Standardized Approach in Children with Abnormal White Blood Count

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Leukopenia

Leukopenia - absolute decrease in the number of circulating leukocytes below 4000/μl.

Leukopenia may be caused by decrease in numbers of one or more specific leukocyte subgroups as a result of various causes.
Lymphocytopenia

Lymphocytopenia occurs relatively rarely.

The most frequent causes:

- **Infection**: Active tuberculosis, malaria
- **Collagen vascular disease**: Systemic lupus erythematosus, regional enteritis
- **Certain immunodeficiency syndromes**
- **Endocrine disorders**: Hyperadrenalism and adrenal corticosteroid administration
- **Hematologic and oncologic disorders**: Hodgkin’s disease, solid tumors (some), aplastic anemia
- **Excessive loss**: Thoracic duct drainage, intestinal lymphangiectasia
Neutropenia

Neutropenia - absolute decrease in the number of circulating neutrophils in blood

White race - lower normal limit:  
- 1000/μl infants
- 1500/μl > 1 year

Black race - lower normal limit: 600/μl

Mild neutropenia: 1000 - 1500/μl
Moderate neutropenia: 500 - 1000/μl
Severe neutropenia: < 500/μl
Normal blood leukocyte counts for children from birth to age 21 years

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Leukocytes</th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (Range)</td>
<td>Mean (Range)</td>
<td>%</td>
<td>Mean</td>
<td>Mean (%)</td>
</tr>
<tr>
<td>Birth</td>
<td>18.1 (9.0 to 30.0)</td>
<td>11.0 (6.0 to 26.0)</td>
<td>61</td>
<td>5.5 (2.0 to 11.0)</td>
<td>31</td>
</tr>
<tr>
<td>12 h</td>
<td>22.8 (13.0 to 38.0)</td>
<td>15.5 (6.0 to 28.0)</td>
<td>68</td>
<td>5.5 (2.0 to 11.0)</td>
<td>24</td>
</tr>
<tr>
<td>24 h</td>
<td>18.9 (9.4 to 34.0)</td>
<td>11.5 (5.0 to 21.0)</td>
<td>61</td>
<td>5.8 (2.0 to 11.5)</td>
<td>31</td>
</tr>
<tr>
<td>1 wk</td>
<td>12.2 (5.0 to 21.0)</td>
<td>5.5 (1.5 to 10.0)</td>
<td>45</td>
<td>5.0 (2.0 to 17.0)</td>
<td>41</td>
</tr>
<tr>
<td>2 wk</td>
<td>11.4 (5.0 to 20.0)</td>
<td>4.5 (1.0 to 9.5)</td>
<td>40</td>
<td>5.5 (2.0 to 17.0)</td>
<td>48</td>
</tr>
<tr>
<td>1 mo</td>
<td>10.8 (5.0 to 19.5)</td>
<td>3.8 (1.0 to 9.0)</td>
<td>35</td>
<td>6.0 (2.5 to 16.5)</td>
<td>56</td>
</tr>
<tr>
<td>6 mo</td>
<td>11.9 (6.0 to 17.5)</td>
<td>3.8 (1.0 to 8.5)</td>
<td>32</td>
<td>7.3 (4.0 to 13.5)</td>
<td>61</td>
</tr>
<tr>
<td>1 y</td>
<td>11.4 (6.0 to 17.5)</td>
<td>3.5 (1.5 to 8.5)</td>
<td>31</td>
<td>7.0 (4.0 to 10.5)</td>
<td>61</td>
</tr>
<tr>
<td>2 y</td>
<td>10.6 (6.0 to 17.0)</td>
<td>3.5 (1.5 to 8.5)</td>
<td>33</td>
<td>6.3 (3.0 to 9.5)</td>
<td>59</td>
</tr>
<tr>
<td>4 y</td>
<td>9.1 (5.5 to 15.5)</td>
<td>3.8 (1.5 to 8.5)</td>
<td>42</td>
<td>4.5 (2.0 to 8.0)</td>
<td>50</td>
</tr>
<tr>
<td>6 y</td>
<td>8.5 (5.0 to 14.5)</td>
<td>4.3 (1.5 to 8.0)</td>
<td>51</td>
<td>3.5 (1.5 to 7.0)</td>
<td>42</td>
</tr>
<tr>
<td>8 y</td>
<td>8.3 (4.5 to 13.5)</td>
<td>4.4 (1.5 to 8.0)</td>
<td>53</td>
<td>3.3 (1.5 to 6.8)</td>
<td>39</td>
</tr>
<tr>
<td>10 y</td>
<td>8.1 (4.5 to 13.5)</td>
<td>4.4 (1.8 to 8.0)</td>
<td>54</td>
<td>3.1 (1.5 to 6.5)</td>
<td>38</td>
</tr>
<tr>
<td>16 y</td>
<td>7.8 (4.5 to 13.0)</td>
<td>4.4 (1.8 to 8.0)</td>
<td>57</td>
<td>2.8 (1.2 to 5.2)</td>
<td>35</td>
</tr>
<tr>
<td>21 y</td>
<td>7.4 (4.5 to 11.0)</td>
<td>4.4 (1.8 to 7.7)</td>
<td>59</td>
<td>2.5 (1.0 to 4.8)</td>
<td>34</td>
</tr>
</tbody>
</table>

