillus* spp., *Fusarium* spp.
- Less common: other gram-negative rods, *Stenotrophomonas*, *Candida*

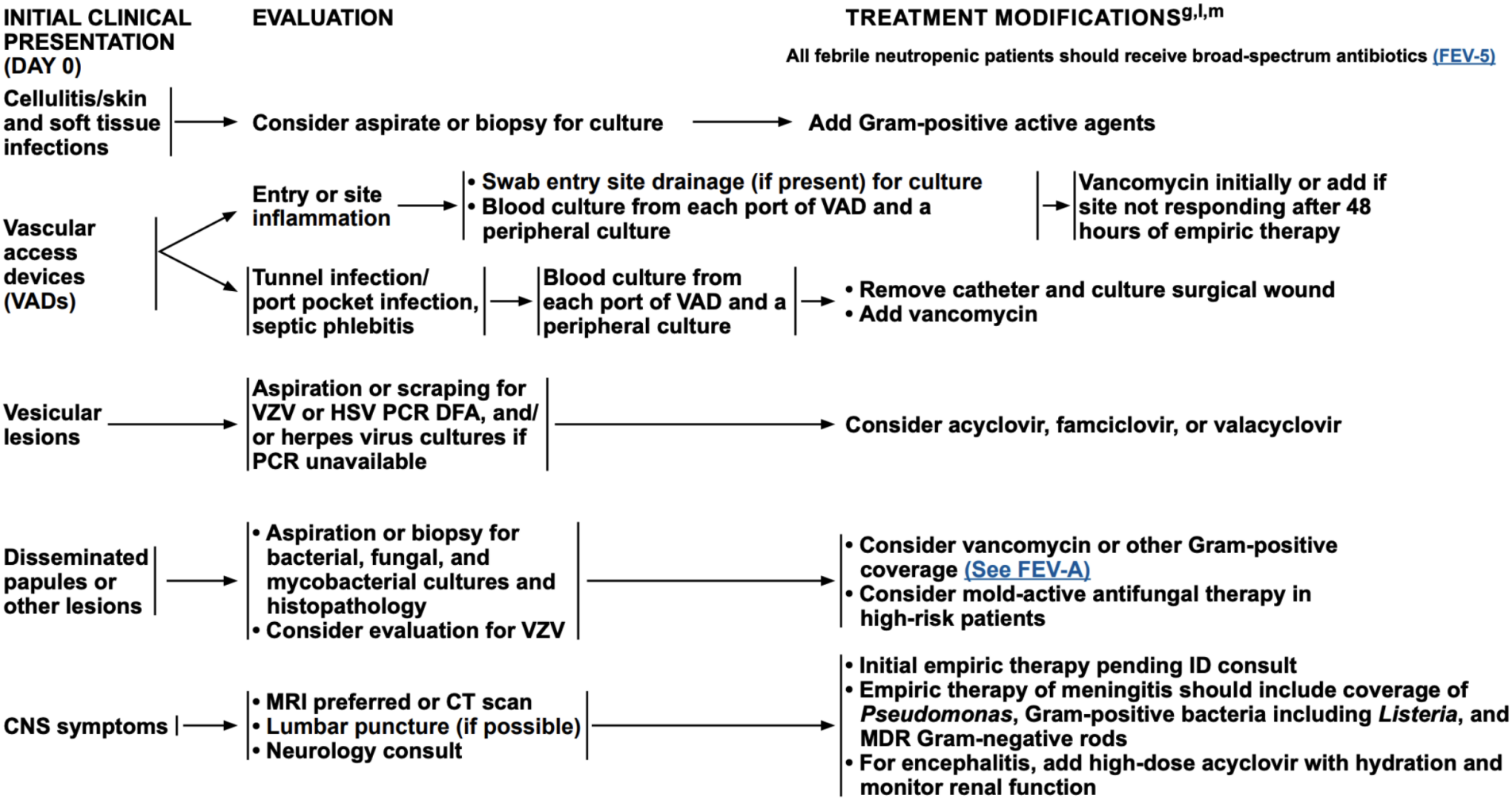
Urgent evaluation:

