

Febrile Neutropenia

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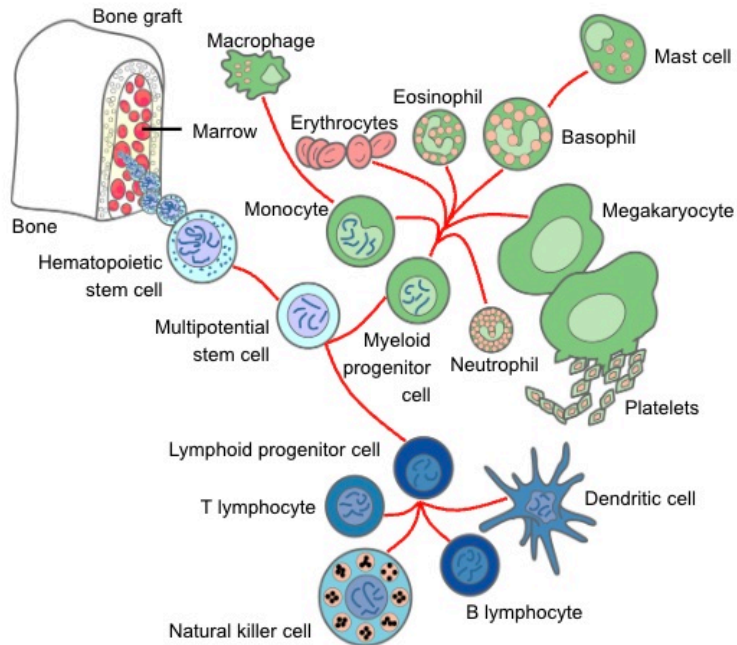
🐙 <https://github.com/Russlewisbo>

Slides and course materials: www.padovaid.com

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 ($\approx 2-3$ weeks)

- **Lymphoid lineage (T, B, NK cells)**

- Highly heterogeneous populations
- Mix of short-lived effector cells and long-lived memory cells

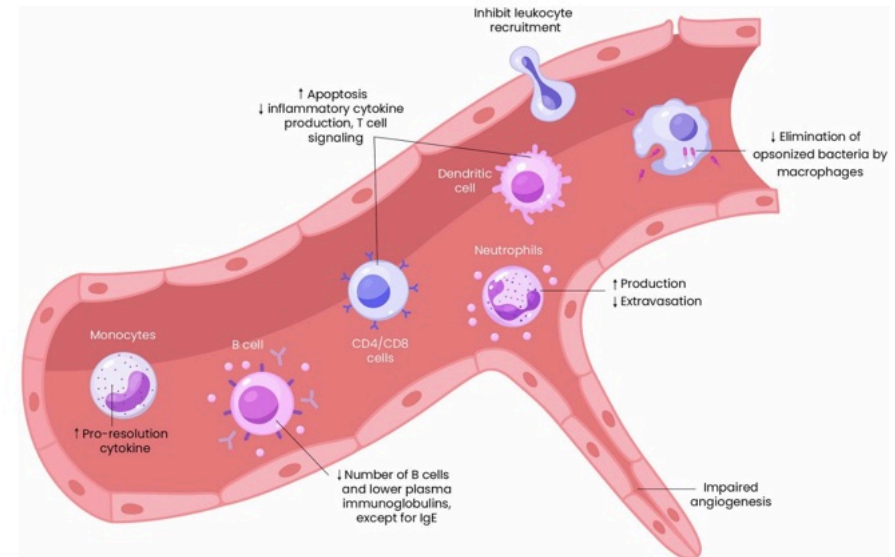
Chemotherapy-associated neutropenia

- **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:

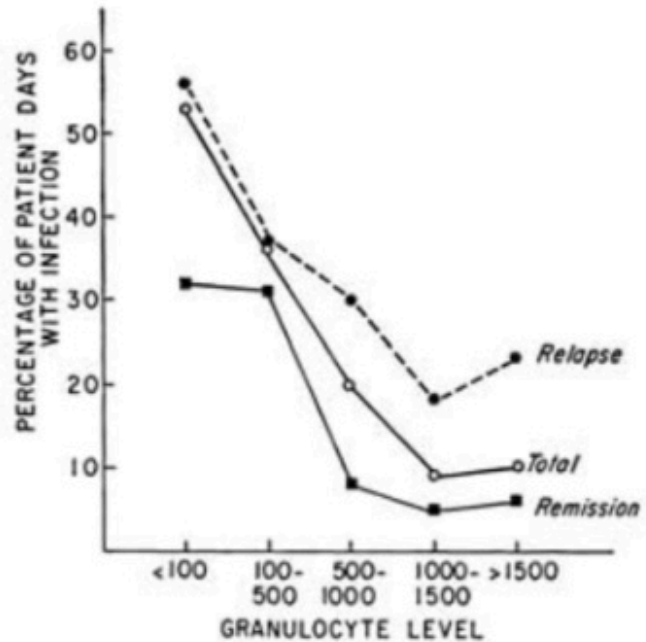
- ↑ Granulocytopoiesis (apparent benefit)
 - ↓ Accumulation at infection site
- ↓ Adherent capacity
- ↓ Chemotaxis
- ↓ Phagocytosis
- ↓ Intracellular killing