*Numbers of leukocytes are in thousands/mcL (×10⁹/L), ranges are estimates of 95% confidence limits, and percentages refer to differential counts. Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few postnatal days.

When should we suspect neutropenia?
When to order CBC in previously „healthy” child?

A CBC is warranted if clinical findings suggest a more severe bacterial infection:

⇒ Recurrent infections
⇒ Prolonged or extreme fever (>39.5°C)
⇒ The spreading of localized bacterial infection
⇒ Infection of the lung, peritoneum, genitourinary tract, or central nervous system
⇒ Suspicion of chronic inflammatory disease, immunodeficiency, or malignancy
⇒ When a patient’s clinical course is atypical, prolonged, or complicated
⇒ Secondary bacterial infection
Pyogenic infections associated with neutropenia

- ulcerations of the oral mucosa or gingival inflammation
- otitis media,
- skin infections that include cellulitis and pustules
- adenitis
- pneumonia
- bacterial sepsis
- perianal infection
- ischiorectal fossa abscesses
- the source of the infection may be the child’s own skin or bowel flora
- the most common offending organisms are *Staphylococcus aureus* and the gram-negative bacteria

Classification of neutropenia

Neutropenia caused by extrinsic factors

Infection
Drug-induced neutropenia
Autoimmune neutropenia
Chronic benign neutropenia
  (including chronic autoimmune neutropenia of childhood)
Neonatal immune neutropenia
Neutropenia associated with immune dysfunction
Neutropenia associated with metabolic diseases
Nutritional deficiencies
Reticuloendothelial sequestration
Bone marrow infiltration
Chronic idiopathic neutropenia
Infection-related neutropenia

Transient bone marrow suppression associated with various viral infections is the most frequent cause of mild-to-moderate neutropenia (cytomegalovirus, Epstein-Barr virus, hepatitis A and B, HIV, influenza A and B, measles, RS virus, parvovirus B19, rubella, and varicella, HHV6)

Neutropenia develops during the first 24 to 48 hours of the illness and may persist for 3 to 6 days

Severe bacterial infections (sepsis) may also cause neutropenia, resulting from excessive destruction of neutrophils and depletion of the bone marrow reserve pool.
# Drug-induced neutropenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Possible Mechanism</th>
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<tbody>
<tr>
<td></td>
<td>Direct Suppression</td>
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<tr>
<td><strong>Analgesics/Anti-inflammatory Agents</strong></td>
<td></td>
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<tr>
<td>Aminopyrine</td>
<td></td>
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<tr>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>X</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>X</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>X</td>
</tr>
<tr>
<td>Penicillins</td>
<td>X</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>X</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
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<tr>
<td>Phenytoin</td>
<td></td>
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<tr>
<td>Carbamazepine</td>
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<tr>
<td><strong>Antithyroid Agents</strong></td>
<td></td>
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<tr>
<td>Propylthiouracil</td>
<td></td>
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<tr>
<td><strong>Cardiovascular Agents</strong></td>
<td></td>
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<tr>
<td>Hydralazine</td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoglycemic Agents</strong></td>
<td></td>
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<tr>
<td>Chlorpropamide</td>
<td></td>
</tr>
<tr>
<td><strong>Tranquilizers</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>X</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>X</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Cimetidine, ranitidine</td>
<td>X</td>
</tr>
<tr>
<td>Levamisole</td>
<td></td>
</tr>
</tbody>
</table>
Neonatal alloimmune neutropenia

Immunologic disorder analogous to Rh hemolytic disease, resulting from maternal sensitization to fetal neutrophils bearing antigens that differ from the mother’s

Maternal IgG antibodies cross the placenta and result in an immune-mediated neutropenia that can be severe and last from several weeks to as long as 6 months.