- **Blood cultures** × 2
- **Skin biopsy** for histopathology + bacterial, fungal, and mycobacterial cultures
- CT imaging to assess for dissemination

Empiric management:

- Add or broaden anti-*Pseudomonas* coverage
- Add mold-active antifungal therapy (liposomal amphotericin B or voriconazole) in high-risk patients pending biopsy results

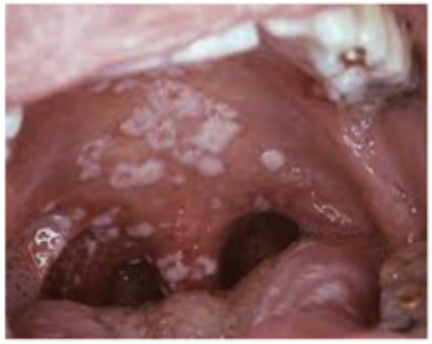
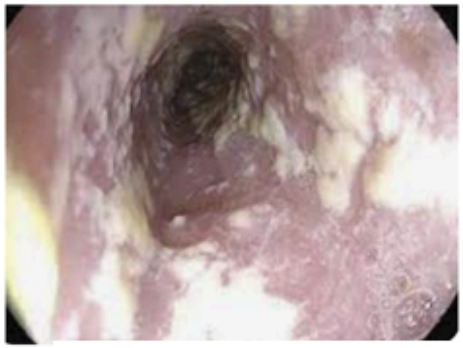
Skin and soft tissue: treatment approach



Oral-Upper GI infections

Candida- Thrush, esophagitis (odynophagia, retrosternal pain)

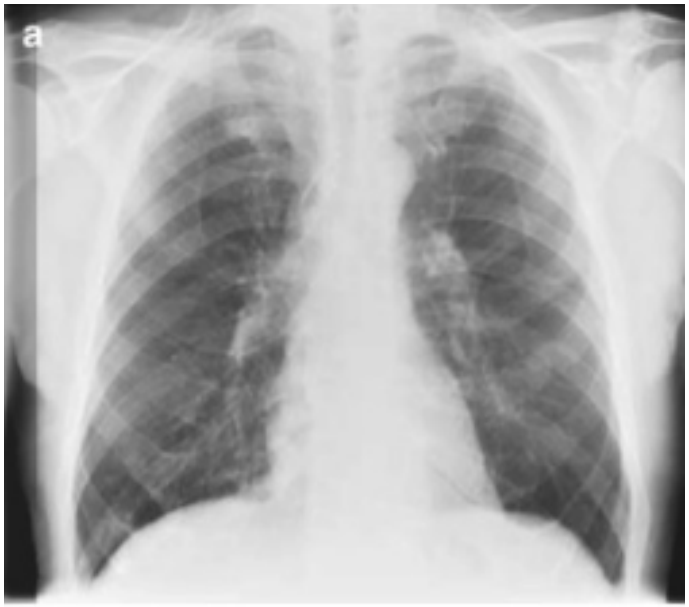
Vesicular lesions- painful grouped lesions→ulceration

