Fever and rash in the non-HIV immunocompromised host
>20% of immunocompromised hosts will develop skin lesions, often with fever

Multiple defects in host defense lead to different types of infection

These lesions may reflect disseminated infection

Evaluation of the skin may provide the most rapid diagnosis
Clues to the diagnosis

1. Presence of signs and symptoms other than the rash
2. Recognize the clinical settings:
   1. Constructions near the hospital leads to suspicion of aspergillosis or mucormycosis
   2. Cellulitis or hemorrhagic bullae in an acute febrile illness after exposure to a salt water environment suggests *Vibrio vulnificus*
   3. Fresh water contamination implicates *Aeromonas*.

*M.E. Grossman et al., Cutaneous Manifestations of Infection in the Immunocompromised Host*
3. Determine the **host factors** that predispose to certain infections: diabetic ketoacidosis, organ transplantation, acute leukemia, etc.

4. **Timing of the skin lesions**: in a patient who has had neutropenia for 3 days, bacterial infection is more probable than fungal infection.

5. In the neutropenic patient, the classic findings of swelling and fluctuance may be absent. There may be scant or no pus.
6. Determine the **host factors** that predispose to certain infections: diabetic ketoacidosis, organ transplantation, acute leukemia, etc.

7. **Don’t exclude pathogens as “contaminants”**

8. Inquire about geographic, nosocomial, occupational, or behavioral exposures

9. History of **travel** and exposure to **animals**

10. **Skin biopsy** should be performed for histology and culture to establish a definitive diagnosis.
Neutropenia or neutrophil dysfunction
Neutropenia or neutrophil dysfunction

- **Bacterial** infections
  - Most likely responsible for the first episode of fever in the neutropenic host (first 7 days)

- **Fungal** infections
  - More likely in patients with fever and neutropenia of greater than 7 to 10 days duration, especially if neutrophil count is less than 100/μL.
A 69-year-old with multiple myeloma developed febrile neutropenia post chemotherapy with Pseudomonas sepsis and ecthyma gangrenosum on the medial thigh. Blood and skin cultures grew *Pseudomonas aeruginosa*. 
Ecthyma gangrenosum

Necrotic skin lesion due to Pseudomonas aeruginosa at the exit site of a Hickman catheter in a neutropenic patient with acute leukemia.

Courtesy of Charles V Sanders, MD.
Ecchyma gangrenosum

- EG lesions become papular and then ulcerative with a necrotic center and hemorrhagic border.
- EG-like lesions can also be caused by:
  - gram-positive organisms such as *Streptococcus pyogenes* and *Staphylococcus aureus*,
  - gram-negative organisms (eg, *Stenotrophomonas maltophilia*, *Aeromonas hydrophila*, *Enterobacteriaceae*), and
P. aeruginosa cellulitis with bullous striae in a 17-year-old neutropenic patient with acute myeloblastic leukemia

M.E. Grossman et al., Cutaneous Manifestations of Infection in the Immunocompromised Host
Approximately 60 nontender, nonfluctuant, red-hot, subcutaneous nodules on the proximal arms, legs, and face of a febrile 56-year-old woman with ovarian adenocarcinoma during chemotherapy. *P. aeruginosa* was cultured from blood, urine, and skin biopsy.
Stenotrophomonas maltophilia

Day 1

Painful, erythematous, poorly demarcated

Day 5

Painful, poorly demarcated, with exfoliative and pigmentary changes

8-yo girl with acute myeloid leukemia. Metastatic skin lesions

Ann Acad Med Singapore 2006;35:897-900
Cutaneous lesions include extensive cellulitis, purpura, ulcers, ecchymoses, and ecthyma gangrenosum.
E. coli sepsis and culture positive hemorrhagic bullae in a 94-year-old with hairy cell leukemia, antiphospholipid antibody syndrome, splenomegaly, and transfusion dependent cold agglutinin hemolytic anemia despite rituximab
Clostridial myonecrosis

**Spontaneous gas gangrene**
Hematogenous seeding of muscle with bacteria from a gastrointestinal tract portal of entry.
Usually *Clostridium septicum*

Cancer. 1991;67(7):1928
Corynebacterium jeikeium

Acute cellulitis of the right first toe due to *C. jeikeium* in a patient with acute myelocytic leukemia.

A 74-year-old man with neutropenia secondary to newly diagnosed follicular lymphoma had *S. aureus* and group B *Streptococcus* ecthyma on the arm

*M.E. Grossman et al., Cutaneous Manifestations of Infection in the Immunocompromised Host*
Staphylococcus aureus hemorrhagic bulla of the ankle was the presenting manifestation of myelodysplastic syndrome.
A monomorphous bullous eruption due to *S. aureus* developed in a 12-year-old during chemotherapy for acute lymphocytic leukemia.
Fungal pathogens

- Candida species
- Aspergillus species
- Agents of mucormycosis
- Fusarium species
- Trichosporon beigelii
Hematogenous dissemination of C. tropicalis produced this hemorrhagic nodule on the arm of a patient with acute myelogenous leukemia and thrombocytopenia.


http://www.lww.com
Purpuric papules and a gray flat bullae due to *Aspergillus flavus* on the palm of a 7-year-old with acute lymphocytic leukemia (ALL) on the 15th day of chemotherapy, febrile with an absolute neutrophil count of 60.