Immunity and innate immune cells

Cells	Molecules	Active against
PMNs <ul style="list-style-type: none">• 1° granules• Specific granules	<ul style="list-style-type: none">• Lysozyme, myeloperoxidase with (with H₂O₂)• Defensins, BPI, lactoferrin	Bacteria, fungi
Macrophages	<ul style="list-style-type: none">• Similar to PMN but no myeloperoxidase• Nitric oxide• Arginase	Intracellular pathogens (depletes arginine)
Eosinophils	<ul style="list-style-type: none">• Cationic proteins• Major basic protein• Peroxidase	Worms (extracellular)
Natural killing (NK) cells	<ul style="list-style-type: none">• Perforins• Granzymes	Viral or bacterial infected cells

Quantitative relationship of neutropenia with infection risk



Granulocyte Level		Episodes	
Initial	Change	Total	Fatal
	<i>/mm³</i>	<i>no.</i>	<i>%</i>
<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

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 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

Clinical signs if infection are muted in neutropenic patients

% of patients who have a neutrophil count/mm³ :

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:

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

Oropharynx:

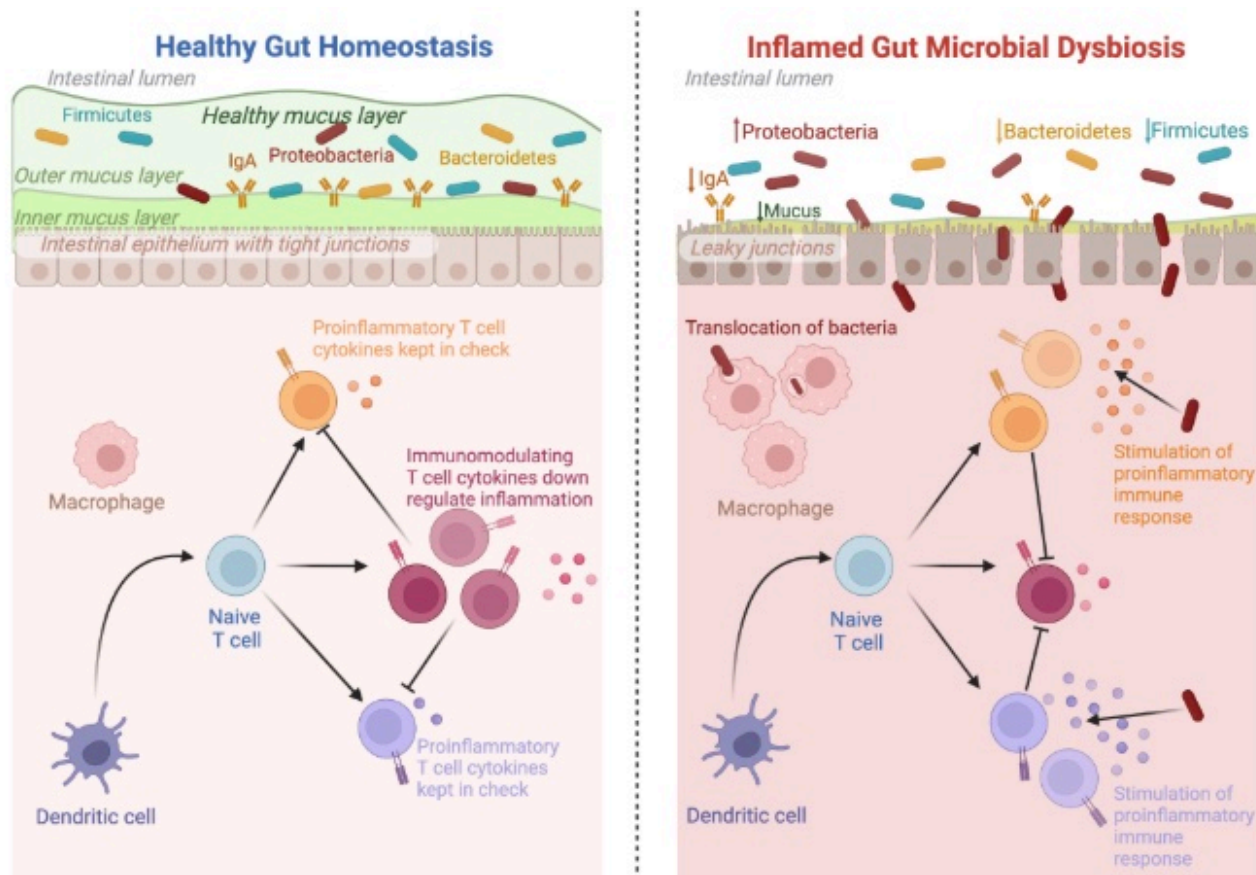
- Xerostomia + antibiotics → thrush, bacterial overgrowth