Treatment with G-CSF, starting at 5 to 10 μg/kg/day intravenously, should be considered for very profound neutropenia or when serious infections develop.
Autoimmune Neutropenia of Childhood

- Most common cause of chronic neutropenia in infancy and childhood;
- Incidence ≥1 per 100,000 children per year;
- Median age at diagnosis, 8-11 months (range, 3-38 months).
- Slight female preponderance;
- The initial ANC often in the severe range (<200 cells/μL) and may approach zero.
- Anti-neutrophil antibodies can be detected in majority of patients and are often directed to the NA1 antigen (neutrophil FcγIII receptor).
Bone marrow in autoimmune neutropenia

Increased cellularity, myeloid hyperplasia

Relatively low numbers of mature granulocytes (segments)

Autoimmune Neutropenia of Childhood

Therapy:
• antibiotics for acute infection;
• G-CSF in the event of serious infection or very high frequency of minor infections;
• prophylactic antibiotics may be helpful in some patients with recurrent otitis media.

Excellent prognosis: although the ANC often remains below 500 cells/μL for 12 or more months, spontaneous remission occurs in almost all patients (median, 20 months; range, 6-54 months)
Neutropenia Caused by Intrinsic Defects in Granulocytes or Their Progenitors

- Reticular dysgenesis
- Severe congenital neutropenia (including Kostmann’s syndrome)
- Cyclic neutropenia
- Myelokathexis/WHIM syndrome
- Shwachman-Diamond syndrome
- Albinism/neutropenia syndromes (including Chédiak-Higashi)
- Familial benign neutropenia
- Bone marrow failure syndromes (congenital and acquired)
Cyclic neutropenia

- sporadic or autosomal dominant disorder characterized by regular periodic oscillations approximately every 21 days in the number of peripheral blood neutrophils, with a nadir of less than 200 cells/μL
- symptoms typically begin during the first year of life but may not commence until adulthood
- during the neutropenic nadir of each cycle, patients may suffer malaise, fever, oral ulcers, gingivitis, periodontitis, and pharyngitis associated with lymph node enlargement.
- improvement in symptoms as patients grow older
- although cyclic neutropenia is frequently viewed as a benign condition, 10% of patients in historical reviews have died of infectious complications.
Cyclic neutropenia and the response to clinical administration of G-CSF

Severe Congenital Neutropenia

- first described by Kostmann in 1956 as an autosomal recessive disorder associated with severe neutropenia
- incidence of 1-2 cases per million population
- patients generally maintain ANC$ s$ of less than 200 cells/µL, which has been documented on the first day of life in several cases
- frequent episodes of fever, skin infections (including omphalitis), stomatitis, pneumonia, and perirectal abscesses typically appear during the first months of life
- infections often disseminate to the blood, meninges, and peritoneum and are usually caused by *S. aureus*, *Escherichia coli*, and *Pseudomonas* species
Bone marrow in severe congenital neutropenia

Normal or slightly decreased cellularity

Maturation arrest of neutrophil precursors at an early stage (promyelocyte/myelocyte level)

Promyelocytes often have morphologically atypical nuclei and vacuolization of the cytoplasm

Welte K et al. Semin Hematol. 2006; 43: 189-195
ELANE gene mutations in severe congenital neutropenia and cyclic neutropenia

- 60% of SCN cases derives from mutations in the *ELANE* (*ELA2*) gene, which encodes neutrophil elastase - *ELA2*-related SCN may be sporadic or inherited in an autosomal dominant mendelian pattern

- The precise cellular mechanisms by which mutant *ELA 2* causes neutropenia are uncertain (mutant *ELA 2* triggers accelerated apoptosis of developing neutrophil precursors ???)