A hemorrhagic bulla with linear vesicular borders on the forearm of a 9-year-old with ALL. Culture: *A. fumigatus*.
Cutaneous mucormycosis can manifest as a superficial or deep infection.

It can appear as pustules, blisters, nodules, necrotic ulcerations, ecchyma gangrenosum-like lesions or necrotizing cellulitis.
Cutaneous zygomycosis in a patient with kidney transplantation
Skin lesions due to *Fusarium* sp.

Ecthyma gangrenosum

“Target” lesions

Multiple, painful

Erythematous papules and papulopustules caused by *T. beigelii* on the face of a patient with acute lymphocytic leukemia

Decreased cellular immunity
Non-HIV causes of decreased cellular immunity

- Lymphoma
- Transplantation
- Sarcoidosis
- Wiskott-Aldrich syndrome
- Irradiation
- Drugs (corticosteroids, cyclosporine, tacrolimus, anti-TNF)
Decreased cellular immunity: associated pathogens

- **Bacteria**
  - *Mycobacteria* spp
  - *Nocardia* spp
  - *Salmonella* spp
  - *Listeria monocytogenes*
  - *Legionella* spp
  - *Bartonella* spp
  - *Brucella* spp

- **Fungi**
  - *Cryptococcus neoformans*
  - *Aspergillus* spp
  - **Endemic fungi**
    - *Pseudallescheria boydii*
    - *Pneumocystis jirovecii*

- **Viruses**

- **Parasites**
  - *Toxoplasma gondii*
  - *Strongyloides stercoralis*
Mycobacterium tuberculosis

Tuberculosis cutis miliaris disseminata in a human immunodeficiency virus (HIV)-positive patient

M.E. Grossman et al., Cutaneous Manifestations of Infection in the Immunocompromised Host
A 49-year-old woman with rheumatoid arthritis treated with methotrexate, infliximab, and prednisone developed *M. marinum* infection of the soft tissue and joint of the fourth finger with sporotrichoid papules.
A 36-year-old renal transplant with no history of trauma presented with 4 months of skin lesions localized to one leg. Multiple subcutaneous nodules with pustules and sinus tracts were caused by *M. chelonae*.
A 47-year-old renal transplant patient presented with fever, a cavitating pulmonary nodule, and a sparse number of pustules on his trunk and face. Gram stain of a pustule showed characteristic Gram-positive, delicately branching filaments of *Nocardia asteroides* cultured from his skin and lung.
Hemorrhagic crusts of the lips and nose in a heart transplant patient with chronic HSV.

Polycyclic HSV ulcer on the hard palate of a renal transplant patient

M.E. Grossman et al., Cutaneous Manifestations of Infection in the Immunocompromised Host
Herpes zoster

Coalescent bullae progressing to epidermal necrosis of herpes zoster involving the first division of the trigeminal nerve in a patient on systemic steroids for sarcoidosis

M.E. Grossman et al., Cutaneous Manifestations of Infection in the Immunocompromised Host
Disseminated herpes zoster

Severe vesiculopustular lesions on erythematous bases present in multiple dermatomes in this patient with squamous cell carcinoma of the vocal cord.

*Courtesy of Charles V Sanders, MD.*

*UpToDate 2013*
A 60-year-old HIV-negative Jamaican man with spastic paraparesis treated with systemic steroids had an ear ulceration for 6 months and a productive cough and fever for 2 months. Multiple cavitary lung lesions and biopsy of the ear demonstrated *Cryptococcus neoformans*
A 66-year-old man with well-differentiated lymphocytic lymphoma on chlorambucil and prednisone developed disseminated papulopustules of *Blastomyces dermatitidis*.
Multiple draining sinuses on the dorsum of the hand of a 47-year-old patient with chronic lymphocytic leukemia due to *Paecilomyces lilacinus* and not a bacterial cellulitis as initially diagnosed.

