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How I diagnose and treat neutropenia

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Abstract

Purpose—Neutropenia (absolute neutrophil count (ANC) > 1.5×10^9L is a common hematological finding, and severe neutropenia, i.e., ANC >0.5×10^9L is a well-known risk factor for susceptibility to bacterial infections. This review provides a succinct clinical approach to the diagnosis and treatment of neutropenia with specific recommendations on the treatment of severe chronic neutropenia with the myeloid growth factor, granulocyte colony-stimulating factor (G-CSF).

Recent Findings—Experts agree that patients with acute febrile neutropenia should be treated with antibiotics and that patients at high risk of severe neutropenia (>20% risk) after myelosuppressive chemotherapy should be treated prophylactically with a myeloid growth factor, usually granulocyte colony-stimulating factor (G-CSF). The diversity of causes and consequences of chronic neutropenia make the diagnosis and management of these patients more complicated.

Summary—This review provides a stepwise approach to neutropenia focusing first reaching a provisional diagnosis and treatment plan then steps to a final diagnosis. It also provides specific recommendations on the treatment of severe chronic neutropenia with G-CSF.

Keywords

Neutropenia; diagnosis; treatment; granulocyte colony-stimulating factor (G-CSF)

Introduction

I have been interested in the diagnosis and treatment of neutropenia for nearly 50 years-from when we had just a few antibiotic choices for managing febrile neutropenia to the present era with a huge array of testing strategies, worries about antibiotic resistance and options for growth factor treatments.

Several experts have recently recommended approaches to acute and chronic neutropenia in children and adults (1-9) and managing chemotherapy-induced neutropenia, including antibiotic therapy. (10-14) In this brief review, I suggest a stepwise clinical approach to diagnose and treat neutropenia.

Conflicts of Interest

David C. Dale, MD serves as a consultant for Amgen, the manufacturer of granulocyte colony stimulating factor (G-CSF) products, Neupogen and Neulasta. G-CSF is used for the treatment of neutropenia. The UW has a contract with Amgen. Dr. Dale is the PI for this contract. Amgen supplies G-CSF through a research pharmacy directly to patients who are in the NIH sponsored Registry. All of these relationships have been previously revealed in UW GIM 10 forms.

Clinical Approach to Neutropenia

I. Always get a complete medical history. The key questions are:

1. Is neutropenia part of an acute illness or was it found on routine examination? If it was found on routine exam and the patient is not ill, making the diagnosis can be deliberative.
2. Are there previous blood cell counts (CBCs)? Establish if neutropenia is acute (days to weeks) or chronic (months to years).
3. What is the clinical context? A newborn? Possibly a reaction to a drug? Associated with cancer chemotherapy? Part of an ongoing autoimmune, infectious or inherited disease?
4. What clinical events have occurred-fevers, mouth ulcers, gingivitis, cellulitis, rectal ulcers, pneumonia, abscesses, and/or bacteremia? What is the frequency? Is there a pattern?
5. Do any family members have similar illnesses or symptoms?

II. Do a careful exam

1. Focus on evidence of infection in skin, respiratory tract, abdominal and perirectal area.
2. Determine if there is lymphadenopathy or hepatosplenomegaly
3. Examine carefully for congenital abnormalities.

III. Gather laboratory data

1. If neutropenia appears to be acute, see when counts were last normal and patterns of decline. If neutropenia may be chronic, get CBCs-back to early childhood. Usually 20 counts over a 40-50 day period are necessary to diagnose cyclic neutropenia.
2. Evaluate each hematological cell lineage-if counts are stable or drifting upward or downward. Neutropenia combined with anemia and/or thrombocytopenia suggests an autoimmune or infectious disease or perhaps a generalized marrow failure disorder. Neutropenia and thrombocytopenia are common with splenic enlargement. Neutropenia and lymphocytopenia occur in autoimmune diseases and idiopathic neutropenia. Severe neutropenia and lymphocytopenia occur in WHIM syndrome.
3. Review other laboratory data and imaging studies

IV. Form a provisional clinical diagnosis and give initial therapy

1. Examples are:
   a. Acute neutropenia associated with a new medication.
   b. Acute febrile neutropenia after cancer chemotherapy.

c. Newly recognized fever and severe neutropenia in infant.

d. Chronic mild neutropenia in asymptomatic adult woman.

2. If the patient is febrile and acutely ill, antibiotics; fluids, and urgent-usually hospital-care are required. I do not hesitate to recommend myeloid growth factor treatment, i.e., G-CSF, especially if the patient has not received it previously. (1-13)

3. If the patient is not acutely ill or has chronic neutropenia, consider out-patient antibiotics and a deliberative work-up. (1-13)

V. Make a specific diagnosis

1. Before a marrow exam: if the diagnosis is not known:

a. Consider anti-neutrophil antibody testing in children; it is generally not very helpful in adults. If ordered, it is very important to identify a specialized laboratory for this testing. Remember, positive test results may occur in patients with congenital as well as autoimmune neutropenia.(3-4)

b. Consider FACS analysis to identify a causal clonal hematological disease, e.g., large granular lymphocyte (LGL) syndrome.(8)

c. Consider antinuclear antibody tests. The ANA reflexive panel will help to identify patients with autoimmune diseases.