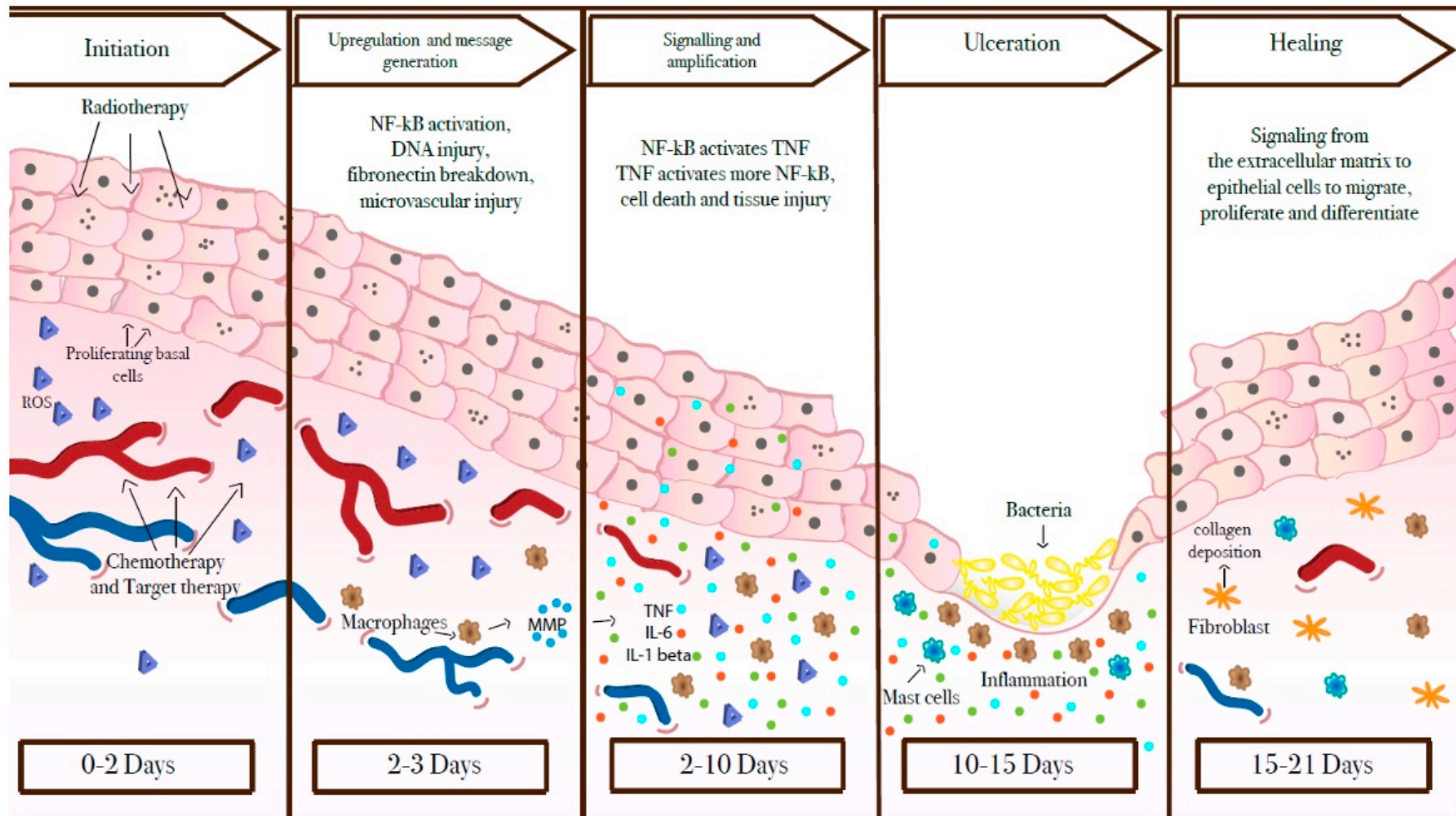
Alimentary Tract

- **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?