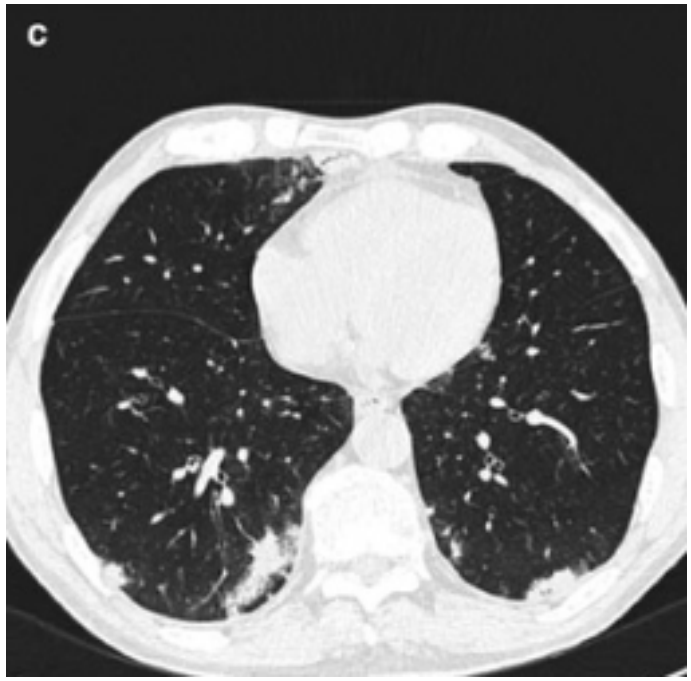




Disseminated HSV- widespread vesicular rash , hepatitis (↑ AST/ALT, sometimes severe), pneumonitis

Pneumonia

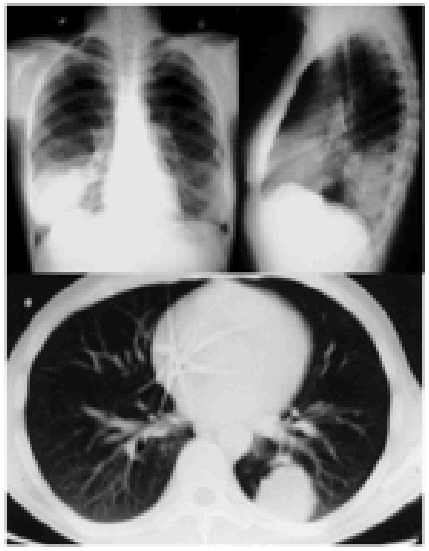
Among febrile neutropenic patients with a “normal” chest x-ray, up to 60% of patients may have findings of pneumonia on CT





Common CT findings

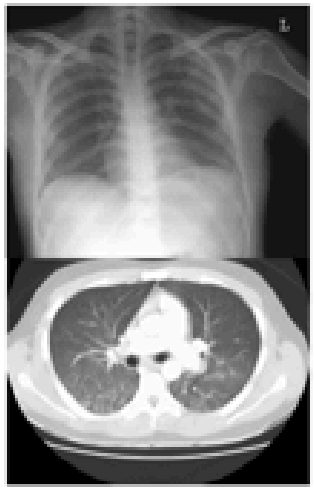
Consolidation



Acute
Bacterial
Thromboembolic
Hemorrhage

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

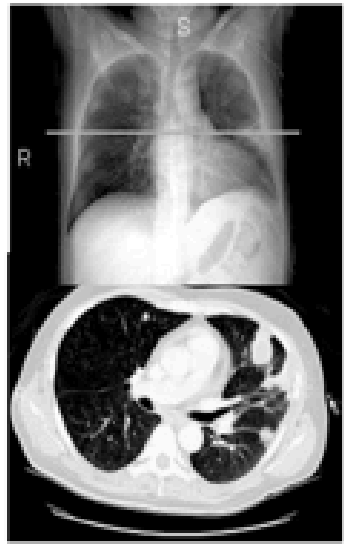
Peribronchovascular infiltrates



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

PCP- pneumocystic (carinii) jirovecii pneumonia, BOOP- bronchiolitis obliterans organizing pneumonia, DAH- disseminated alveolar