d. Consider measuring vitamin B12, folate and other vitamin levels; transcobalamin deficiency is a very rare cause of neutropenia. (2)

e. Consider genetic sequencing to identify mutations in genes associated with neutropenia. Mutations in *ELANE* are by far the most common cause of cyclic and congenital neutropenia. Use evidence of autosomal or recessive inheritance and clinical clues, i.e., cardiac or urogenital abnormalities suggest *G6PC3* mutation, malabsorption, short stature suggest Shwachman-Diamond syndrome, etc. Testing for a broad panel of genetic causes for neutropenia (*HAX1*, *G6PC3*, *WAS*, *SBDS*, etc.) are appropriate in children with no associated anomalies to guide testing or when a panel is less expensive than several individual tests.(2-7)

2. Marrow exam

a. A marrow exam is not routinely done for acute chemotherapy or drug associated neutropenia. It is also not necessary when patients have a long history of mild to moderate isolated neutropenia. It is very important to diagnose myelodysplasia, acute leukemia, severe neutropenia or generalized marrow failure

b. The differential cell count and cytogenetics are useful tests. In the congenital neutropenias, “maturation arrest” is the expected finding,

but it not always present, especially if the patient is ill when the test is performed.

Usually these tests are sufficient for making the diagnosis. If not and the patient is not very ill, it is best to observe at intervals of 3-6 months or refer.

VI. Make treatment plan-acute neutropenia

1. Broad spectrum antibiotics are the critical for acutely ill patients with severe neutropenia. The specifics depend on the patient's diagnosis, the severity of illness and the results of microbial cultures.(11-13)
2. The availability of G-CSF is the most important advance in the management of neutropenia. There are recent evidence based guidelines for prevention of infections associated with chemotherapy-induced neutropenia. (10, 13,14)

VII. Make treatment plan-chronic-neutropenia.

The use of G-CSF to prevent and treat infections in patients with severe chronic neutropenia differs significantly from the use of this myeloid growth factor for prevention of infection in patients with chemotherapy-induced neutropenia. My recommendations are:

1. For chronic neutropenia, the minimal criteria for G-CSF are: ANC repeatedly $<0.5 \times 10^9$/L with recurrent mouth ulcers and gum disease. The goal is to prevent pain and loss of permanent teeth. Recurrent fevers, cellulitis, abscesses, sinusitis, pneumonia, perirectal infections are stronger criteria for recommending long term G-CSF treatment.
2. The use of G-CSF for preventing infections in idiopathic, cyclic and congenital neutropenia is based on a randomized controlled trial. (15) Effective doses of G-CSF vary by diagnosis (expressed as mcg/kg/day and given daily, alternate day or three times per week): idiopathic: median 1.2; cyclic: median 2.4; congenital: 7.3. Patients with SCN presenting with a serious infection should be administered both G-CSF and antibiotics immediately.
3. Patients should be advised that the acute adverse events associated with initiation of G-CSF are primarily bone pain, arthralgias, myalgias, and headache with onset a few hours after the injections. (16) There are less common adverse events including thrombocytopenia, skin rash, injection site reactions, vasculitis, and glomerulonephritis. Decreased bone density and osteoporosis are also reported but pathological fractures are uncommon. (16) The potential for increasing the risk of myeloid leukemia should also be discussed with each patient. Severe congenital neutropenia patients have a high risk of evolving to MDS and AML. (17) Certain ELANE mutations appear to carry a much higher risk. (18)
4. For most patients with chronic neutropenia and infections, I recommend:

a. Start with a low daily dose of G-CSF. I recommend daily dose for idiopathic 1.0 mcg/kg/day, cyclic 2.0 mcg/kg/day, congenital 3.0 mcg/kg/day.

b. Use daily therapy initially, the advantage of daily treatment is to avoid or minimize bone pain and other acute adverse effects.

c. Switch to every other day on MWF schedule for good responders (daily dose 3mcg/kg/day or less).

d. If initial therapy is insufficient to reach target median count, increase dose by 1-2 mcg/kg/day at 1 to 2 week intervals; above 10 mcg/kg/day increase the dose by 3 to 5 mcg/kg/day to maximum dose of 20-30 mcg/kg/day. Consult with a neutropenia specialist in all non-responding or poorly responding patients to consider alternate strategies, including hematopoietic transplantation.

e. Monitor CBC at least weekly in the initial 2 months on treatment, at least once per month for the first six months and quarterly thereafter for stable patients.

f. For severe congenital neutropenia patients, evaluate with bone marrow aspirate and cytogenetics pre-treatment and annually. For others, consult with a neutropenia specialist.

g. Other than G-CSF, hematopoietic transplantation is the only other predictably effective treatment for congenital, cyclic or idiopathic neutropenia.

h. Patients with autoimmune neutropenia will respond to G-CSF, similar to idiopathic neutropenia.

Conclusions

Neutropenia is no longer the challenge it once was to clinicians. The greatest challenge now is to provide truly useful “point of care” information to clinicians, patients and families when they need it.

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Keypoints

- This paper provides a step-wise approach to making the diagnosis in patients presenting with neutropenia.
- Patients with fever and severe neutropenia should always have a careful exam and receive antibiotics as soon as possible.
- Patients with severe chronic neutropenia benefit from treatment with granulocyte colony stimulating factor (G-CSF); this review gives specific guidelines for treatment of these patients.