Gram-negative Bacilli

Aerobic

Pseudomonas aeruginosa

Facultatively Anaerobic

Escherichia coli

Klebsiella pneumoniae

Enterobacter cloacae

Capnophilic

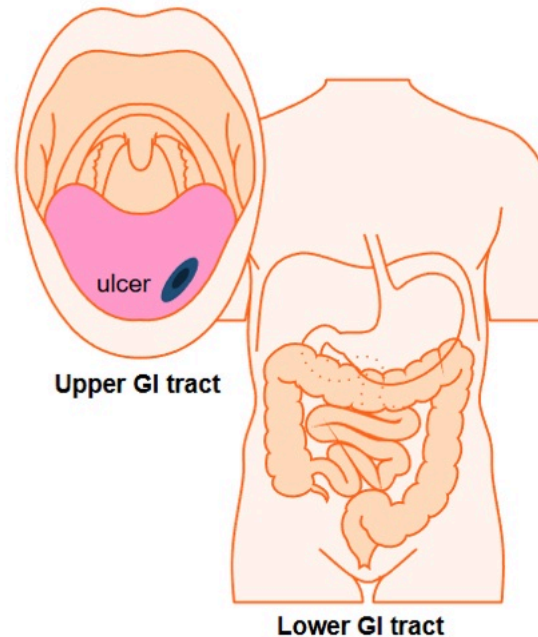
Capnocytophaga species

Anaerobic

Fusobacterium species

Leptotrichia buccalis

Prevotella species



Gram-positive Cocci

Oral viridans streptococci

Streptococcus mitis

Streptococcus oralis

Streptococcus sanguis

Staphylococci

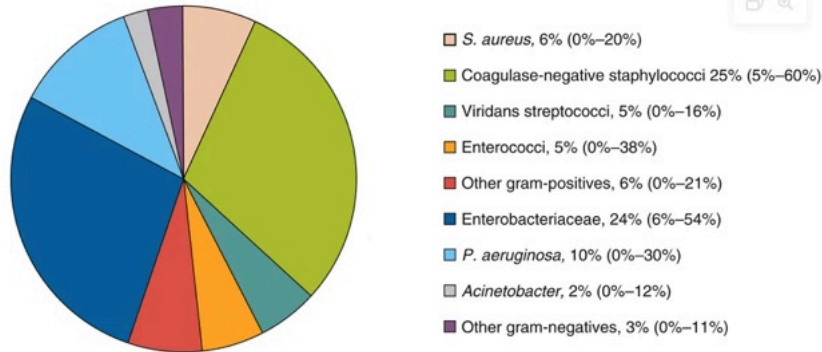
Staphylococcus epidermidis

Others

Stomatococcus mucilaginosus

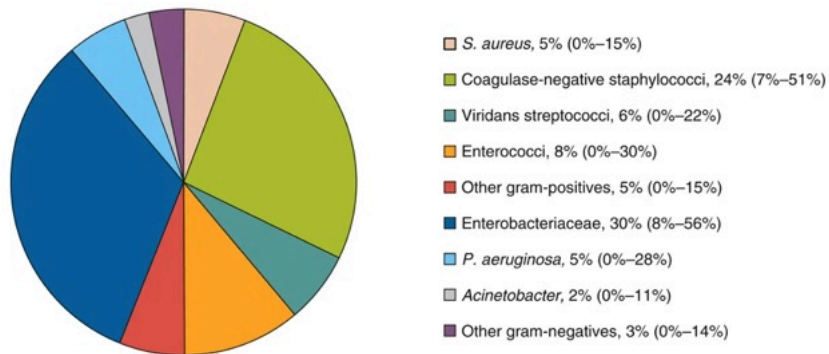
Most common bacterial pathogens

REVIEW OF LITERATURE FROM YEARS 2005–2011

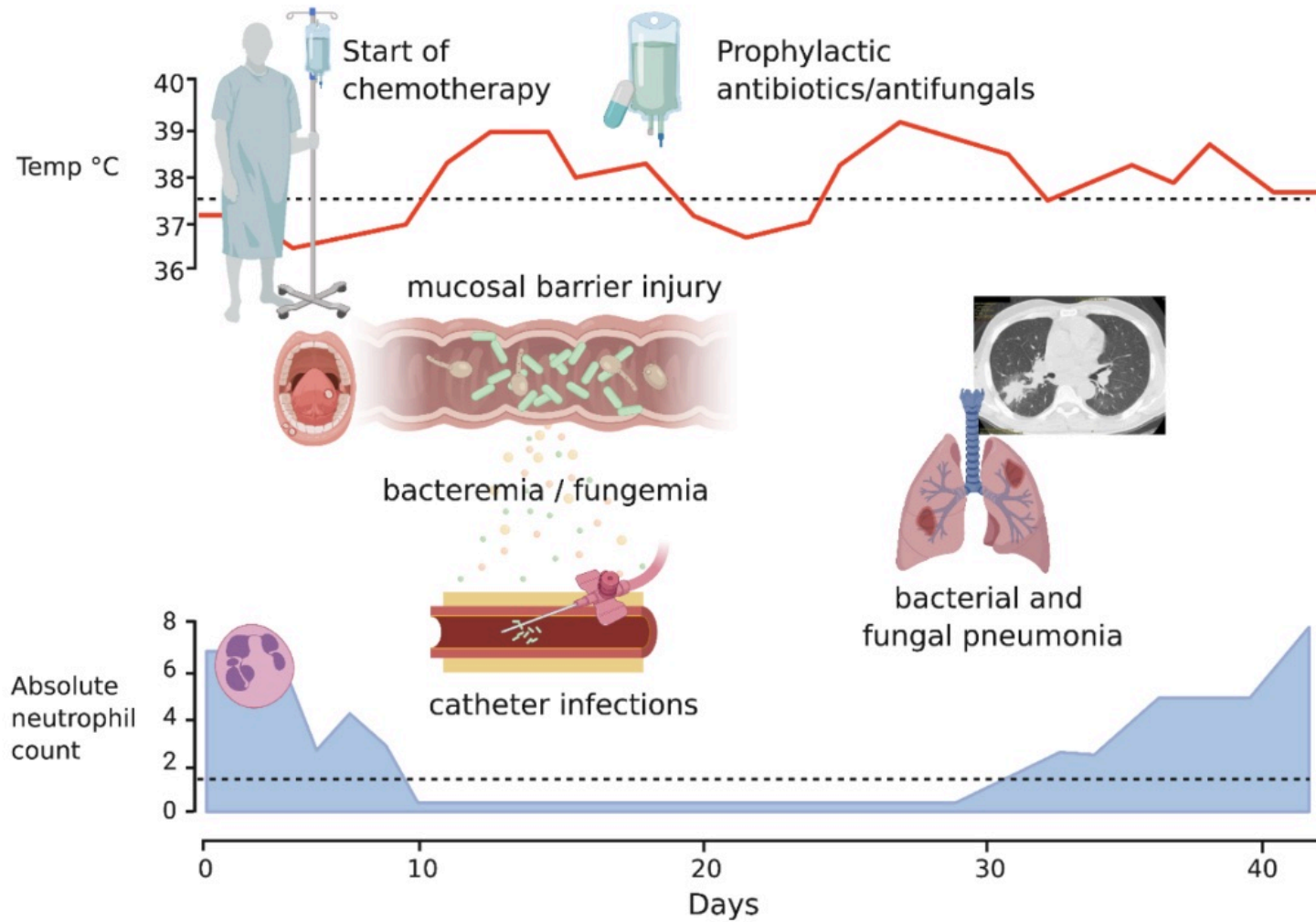


- Infectious source documented in only 20-30% of episodes
- Bacteremia documented in 10-25% of patients with fever
- Aerobic Gram-positive and Gram-negative

2011 ECIL-4 SURVEILLANCE STUDY



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)