HAX1 gene mutations in Kostmann syndrome

Severe congenital neutropenia - treatment

• More than 95% SCN patients respond to rHuG-CSF treatment with an increase in ANCs to 1.0 × ≥10⁹/L
• Most SCN patients respond to a dose between 3 and 10 μg/kg/d
• After initiation of rHuG-CSF at 5 μg/kg/d, the dose should be escalated to 10 μg/kg/d and then by increments of 10 μg/kg at 14-day intervals if the ANC remains below 1.0 × 10⁹/L.
• The dose of rHuG-CSF can be reduced if the ANC increases to ≥5.0 × 10⁹/L
• Non-responders to rHuG-CSF are defined by failure to benefit at dose levels exceeding 120 μg/kg/d - HSCT is the only currently available treatment
The cumulative incidence of myelodysplastic syndrome or acute myeloid leukemia in congenital neutropenia patients

## Genetic Aberrations Causing Congenital Neutropenia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genetic Defect</th>
<th>Recessive (R-CN)</th>
<th>Dominant (D-CN)</th>
<th>Neutropenia Plus:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital neutropenia with <em>ELA2</em> mutations*</td>
<td><em>ELA2</em></td>
<td>−</td>
<td>+</td>
<td>Preleukemic syndrome</td>
</tr>
<tr>
<td>Congenital neutropenia with <em>GFI-1</em> mutation</td>
<td><em>GFI-1</em></td>
<td>−</td>
<td>+</td>
<td>B-/T-cell deficiency</td>
</tr>
<tr>
<td>WHIM syndrome</td>
<td><em>CXCR4</em></td>
<td>−</td>
<td>+</td>
<td>Myelokathexis, IgG deficiency, warts</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td><em>SBDS</em></td>
<td>+</td>
<td>−</td>
<td>Exocrine pancreas insufficiency</td>
</tr>
<tr>
<td>Glycogen storage disease, type Ib</td>
<td><em>Glucose-6-phosphate-Translocase</em></td>
<td>+</td>
<td>−</td>
<td>Hypoglycemia, lactic acidosis</td>
</tr>
<tr>
<td>Hyper IgM</td>
<td><em>CD40-L</em></td>
<td>X-linked</td>
<td>−</td>
<td>IgG, IgA, IgE deficiency</td>
</tr>
<tr>
<td>Barth syndrome (3-methylglutaconic aciduria)</td>
<td><em>Taz 1</em></td>
<td>X-linked</td>
<td>−</td>
<td>Dilatative cardiomyopathy, skeletal myopathy, short stature,</td>
</tr>
<tr>
<td>Congenital neutropenia with WASP mutation</td>
<td><em>WASP</em></td>
<td>X-linked</td>
<td>−</td>
<td>Monocytopenia, platelets normal</td>
</tr>
<tr>
<td>Hermansky-Pudlak syndrome</td>
<td><em>AP3B1</em></td>
<td>+</td>
<td>−</td>
<td>Partial albinism, short stature, IgG deficiency, platelet dysfunction</td>
</tr>
<tr>
<td>Congenital neutropenia with <em>p14</em> (MAPBPPIP) mutation</td>
<td><em>P14/MAPBPPIP</em></td>
<td>+</td>
<td>−</td>
<td>Partial albinism, short stature, IgG deficiency</td>
</tr>
<tr>
<td>Griscelli syndrome</td>
<td><em>Rab27a</em></td>
<td>+</td>
<td>−</td>
<td>Partial albinism, hemaphagocytosis</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td><em>LYST (CHS1)</em></td>
<td>+</td>
<td>−</td>
<td>Partial albinism, T-/natural killer cytotoxicity and chemotaxis defect</td>
</tr>
<tr>
<td>Congenital neutropenia (unclassified)</td>
<td>Not known</td>
<td>+</td>
<td>?</td>
<td>Elevated IgG levels</td>
</tr>
</tbody>
</table>

*Welte K et al. Semin Hematol. 2006; 43: 189-195*
Initial Evaluation for Patients Who Have Neutropenia

History

• underlying disease associated with neutropenia
• congenital anomalies
• medication exposure
• recent infection
• mouth ulceration
• other family members who have neutropenia and serious infections, hospitalizations, or blood diseases

Physical Examination

• short stature, malnutrition, skeletal abnormalities
• abnormal skinpigmentation, dystrophic nails,
• leukoplakia, warts, albinism, fine hair, eczema, skin
• infections
• lymphadenopathy, organomegaly

Initial Evaluation for Patients Who Have Neutropenia cd.

