

Location: Emergency room

Vital signs: B.P: 130/70 mm Hg; H.R: 80/min; R.R: 18/min; Temperature: 38.7° C.

HPI:

A 50-year old lady, with a history of chemotherapy post a successful breast surgery, came to the ER with a fever. Patient was diagnosed with breast cancer three months earlier. She underwent surgery that was followed by two cycles of combination chemotherapy. She was advised to come back to the office immediately if she developed any fever. She denies any cough, cold, headache, neck stiffness, SOB, chest pain, diarrhea, abdominal pain, blood in the stools, ulcers, or burning urination. Her other medical problems include reflux disease and osteoarthritis. She takes lansoprazole QD, and acetaminophen as needed. She denies smoking, alcohol, and IV drug abuse. Family history is nothing significant. She is allergic to sulfa drugs, and codeine. ROS is unremarkable.

(Patient with history of chemotherapy and fever should make you think about possible infection secondary to immunocompromised status. First step is to get a good history and physical exam.)

Order physical examination:

General appearance

Skin - check for skin lesions

Lymphnodes

HEENT/Neck- evidence of fungal infection.

Chest/Lung- evidence of respiratory infection i.e. decreased breath sounds, rales, rhonchi.

Lungs are the most frequent site of infection in immunocompromised patients.

Heart/CVS

Abdomen

Extremities

Neuro/Psych.- mental status evaluation looking for meningism or focal deficits

Note: Digital rectal exam is not routinely performed as trauma of these frail mucosal areas can precipitate infection. However, we generally inspect the peri anal areas for any focus of infection. If there is suspicion for prostatitis or perirectal abscess, it can be performed after the broad-spectrum antibiotics have been administered.

Results:

Completely normal physical exam

Order:

Continue lansoprazole

IV access

CBC with differential, stat

Urinalysis, urine culture & sensitivity, and Gram stain, stat

Blood culture, stat

Sputum Gram stain, and cultures (if the patient has symptoms)

Comprehensive metabolic panel, stat

Chest X-ray, PA, and lateral, stat

Ceftazidime, IV, continuous

Treatment:

Admit to floor

Regular diet

Activity - As tolerated

Nursing - Vitals Q 4 hours

Acetaminophen, oral, as needed (Do not give continuously, as you have to monitor whether he is responding to antibiotics or not)

CBC with diff, daily

Consider PT/PTT for baseline if there is a risk of developing DIC.

Consider use of Neupogen (G-CSF) - Not in this patient

Re-examine the patient in six hours, obtain interim history, then see the patient Q 12 hours and monitor.

Consider changing the antibiotics according to the culture and sensitivities

During discharge:

After 3 days D/C IV antibiotics

Start oral antibiotics

D/C daily CBC with diff

Educate patient and family:

Counsel patient to avoid people with cold/flu

Counsel patient to seek medical help if a fever develops

Final Diagnosis:

Febrile neutropenia secondary to chemotherapy

Discussion:

Fever in a neutropenic patient is a medical emergency. Febrile neutropenia is defined as a single temperature of $>38.3^{\circ}\text{C}$ (101.3°F), or a sustained temperature $>38^{\circ}\text{C}$ (100.4°F) for more than one hour. However, patients who are on corticosteroids may not develop fever. Neutropenia is defined as an absolute neutrophil count (ANC) <500 cells/mm³. Disruption of the skin and mucosal barrier resulting from the chemotherapy often results in seeding of bacteria into the blood stream (bacteremia) and the most common site of mucositis is in gastrointestinal tract. Chemotherapy also results in impaired immunologic function.

The frequently identified organisms in febrile neutropenic patients are Gram negatives, particularly *P. aeruginosa*. But there has been a recent increase in Gram positive infections for several reasons. Although GI tract has abundant anaerobic organisms, anaerobic coverage is not indicated in the initial empirical antibiotic regimen. Anaerobic coverage is indicated if there is any evidence of necrotizing mucositis, periodontal abscess, perirectal abscess/cellulitis, intraabdominal or pelvic infection, typhilitis (necrotizing neutropenic colitis), or anaerobic bacteremia.

Evaluation should include CBC with diff, basic metabolic panel, LFTs, blood cultures, urine Gram stain and cultures, sputum Gram stain and cultures, and chest X-ray. Lumbar puncture is not routinely indicated unless the clinical features suggestive of meningitis present. Other tests are indicated if the patient has localizing signs or symptoms. For example, patients with diarrhea should be evaluated with: Stool for Gram stain, culture, *Clostridium difficile* toxin, and ova and parasites.

All central lines and catheters should be inspected carefully and may need to be removed if clinically infected and infection not responding to appropriate antibiotics. We generally repeat the blood culture if the fever persists for more than 48 hours. Chest x-ray should also be repeated for persistent pulmonary symptoms. The findings on chest X-ray may be subtle or absent even in a patient with pneumonia. It is important to remember that the absence of neutrophils on sputum Gram stain, blood smear, or CSF does not exclude the presence of infection.

Treatment:

The empirical antibiotic choice should cover the Gram negative organisms especially *Pseudomonas*. The following are the commonly used regimens. We usually prefer monotherapy.

- Monotherapy: Cefepime, ceftazidime, imipenem, or meropenem.
- Double coverage: Aminoglycoside + extended spectrum antipseudomonal penicillin.

When should I consider vancomycin?

In general, vancomycin is added if there is no response to the above monotherapy in 2-3

days. The addition of vancomycin to the initial empiric antibiotic regimen should be considered in patients who present with hypotension, mucositis, skin or catheter site infection, history of MRSA colonization, or recent quinolone prophylaxis.

When to add antifungal therapy?

Antifungal therapy with amphotericin B should be considered at five to seven days of neutropenia in patients with persistent fever.

When to use G-CSF:

The benefit of colony stimulating factors as an adjuvant to antibiotic therapy in an uncomplicated febrile neutropenic patients is not proven and is not indicated. However, it is considered in patients with predictive poor outcome such as patients with ANC $<100/\mu\text{L}$, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction, or invasive fungal infection.

General approach to the therapy:

What is the initial antibiotic choice?

Does the patient need vancomycin?

If yes, order vancomycin + ceftazidime.

If no, order ceftazidime or aminoglycoside + extended spectrum antipseudomonal penicillin.

If patient became afebrile in three days: change to oral antibiotics, either cefixime or quinolone.

If patient is still febrile after three days: stop the vancomycin if added initially and cultures are negative; add vancomycin, if not administered initially, obtain repeat cultures, and chest X-ray.

Duration of therapy:

If the source of the infection is identified, antibiotics should be continued for the standard duration (14 days for Staph aureus bacteremia). If the source is unknown, then the following approach is indicated:

If the patient is afebrile in 3 days and the ANC is >500 , stop antibiotics after 7 days; If the patient is afebrile and the ANC is less than 500 continue antibiotics.

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