Bronchoscopy

Bronchoscopy: Timing is critical

501 consecutive allo HSCT patients

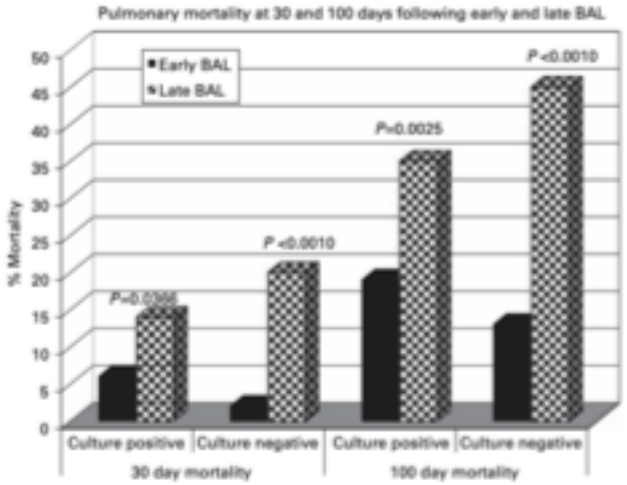


Figure 1 Pulmonary mortality at 30 and 100 days following early and late bronchoalveolar lavage (BAL). Significantly lower mortality rates were observed when a diagnosis of infection was confirmed by early fiberoptic bronchoscopy (FOB; black bars) compared to late examinations (checkered bars). Early 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.

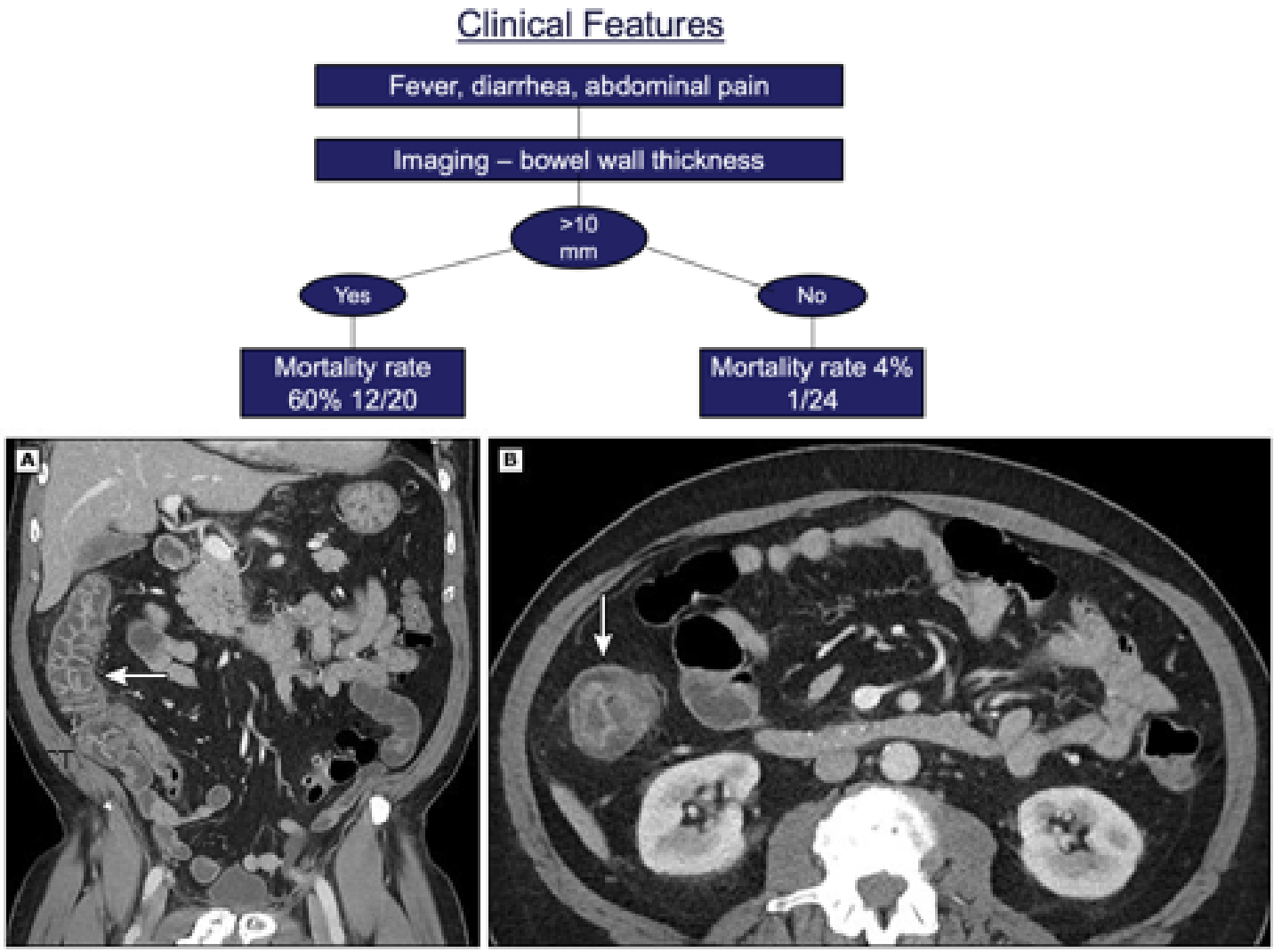
Shannon VR et al. Bone Marrow Transplant 2010; 45:647–655.