CBC With Differential Count and Reticulocyte Percentage
- confirming the finding of neutropenia
- evaluation of neutrophil morphology
- assessment whether red cell production is increased or decreased
- if the neutropenia resolves and is recurrent, repeat two to three times per week for 6 weeks

Other laboratory tests
- Blood smear
- Coombs test (direct antiglobulin test) for associated hemolytic anemia
- Immunoglobulins (IgA, IgG, IgM)
- Serology (Epstein-Barr virus, cytomegalovirus, respiratory syncytial virus, parvovirus, etc, as indicated clinically)
- Anti-neutrophil antibodies

### Detailed Laboratory Evaluation of Neutropenia

<table>
<thead>
<tr>
<th>Test</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC and Differential Count</td>
<td>ANC less than lower limit for age (Table 1) ± anemia and thrombocytopenia</td>
</tr>
<tr>
<td>Reticulocyte % (Index)</td>
<td>Increased if RBC destruction, as in Evans syndrome (or bleeding)</td>
</tr>
<tr>
<td></td>
<td>Decreased in marrow failure syndromes</td>
</tr>
<tr>
<td>Blood Smear</td>
<td>Confirms decreased ANC</td>
</tr>
<tr>
<td></td>
<td>Morphologic abnormalities of neutrophils, as in Chediak–Higashi syndrome</td>
</tr>
<tr>
<td></td>
<td>Associated RBC or platelet findings</td>
</tr>
<tr>
<td>Coombs Test (Direct Antiglobulin Test)</td>
<td>Detects antibodies to RBC, as in Evans syndrome or systemic lupus erythematosus</td>
</tr>
<tr>
<td>ANA Anti-double-stranded DNA</td>
<td>Screen for systemic lupus erythematosus</td>
</tr>
<tr>
<td>Antineutrophil Antibody</td>
<td>May be found in alloimmune or autoimmune neutropenia</td>
</tr>
<tr>
<td>IgG, IgA, IgM</td>
<td>Screen for underlying immunodeficiency</td>
</tr>
<tr>
<td></td>
<td>IgG and IgA may be decreased and IgM elevated</td>
</tr>
<tr>
<td>Lymphocyte Subtypes</td>
<td>Decreased T, B, or NK cells in underlying immunodeficiency</td>
</tr>
<tr>
<td>Marrow Examination</td>
<td>May show no maturation beyond the promyelocyte stage in severe congenital neutropenia; myeloid hyperplasia with few or no bands or mature neutrophils in immune neutropenia. Cytogenetics may reveal a neoplastic clone, as in leukemia. Specific for genetic diagnosis—see Table 6 for specific genes.</td>
</tr>
<tr>
<td>DNA Analysis <em>(HAX1, ELA2, Gfi1)</em> <em>(FANC, DKC, RPS19)</em></td>
<td>Low serum trypsinogen and elevated stool fat found in Shwachman-Diamond syndrome. Serum vitamin B₁₂, RBC, and serum folic acid.</td>
</tr>
</tbody>
</table>

ANA = antinuclear antibody, ANC = absolute neutrophil count, CBC = complete blood count, RBC = red blood cell.
# Treatment of neutropenia

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocyte Colony-stimulating Factor</td>
<td>Initially 5 mcg/kg per day subcutaneously. If no response after 1 wk, the dose may be doubled repeatedly up to 100 mcg/kg per day.</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Prednisone 2 mg/kg per day PO for immune neutropenia.</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; 1,000 mcg each week for 5 to 6 wk, then q 1 mo subcutaneously if B&lt;sub&gt;12&lt;/sub&gt;-deficient. Folic acid 1 mg/d PO.</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Prior immunization to encapsulated bacterial (pneumococcus, Haemophilus influenzae type b, meningococcus) required. Prophylactic penicillin after splenectomy 125 mg bid &lt;age 5 y; 250 mg bid ≥age 5 y.</td>
</tr>
<tr>
<td>Medication Revision</td>
<td>If possible, reduce dosage or discontinue any medications associated with neutropenia.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>As appropriate for patient's age, type and location of infection, and if possible, culture results.</td>
</tr>
<tr>
<td>Granulocyte Transfusion</td>
<td>May be useful in invasive bacterial or fungal infections for patients who have severe neutropenia (ANC &lt;500/mcL [0.5×10&lt;sup&gt;9&lt;/sup&gt;/L]) who are not responding to antibiotics.</td>
</tr>
</tbody>
</table>
# Fever and neutropenia