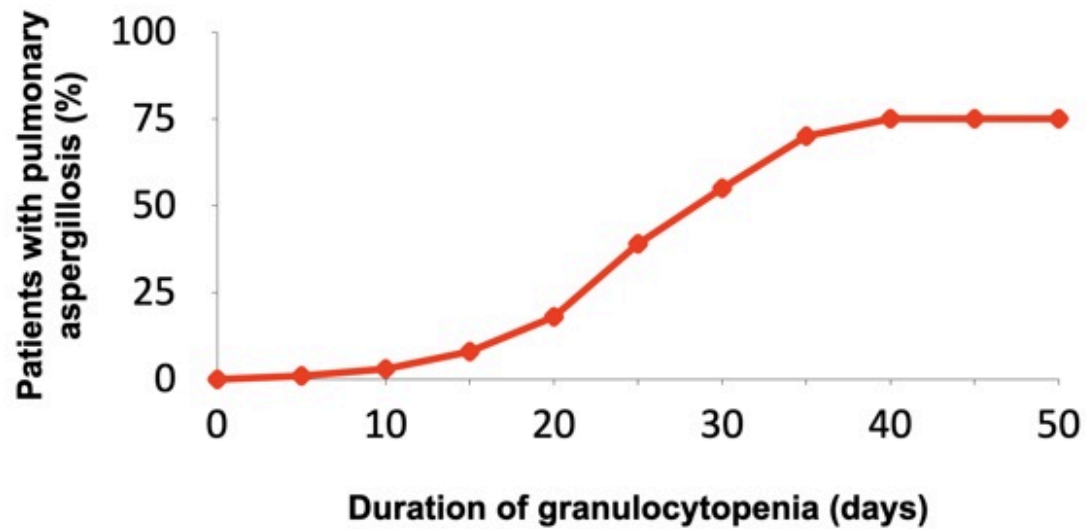
- Phase I pathogens *plus*
- Methicillin-resistant S. aureus (MRSA)
- Vancomycin-resistant Enterococcus (VRE)
- Resistant gram-negative bacteria
- *Stenotrophomonas maltophilia*

- 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

CVC-related infection rates

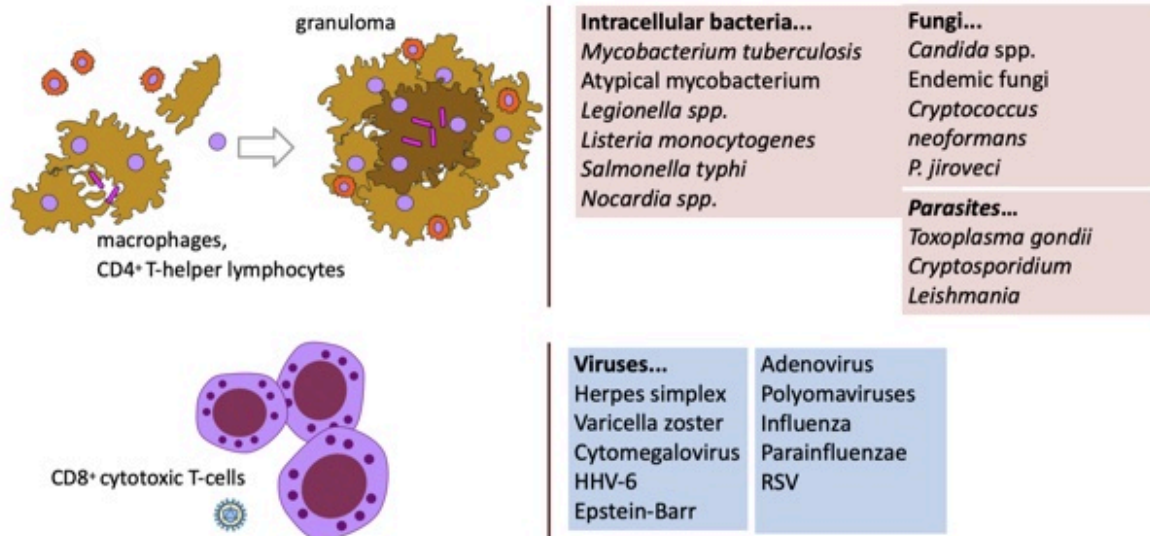
Catheter Type		Per 100 devices	Per 1000 catheter-days
Hickman/Broviac		22.5	1.6
Port-a-cath		3.5-4	0.1
PICC		3.1	1.1

Biologic agents and infection risk

Agent	Key Infections
Rituximab	HBV reactivation, PML
Brentuximab	PCP, PML
Bortezomib	VZV reactivation
Ruxolitinib	VZV, TB
Idelalisib	HSV, CMV, PCP
Ibrutinib	IFD (with steroids)

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

Impaired cell-mediated immunity increases the spectrum of possible pathogens



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)

:

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 (now > *Candida* in hematology)
- *Candida* species (increasing non-albicans)

Emerging concerns:

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

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:

- HSV reactivation: 60% of seropositive with acute leukemia
- VZV: Increased with bortezomib, ruxolitinib
- CMV: T-cell suppressing regimens

Respiratory viruses:

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

Prophylaxis Strategies

Antibacterial Prophylaxis

Fluoroquinolone prophylaxis:

Pros

Reduces febrile episodes

Reduces BSI

Oral administration

Cons

Increasing resistance,
especially selection of ESBL

No mortality benefit (recent data)

Drug interactions

QT prolongation, tendinopathy

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

Antifungal prophylaxis - Key points

When to use mold-active prophylaxis:

- Anticipated IFD incidence >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 prophylaxis

Indications:

- ALL (all ages)
- Fludarabine, alemtuzumab, idelalisib therapy (T-cell suppressing chemotherapy)
- Corticosteroids ≥ 10 -20 mg/day \times 4 weeks
- CD4 $< 200/\mu\text{L}$

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

Alternatives: Dapsone, atovaquone, aerosolized pentamidine

Antiviral prophylaxis

HSV/VZV:

- Acyclovir 800 mg BID or valacyclovir 500 mg BID
- For 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