- **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

Neutropenic enterocolitis (typhlitis)



Neutropenic enterocolitis (typhlitis)

Key features:

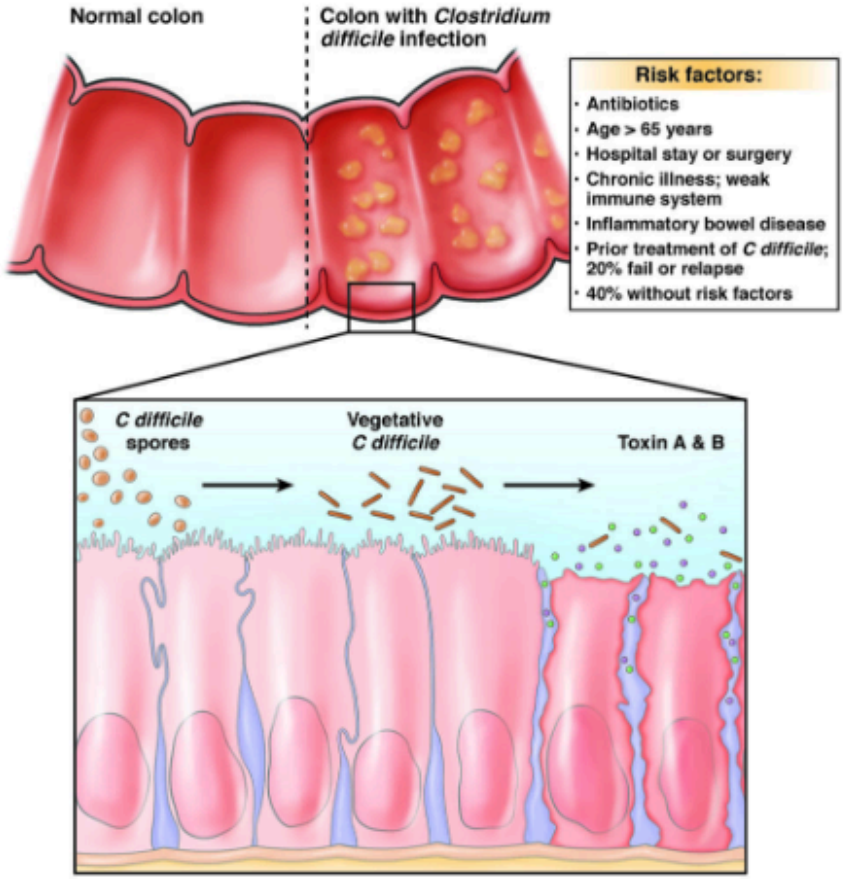
- Fever, abdominal pain, diarrhea
- RLQ tenderness
- CT: Bowel wall thickening

Management:

- Broad-spectrum antibiotics including anaerobes
- Bowel rest, NG suction if obstruction
- Surgery only for perforation/hemorrhage

Clostridioides difficile colitis

- **First-line treatment:** Stop unnecessary antibiotics →oral vancomycin 125 mg QID for 10 days or fidaxomicin 200 mg BID for 10 days
- **Fulminant disease:** Oral vancomycin 500 mg QID (or via NG tube) combined with IV metronidazole 500 mg TID; →consider rectal vancomycin instillation if ileus is present
- **Ongoing/worsening CDI:** Fidaxomicin if initially treated with vancomycin→ fecal microbiota transplant (if not neutropenic)
- **CDI resolved but at risk of recurrence:** Consider continuing vancomycin or fidaxomicin if diarrhea recurs, and prophylactic vancomycin during subsequent antibiotic courses → taper regimens, fecal transplant (if patient not neutropenic) or bezlotoxumab



How to assess clinical response in febrile neutropenic patient?