<table>
<thead>
<tr>
<th>ANC</th>
<th>Etiology of Fever</th>
<th>Management</th>
<th>Outpatient/Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 to 1,500/mcL</td>
<td>Viral (frequent)</td>
<td>Supportive</td>
<td>Outpatient</td>
</tr>
<tr>
<td>(1.0 to 1.5×10⁹/L)</td>
<td>Bacterial: URI (sinusitis, purulent rhinitis, otitis media, local skin infections)</td>
<td>Indicated PO antibiotics</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Mild</td>
<td>Bacterial pneumonia, systemic symptoms, GU infections, lymphadenitis</td>
<td>Blood cultures</td>
<td>Outpatient unless progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specific cultures</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Best estimate antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observation for progression</td>
<td></td>
</tr>
<tr>
<td>500 to 1,000/mcL</td>
<td>Viral</td>
<td>Supportive</td>
<td>Outpatient/Hospital*</td>
</tr>
<tr>
<td>(0.5 to 1.0×10⁹/L)</td>
<td>Bacterial: URI (sinusitis, purulent rhinitis, otitis media, local skin infections)</td>
<td>Blood and other cultures</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>Indicated PO or IV antibiotics</td>
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</tr>
<tr>
<td></td>
<td>Bacterial pneumonia, systemic symptoms, GU infections, lymphadenitis</td>
<td>Blood cultures</td>
<td>Hospital</td>
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<td></td>
<td></td>
<td>Specific cultures</td>
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<td>Sepsis evaluation</td>
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<td></td>
<td>Parenteral broad-spectrum antibiotics</td>
<td></td>
</tr>
<tr>
<td>&lt;500/mcL</td>
<td>Assume bacterial</td>
<td>Blood cultures</td>
<td>Hospital</td>
</tr>
<tr>
<td>(0.5×10⁹/L) Severe</td>
<td></td>
<td>Specific cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis evaluation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parenteral broad-spectrum antibiotics</td>
<td></td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count, GU = genitourinary, IV = intravenous, PO = oral, URI = upper respiratory tract infection.
Leukocytosis

Leukocytosis – increase of a total white blood count above 2 standard deviations in relation to average leukocyte count for particular child age.

Leukocytosis may be acute or chronic and may result from an increase in one or more specific classes of leukocytes.
Leukocytosis

Physiologic
Newborn (maximal 38 000/mm³)
Strenuous exercise
Emotional disorders; fear, agitation
Ovulation, labor, pregnancy

Acute infections (Bacterial, viral, fungal, protozoal, spirochetal)

Metabolic causes (Diabetic coma, Acidosis, Anoxia, Azotemia, Thyroid storm, Acute gout, Burns, Seizures)

Drugs (Steroids, Epinephrine, Endotoxin, Lithium, Ranitidine, Serotonin, Histamine, Heparin, Acetylcholine)

Poisoning (Lead, Mercury, Camphor)

Acute hemorrhage

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Leukocytosis cd.

Malignant neoplasms (Carcinoma, Sarcoma, Lymphoma)

Connective tissue diseases (Rheumatic fever, Rheumatoid arthritis, Inflammatory bowel disease)

Hematologic diseases
- Splenectomy, functional asplenia
- Leukemia and myeloproliferative disorders
- Hemolytic anemia
- Transfusion reaction
- Infectious mononucleosis
- Megaloblastic anemia during therapy
- Postgranulocytosis
Acute Lymphoblastic Leukemia (ALL)
B-cell precursor acute lymphoblastic leukemia - common-ALL

<table>
<thead>
<tr>
<th>Population</th>
<th>%Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>blasty</td>
<td>59.0</td>
</tr>
<tr>
<td>lymphocyte B</td>
<td>9.0</td>
</tr>
</tbody>
</table>
Neutrophilia

Increased production

Clonal disease
- Myeloproliferative disorders
- Chronic myelogenous leukemia
- Chronic neutrophilic leukemia
- Juvenile myelomonocytic leukemia
- Transient myeloproliferative disorder of Down syndrome

Hereditary
- Autosomal dominant form of hereditary neutrophilia
- Familial cold urticaria
Chronic Myeloid Leukemia (CML)
Neutrophilia cd.

Increased production

Reactive

Chronic infection
Chronic inflammation
Juvenile rheumatoid arthritis
Inflammatory bowel disease
Kawasaki disease
Hodgkin lymphoma
Drugs: Lithium, G-CSF, GM-CSF,
    chronic use of corticosteroids
Leukemoid reaction
Chronic idiopathic neutrophilia
Neutrophilia cd.