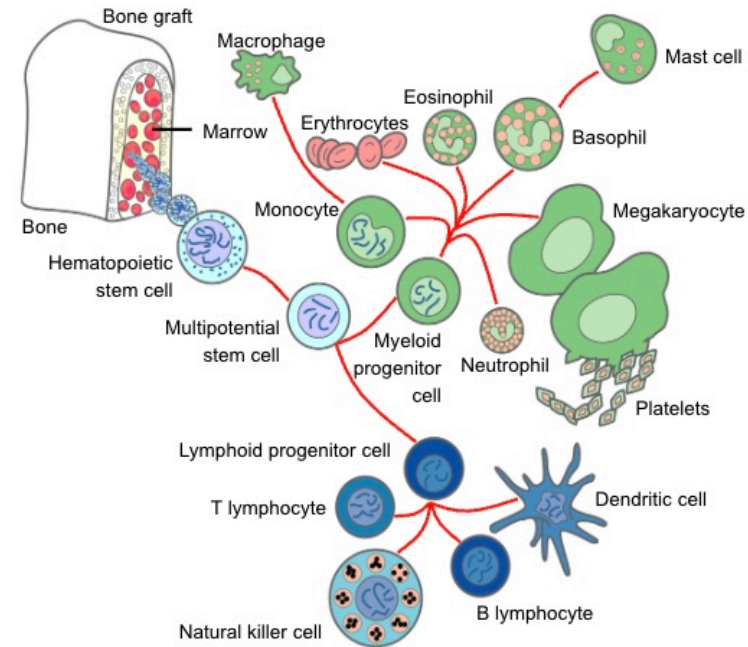
Granulocyte-colony stimulating factor (G-CSF)

Primary prophylaxis:

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

Secondary prophylaxis:

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



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

Definition of Fever

For starting empirical antibiotics:

- **Single temperature** $\geq 38.5^{\circ}\text{C}$ (oral/axillary), OR
- **Two measurements** $\geq 38.0^{\circ}\text{C}$ separated by ≥ 1 hour

Also treat infection suspected with:

- Hypothermia ($< 35.5^{\circ}\text{C}$)
- 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 $< 200/\mu\text{L}$	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
- Add aminoglycoside and/or change to anti-pseudomonal carbapenem if septic
- 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 <i>P. aeruginosa</i>

Glycopeptide use (to cover MRSA)

Add vancomycin or alternative for:

- Suspected catheter-related infection
- Skin/soft tissue infection
- Known MRSA colonization
- Severe sepsis with hypotension
- Pneumonia
- 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
- 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)	<i>Aspergillus</i>	Serum, BAL
β -D-glucan (BDG)	Broad fungi (not Mucorales)	Serum
PCR	Species-specific	Blood, BAL
CT imaging	Structural changes	Chest/sinuses

Mucormycosis



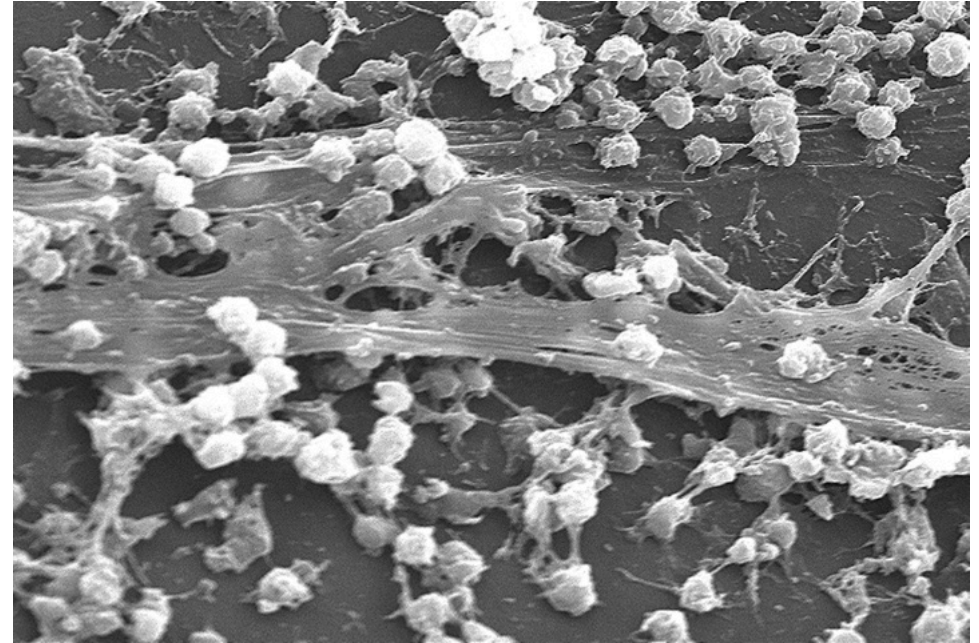
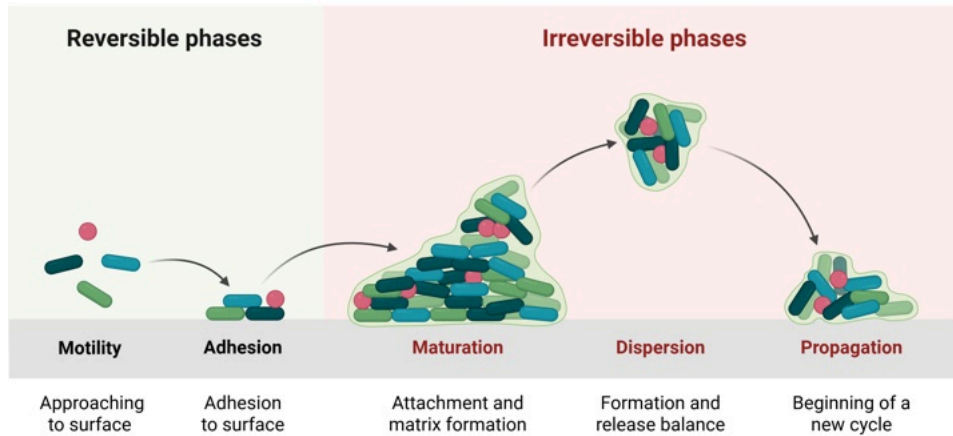
Rhinocerebral mucormycosis evolution over 24 hours in a neutropenic patient