- **Documented infection:** Treat for the appropriate duration based on the specific pathogen and site (see relevant guidelines)
  - Duration of treatment is not necessarily longer in neutropenia
- **Fever resolved, unknown origin, ANC ≥500**: Discontinue empiric antibiotics.
- **Fever resolved, unknown origin, ANC <500:** Options include discontinuing therapy, de-escalating to prophylaxis, or continuing the current regimen until neutropenia resolves.
- **Not responding/clinically worsening:** Broaden antimicrobial coverage based on clinical and microbiologic data, obtain imaging, consider adding G-CSF, and obtain ID consultation.
- **Persistent fever ≥4 days on empiric antibiotics:** Consider adding antifungal therapy with anti-mold activity; duration guided by clinical course, neutrophil recovery

Typical treatment duration (NCCN 2025 Guidelines)

Documented Infection →

Follow-up Therapy Principles

- Targeted treatment of documented infections
- Reassess empiric broad-spectrum therapy
- De-escalation and duration 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

→

Suggested Minimum Duration of Therapy

Skin / Soft Tissue

Standard	**5–14 days**

Bloodstream Infection

Gram-negative	**7–14 days**
Gram-positive	**7–14 days**
S. aureus *ID consult advised for S. aureus bacteremia*	**4 weeks after 1st negative BC**
Yeast	**≥2 weeks after 1st negative BC**

Catheter removal favored for BSI with *Candida*, other yeasts, *S. aureus*, *P. aeruginosa*, *C. jeikeium*, *Acinetobacter* spp., *Bacillus* spp., atypical mycobacteria, molds, VRE, *S. maltophilia*, and other MDROs

Respiratory

Bacterial sinusitis	**7–14 days**
Bacterial pneumonia	**5–14 days**

Fungal (Mold and Yeast)

Candida	**≥2 weeks after 1st negative BC**
Mold (e.g. *Aspergillus*)	**Minimum 12 weeks**

Viral

HSV / VZV *Acyclovir, valacyclovir, or famciclovir (uncomplicated, localized skin)*	**7–10 days**
Influenza	**Minimum 5 days oseltamivir**

Causes of treatment failure

Persistent neutropenic fever

F → **False** diagnosis

A → **Allergy**

I → **Infections** with resistant pathogens

L → **Localized** problems *(i.e. prosthetic materials)*

Antimicrobial stewardship

Core components

1. **Surveillance** - Resistance patterns, consumption, outcomes
2. **Protocols** - Local guidelines for prevention and treatment
3. **Rapid diagnostics** - Enable early de-escalation
4. **Dose optimization** - TDM for azoles, drug interaction screening, PK/PD-guided dosing

Requires multidisciplinary collaboration

Key stewardship interventions

- Timely de-escalation based on culture results
- Duration optimization (avoid excessive courses)
- IV to PO conversion when appropriate
- Prospective audit and feedback
- Restricted antibiotic authorization
- Education for prescribers

Summary: Key takeaways

1. **Neutropenia** is the primary risk factor, but many others contribute
2. **Epidemiology** is shifting toward gram-negatives and MDR
3. **Prophylaxis** must be tailored to risk and local epidemiology
4. **Febrile neutropenia** requires prompt empirical therapy
5. **Escalation vs de-escalation** strategies depend on patient risk
6. **Antifungal therapy** can be empirical or diagnostic-driven
7. **Stewardship** is essential to preserve antimicrobial efficacy

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