Increased mobilization from marrow storage pool

**Drugs**: Corticosteroids, G-CSF

**Stress**
- Acute infection
- Hypoxia

**Decreased Margination**
- Exercise
- Epinephrine

**Decreased egress from circulation**

**Leukocyte adhesion deficiency (LAD)**
- LAD type I: deficiency of CD11 / CD18 integrins on leukocytes
- LAD type II: absence of neutrophil sialyl Lewis X structures

**Asplenia**
Eosinophilia

**Allergic disorders**
Asthma, hay fever, urticaria, drug hypersensitivity

**Immunologic disorders**
Omenn syndrome (SCID and eosinophilia)

**Skin disorders**
Eczema, scabies, erythema toxicum, dermatitis herpetiformis, angioneurotic edema, pemphigus

**Parasitic infestations**
Helminthic: Ascaris lumbricoides, trichinosis, echinococciosis, visceral larva migrans, hookworm, strongyloidiasis, filariasis
Protozoal: malaria, pneumocystis, toxoplasmosis

**Hematologic disorders**
Hodgkin disease, postsplenectomy state, eosinophilic leukemoid reaction, congenital immune deficiency syndromes, Fanconi anemia, thrombocytopenia with absent radii, Kostmann disease, infectious mononucleosis, familial reticuloendotheliosis
Eosinophilia cd.

**Familial eosinophilia**

**Irradiation**

**Pulmonary eosinophilia**

Eosinophilic pneumonitis (Loeffler syndrome), pulmonary eosinophilia with asthma, tropical eosinophilia

**Miscellaneous**

Idiopathic hypereosinophilic syndrome, periarteritis nodosa, metastatic neoplasm, cirrhosis, peritoneal dialysis, chronic renal disease, Goodpasture syndrome, sarcoidosis, thymic disorders, hypoxia

**Gastrointestinal disorders**

Eosinophilic gastroenteritis, milk precipitin disease, ulcerative colitis, protein-losing enteropathy, regional enteritis, allergic granulomatosis

**Idiopathic**

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Lymphocytosis

Physiologic: 4 months–4 years

Infections

Acute

Moderate lymphocytosis: measles, rubella, varicella, mumps, roseola infantum, brucellosis, typhoid, paratyphoid, autoimmune diseases, granulomatous diseases, postimmunization states, drug reactions, graft rejection

Marked lymphocytosis: infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, pertussis

Chronic

Tuberculosis, syphilis

Leukemia: acute lymphoblastic leukemia
Atypical lymphocytes in infectious mononucleosis

From B Bain Interactive Haematology Image Bank
Atypical Lymphocytosis

Less than 20%

Infections

Bacterial: brucellosis, tuberculosis
Viral: mumps, varicella, rubeola, rubella, atypical pneumonia, herpes simplex, herpes zoster, roseola infantum, HIV
Protozoal: toxoplasmosis
Rickettsial: rickettsialpox
Spirochetal: congenital syphilis, tertiary syphilis

Radiation

Miscellaneous

Hematologic: Langerhans cell histiocytosis, leukemia, lymphoma, agranulocytosis
Other: lead intoxication, stress

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Atypical Lymphocytosis

More than 20%

- Infectious mononucleosis
- Infectious hepatitis
- Post-transfusion syndrome
- Cytomegalovirus syndrome
- Drug hypersensitivity: p-aminosalicylic acid, phenytoin, mephenytoin, organic arsenicals

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Monocytosis

Hematologic disorders
Leukemia
Acute myelogenous leukemia
Chronic myelogenous leukemia
Lymphoma (Hodgkin and non-Hodgkin)
Chronic neutropenia
Histiocytic medullary reticulosis
Recovery from myelosuppressive chemotherapy

Connective tissue disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Myositis

Granulomatous diseases
Inflammatory bowel disease
Sarcoidosis

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Monocytosis

**Infections**
- Subacute bacterial endocarditis
- Tuberculosis
- Syphilis
- Rocky Mountain spotted fever
- Kala-azar

**Malignant disease** (usually carcinomas)

**Miscellaneous disorders**
- Postsplenectomy state
- Tetrachlorethane poisoning
- Lipoidoses (e.g., Niemann–Pick disease)
Thank you for your attention!!!