Antifungal Selection

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

Specific 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:

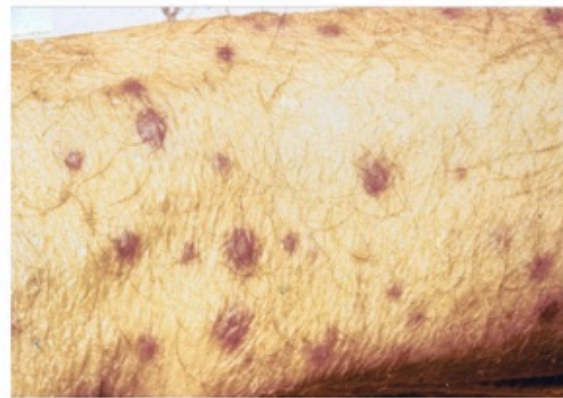
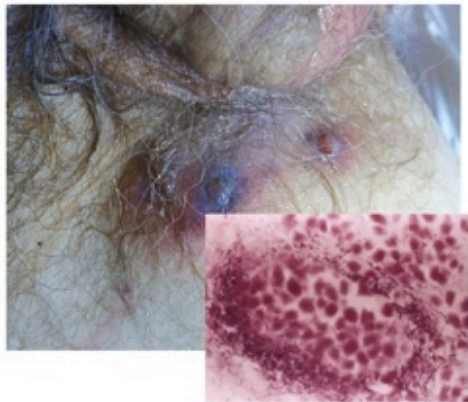
- *S. aureus*, *Candida*, *Pseudomonas* bacteremia
- Tunnel infection
- Persistent bacteremia despite antibiotic therapy

Skin lesions

Evidence of disseminated infection (hematogenous spread)



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



Skin Lesions in Disseminated Candidiasis

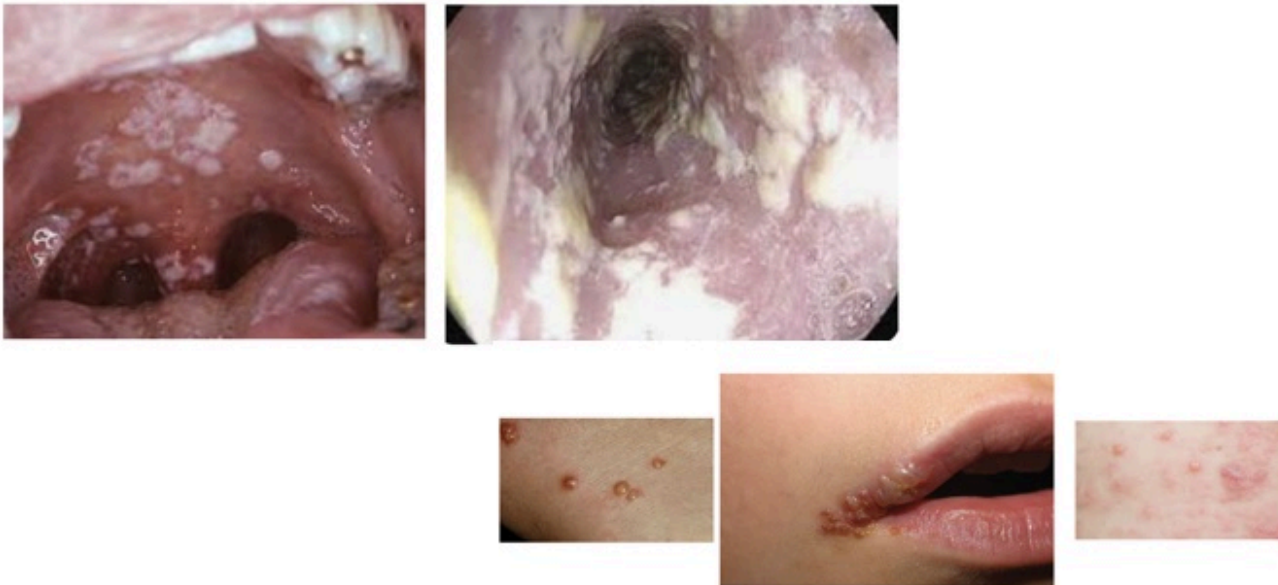


Leukemic Patient with *Clostridium perfringens*
Septicemia

Oral- Upper GI infection

Candida- Thrush, esophagitis (odynophagia, retrosternal pain)

