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AMPATHCHAT

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Approach to the neutropaenic patient

The extent of evaluation and the nature of intervention depends on duration, severity and clinical findings. The normal absolute neutrophil count (ANC) in adults is 1.5 to 7 x 10/9 per l. The following grading evolved from clinical experience with patients on cancer chemotherapy:

Grade		Risk
Mild	1–1.5	Does not impair host defense
Moderate	0.5–1	Mildly increased, especially if other components of the immune system are impaired
Severe	<0.5	Increased
	<0.2	Agranulocytosis with risk of severe life-threatening infections and increased susceptibility to opportunistic infections

OVERVIEW OF CAUSES AND DISTINGUISHING FEATURES

Congenital

1. Benign ethnic neutropaenia: especially common in Mediterranean and African ethnic groups as an isolated finding in an otherwise healthy individual. The ANC is generally >1 000 with no significant infection history. Patients do not benefit from extensive investigation in the absence of clinical signs and other FBC abnormalities.
2. Benign familial neutropaenia – hereditary with no ethnic predilection with features similar to above.
3. Severe congenital neutropaenia (SCN) – onset in infancy typified by agranulocytosis and recurrent sever infections. Results from inherited mutations in a number of neutrophil-specific genes. In the autosomal dominant type, there is selective myeloid impairment. Autosomal recessive inheritance has defects in several genes so that disease phenotype is expressed in a number of different tissues: myeloid, neurological, cardiac and urogenital. There is a 10 to 30% risk of transforming to myelodysplastic syndrome and acute myeloid leukaemia.
4. Cyclic neutroapenia (CyN) – with a varying two- to five-week periodicity, but tending to be consistent in an individual patient. Usually mild, but can complicate with infection and oral ulcers during nadir. No increased risk of haematological malignancies.
5. Other congenital syndromes, for example, Fanconis, Dyskeratosis congenital, myelokathexis, Chediak Higashi.

Acquired

1. Post-infectious – most common in children after viral infections. Mycobacteria, ricketssia and Brucela are the most common bacterial causes. Neutropaenia occurring with severe sepsis from any pathogen is due to depletion of marrow reserve and portends a grave outcome.
2. Drugs and toxins – complete review to include herbal, homeopathic and occupational exposure. Medications may cause dose-related neutropaenia, which is usually mild and of limited concern. Agranulocytosis is more likely to present as acute febrile illness. Early neutropaenia with drugs having a high rate of agranulocytosis warrants immediate cessation.
3. Diet – severe malnutrition, B12, folate and copper deficiency.
4. Neonatal alloimmune neutropaenia – transient neutropaenia due to fetal maternal neutrophil antigen incompatibility. Usually resolves by 6/52 as maternal antibody decays. Can occasionally persist up to six months or complicate with sepsis.
5. Chronic autoimmune neutropaenia of infancy and early childhood – moderate to severe neutropaenia most commonly detected during acute febrile illness and persists after recovery from illness. There are no signs of autoimmune disorders or constitutional syndromes. Usually resolves by three to five years. Persistence in the older child must provoke consideration of congenital immunological disorders like autoimmune lymphoproliferative syndrome or common variable immune deficiency.
6. Feltys Syndrome – triad of rheumatoid arthritis, splenomegaly and neutropaenia.

7. Large granulocytic lymphocytic leukaemia. May occur in setting of rheumatoid arthritis or as isolated entity.Diagnosis rests on detecting a clonal population of large granular lymphocytes (>0.5 x 10/9 l) with markers of activated T-cells or natural killer cells.
8. Chronic idiopathic neutropaenia (CIN) – discovered in adulthood and is a diagnosis of exclusion. Condition may be mild, moderate or severe with no phasic variations and persists up to three months. Recurrent fevers, upper respiratory tract infection and skin infections can complicate severe neutropaenia.
9. HIV – incidence varies from 10–50%, increasing in frequency with advancing age and therapeutic interventions. Mechanisms include decrease in growth factors normally produced by activated T lymphocytes and monocytes due to viral invasion of cells, bone marrow involvement by infectious agents and malignancy, ARVs.

MANAGEMENT

- Febrile neutropaenia = medical emergency. Oral temperature >38.5 or two consecutive readings >38 for 2 hours and absolute neutrophil count <0.5 or expected to fall below 0.5. Written policies especially in emergency department are critical for rapid response.
- Requires multidisciplinary care involving microbiologist and haematologist. Record and monitor temperature and cardio-respiratory parameters with immediate resuscitative parameters as necessary.
- Look for source of infection – complete ENT examination – document presence of mouth ulcers, gingivitis, periodontitis, pharyngitis, sinusitis and otitits.Careful systemic evaluation to include skin, perirectal and anal areas. Digital examination is contraindicated when ANC is 0.5.
- Acute abdominal pain raises the possibility of neutropaenic colitis.
- Take two sets of blood cultures from a peripheral vein and any indwelling catheter; sputum, urine, skin swabs and stool for culture. Initiate broad spectrum antibiotics, taking into account local bacterial isolates and resistance patterns. Hence the involvement of a microbiologist is critical.
- A stable afebrile patient can be investigated as an outpatient.

HISTORY AND EXAMINATION

- General health, growth and development, especially in children.
- Presence of constitutional symptoms.
- Associated disorder of other systems.
- Complete medication and toxin review (herbal, homeopathic, occupational)
- Any symptoms of collagen vascular disease.
- Infections – frequency, type, severity (hospital admission, antibiotics use)
- Family history – recurrent infection, morbidity, haematological malignancy, unexplained infant deaths.
- Lymphadenopathy, hepatosplenomegaly, bone pain.
- Complete ENT exam – mouth ulcers, gingivitis, periodontitis, pharyngitis.

LABORATORY INVESTIGATIONS

- Minimum of 3 FBC over period of 3/12 to determine severity and duration.
- Cyclic neutropaenia – FBC three times a week over 4–6 weeks.
- Discuss clinical findings with haematologist, who will guide selective testing.
- FBC – is neutropaenia isolated or accompanied by other disturbances. Peripheral smear-morphology – dysplastic changes. Presence of immature cells – left shift and blasts. Abnormal lymphocytes forms.
- HIV, ANF, rheumatoid factor; B12, folate.
- Bone marrow sampling, immunophenotyping, cytogenetics, depending on presentation and FBC findings.
- Antineutrophil antibody testing – limited utility outside of neonatal neutropaenia.
- Microbiology – as appropriate to clinical findings. May need to discuss with microbiologist regarding array of testing and antibiotic selection.

GENERAL PRINCIPLES

- Treat episodes of acute infection according to local guidelines.
- Specific management of associated underlying disorder, for example, autoimmune, haematological malignancy.
- Patients at risk of febrile neutropaenia should be counselled for immediate presentation at first sign of feeling unwell.
- Decrease risk of invasive fungal infection by avoiding contaminated sources – mulch, dusty construction sites, bird and animal waste.
- Manintain good dental hygiene
- Avoid crowded areas (viral initiated mucosal breach that will increase susceptibility for secondary bacterial infection).

ROLE OF GCSF

Should not be initiated on the basis of ANC alone in patients with congenital, cyclic and idiopathic neutropaenia. History of recurrent or severe infection, symptomatic mucosal erosisons or skin infections will warrant trial of therapy. Start with .5–3 ug per kg daily. Increase gradually to find the lowest effective dose and reduced frequency to maintain safe, incident-free count. No risk of haematological malignancy in this group.

In severe congenital neutropaenia, poor responders requiring more than 8 ug per kg daily have a greater risk of AML.

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