*Arch Dermatol. 1986;122:1169*
Decreased humoral immunity
Non-HIV causes of decreased humoral immunity

- Decreased splenic function / asplenia
- Chronic lymphocytic leukemia
- Nephrotic syndrome
- Non-Hodgkin lymphoma
- Paraproteinemias
- Intestinal lymphangiectasia
- Primary hypogammaglobulinemias
Decreased humoral immunity: associated pathogens

- **Bacteria**
  - *Streptococcus pneumoniae*
  - *Neisseria meningitidis*
  - *Haemophilus influenzae*
  - Encapsulated gram-negative bacilli

- **Viruses**
  - Enteroviruses

- **Parasites**
  - *Giardia lamblia*
Gangrene due to pneumococcus in a bacteremic splenectomized patient

Gangrenous toes developed secondary to prolonged hypotension and tissue ischemia in this patient with pneumococcal bacteremia and septic shock. A splenectomy had been performed years earlier for the treatment of immune thrombocytopenia (ITP).


http://www.lww.com
Purpura fulminans

Skin lesions in acute meningococcemia can begin as papules but quickly progress to petechiae and purpura. As seen here, the purpuric lesions can coalesce.

Courtesy of Charles V Sanders. (The Skin and Infection: A Color Atlas and Text, Sanders, CV, Nesbitt, LT Jr (Eds), Williams & Wilkins, Baltimore, 1995).
Infant with severe vasculitis with disseminated intravascular coagulation (DIC) with gangrene of the hand secondary to Hib septicemia
Other diseases leading to immunosuppression
Cirrhosis

- Impaired phagocytosis and chemotaxis, decreased complement levels and poor opsonization
- Vulnerable to skin and soft tissue infections due to *Vibrio vulnificus* after consumption of raw shellfish or exposure to warm seawater.
- *Aeromonas spp, E.coli*: similar necrotizing lesions


*J Formos Med Assoc. 1998;97(7):498*
Severe *Vibrio vulnificus* infection

Bullous lesions and hemorrhagic necrosis of the hand and forearm were caused by *Vibrio Vulnificus* in this immunocompromised patient.  
*Courtesy of Rolando E. Saenz, MD.*
Underlying diseases:
- Cirrhosis
- Hematologic diseases
- Long-term steroid use
- Organ transplantation
- Malignancy
- Lymphoma

The organism is acquired through the GI tract, after recent consumption of raw seafood or by wound infection in sea water.
Necrotizing hemorrhagic bullae of a human immunodeficiency virus (HIV)-negative, intravenous drug abuser with **cirrhosis** who developed septic shock and multiorgan failure and then died. Aeromonas species was cultured from the blood and bullae.
Diabetes mellitus

- Depressed neutrophil and T-cell function
- Skin and soft tissue infections
  - Monomicrobial or polymicrobial
  - Anaerobes, aerobic staphylococci and streptococci, aerobic gram-negative bacilli
  - Mucormycosis
Diabetic foot

Necrotic toe and dorsal abscess from tight shoes

4th toe necrotic cellulitis in a diabetic
Clostridial myonecrosis

An 80-year-old woman with diabetes
- febrile, toxic, and with a rapidly spreading cellulitis with hemorrhagic bullae.
- Gram stain of the fluid showed Gram-positive rods.
- Surgery confirmed the myonecrosis
- *C. septicum* was cultured and carcinoma of the cecal colon was subsequently discovered
Aeromonas hydrophila necrotizing fasciitis and gas gangrene in a diabetic patient on haemodialysis

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Rhinocerebral mucormycosis

- Necrotic eschars
Skin infections in as many as 34% of patients with SLE
Defects in complement, neutrophil, immunoglobulin, T-cell and splenic/reticuloendothelial function.
Therapy for SLE produces further immunosuppression
Staph. aureus, group A streptococcus, VZV, HSV
E.coli, Candida spp, mycobacterial spp, less often.

Infectious Diseases in Clinical Practice. 1999; 8:225
A 28-year-old woman with systemic lupus erythematosus (SLE) on prednisone, mycophenolic acid and hydroxychloroquine developed fever, swelling of her left eye, nausea, and vomiting. Magnetic resonance imaging (MRI) showed periorbital cellulitis and inflammatory changes in the masseter and temporalis muscles. *Streptococcus group A* cellulitis/gangrene resolved with antibiotics and no surgical debridement.
- 48 yo man with acute promyelocytic leukemia
- Induction chemo with daily all-trans retinoic acid (tretinoin), cytarabine (1-7) and daunorubicin (1-3)
- Day 15: low-grade fever and rash
- Rash starts as tender purple papules on upper extremities and quickly disseminates to ears and shoulders.
- Blood cultures negative
- Imaging normal
- Rash appears on lower extremities.
- Tretinoin discontinued.
- Biopsy:

  Sweet syndrome!
Non-infectious causes of fever and rash

- **Sweet syndrome** (acute febrile neutrophilic dermatosis): fever, neutrophilia, erythematous skin lesions and prompt improvement after initiation of systemic corticosteroids.
- **Graft-versus-host disease**
- **Drug eruptions**
Conclusions

- For any new skin lesion in an immunocompromised patient, you should have a very low threshold to obtain a skin biopsy to rule out infection.
- Any chronic or unexplained skin lesion in the immunocompromised host should be biopsied at an early stage for fungal, viral, bacterial and protozoal causes.
- A lesion of the skin may be the hallmark of disseminated disease.
Thank you!