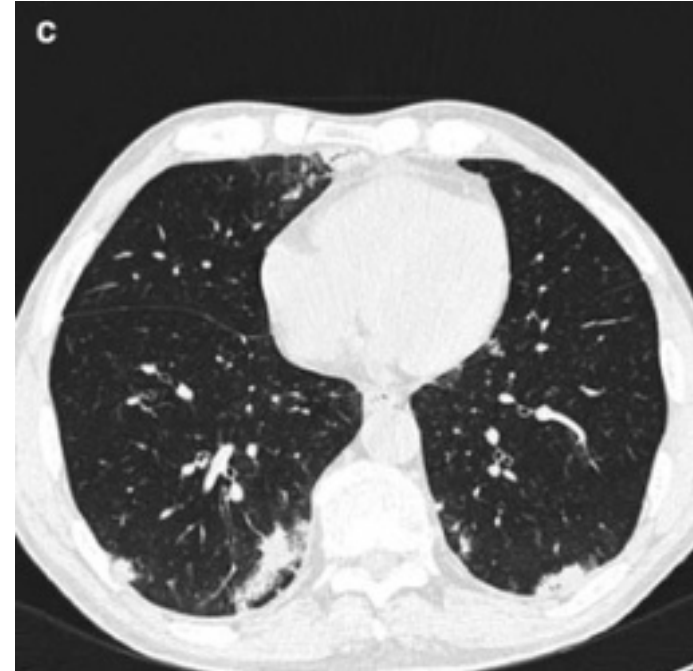
Vesicular lesions- painful grouped lesions→ulceration



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

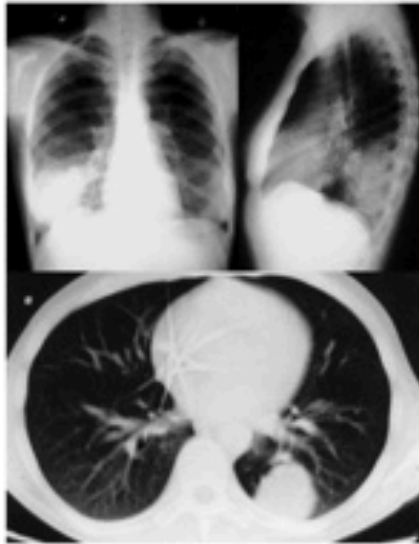
Pneumonia

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

Bronchoscopy

Bronchoscopy: Timing is critical



501 consecutive allo HSCT patients

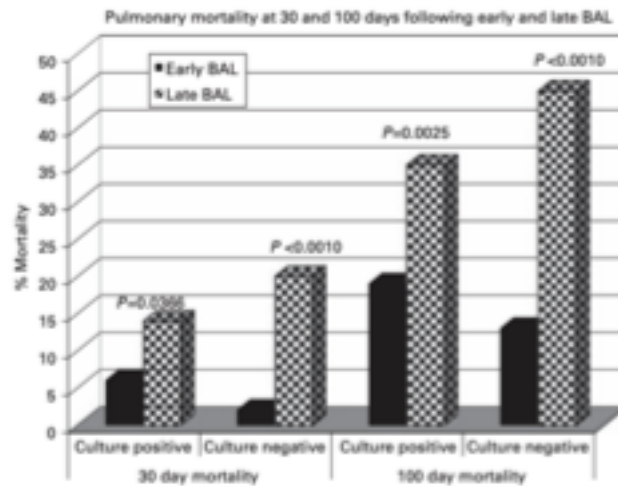


Figure 1 Pulmonary mortality at 30 and 100 days following early and late bronchoalveolar lavage (BAL). Significantly lower mortality rates were observed when a diagnosis of infection was confirmed by early fiberoptic bronchoscopy (FOB; black bars) compared to late examinations (checkered bars). Early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

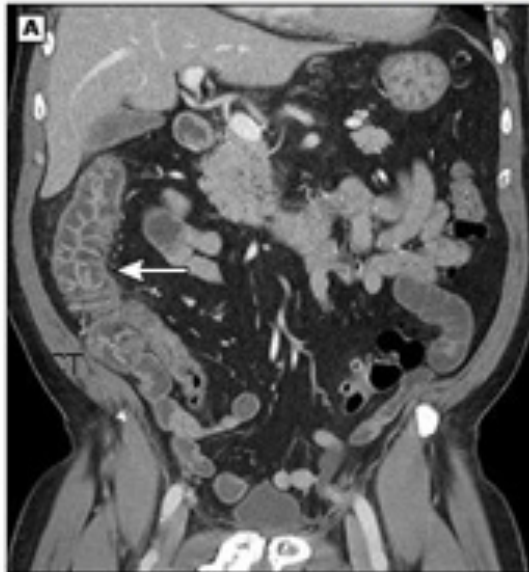
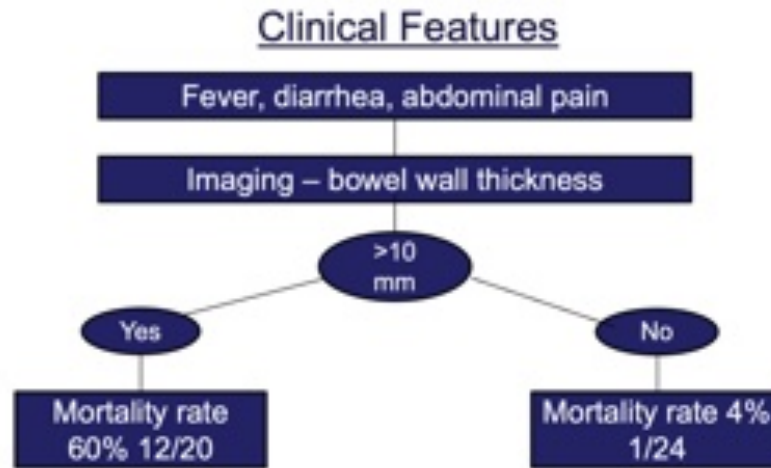
Shannon VR et al. Bone Marrow Transplant 2010; 45:647-655.

- 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:** Reduce 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 (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)

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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