

## Agranulocytosis

Agranulocytosis is characterized by a greatly decreased number of circulating neutrophils. Severe neutropenia is the term usually applied to patients with fewer than 500 neutrophils per micro liter (including bands). Agranulocytosis usually refers to patients with fewer than 100 neutrophils per micro liter.

The reduced number of neutrophils makes patients extremely vulnerable to infection. Cardinal symptoms include fever, sepsis, and other manifestations of infection.

Causes can include drugs, chemicals, infective agents, ionizing radiation, immune mechanisms, and heritable genetic aberrations.

### Pathophysiology

Agranulocytosis may be broadly divided into:

- Hereditary disease due to genetic mutations
- Acquired disease

### Hereditary disease due to genetic mutations

Many of these disorders are due to mutations in the gene encoding neutrophil elastase, or *ELA2*. Several alleles are involved. The most common mutations are intronic substitutions that inactivate a splice site in intron 4. Genes other than *ELA2* are also involved.

The Table summarizes the genetic conditions; these are uncommon conditions. A strong family history of recurrent infections, usually beginning in childhood, is strongly indicative of a genetic defect.

#### Genetic Conditions in Agranulocytosis

Syndrome	Inheritance	Gene	Clinical Features
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Cyclic neutropenia	Autosomal dominant	<i>ELA2</i>	Alternate 21-d cycling of neutrophils and monocytes
Kostman syndrome	Autosomal recessive	Unknown	Stable neutropenia, no MDS or AML
Severe congenital neutropenia	Autosomal dominant	<i>ELA2</i> (35-84%)	Stable neutropenia, MDS or AML
	Autosomal dominant	<i>Gfi1</i>	Stable neutropenia, circulating myeloid progenitors, lymphopenia
	Sex linked	<i>Wasf</i>	Neutropenic variant of Wiskott-Aldrich syndrome
	Autosomal dominant	<i>G-CSFR</i>	G-CSF refractory neutropenia, no AML or MDS
Hermansky-Pudlak syndrome type 2	Autosomal recessive	<i>AP3B1</i>	Severe congenital neutropenia, platelet dense-body defect, oculocutaneous albinism
Chadiak-Higashi syndrome	Autosomal recessive	<i>LYST</i>	Neutropenia, oculocutaneous albinism, giant lysosomes, impaired platelet function
Barth syndrome	Sex linked	<i>TAZ</i>	Neutropenia, often cyclic; cardiomyopathy, methylglutaconic aciduria
Cohen syndrome	Autosomal recessive	<i>COH1</i>	Neutropenia, mental retardation, dysmorphism

Source: Modified from Berliner et al, 2004.

Note: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome.

### Acquired disease

Acquired disease may be due to drugs, chemicals, autoimmunity, infectious agents, or other causes.

Bone marrow and peripheral blood is the organ systems affected. The condition is characterized by inadequate production of neutrophils, excessive destruction of neutrophils, or both. The resulting infections tend to involve the oral cavity, mucous membranes, and skin. Systemic life-threatening sepsis may ensue. The most common infecting organisms are staphylococci, streptococci, gram-negative organisms, and anaerobes. Fungi are also commonly involved as secondary infective agents.

The occurrence of infection depends on the degree and duration of neutropenia. When the ANC is persistently fewer than 100/mcL for longer than 3-4 weeks, the incidence of infection approaches 100%.

The estimated frequency is 1.0-3.4 cases per million population per year.

#### Mortality/Morbidity

- If untreated, the risk of dying is high. Death results from uncontrolled sepsis.
- If the condition can be reversed with treatment, the risk of dying is low. Antibiotic and antifungal medications can cure the infection if the ANC rises.
- Morbidity is entirely due to infections that complicate agranulocytosis. The infections may be superficial, involving mainly the oral mucosa, gums, skin, and sinuses, or they may be systemic, with life-threatening septicemia.

The condition has no racial predilection.

Agranulocytosis occurs slightly more frequently in women than in men, possibly because of their increased rate of medication usage.

Whether this higher frequency is related to the increased incidence of autoimmune disease in women is unknown.

### Age

- The disease occurs in all age groups.
- The congenital forms are most common in childhood
- Acquired agranulocytosis is most common in the elderly population

### History

Patients with agranulocytosis usually present with the following:

- Sudden onset of malaise
- Sudden onset of fever, possibly with chills and prostration
- Stomatitis and periodontitis accompanied by pain
- Pharyngitis with difficulty in swallowing
- If treatment is not promptly instituted, the infection progresses to generalized sepsis, which may become life threatening.
- The most commonly involved organisms are from endogenous flora.
  - *Staphylococcus aureus* organisms are found in cases of skin infections.
  - Gram-negative organisms are observed in infections of the urinary and gastrointestinal tracts, particularly *Escherichia coli* and *Pseudomonas* species. *Candida albicans* infections may also occur.
  - Mixed flora may be found in the oral cavity.
- Patients often report a history of a new drug being used or a recent change in medication. However, the offending medication may no longer be in use; therefore, the inquiry should extend back for some time.

- Occupational or accidental exposure to chemicals or physical agents (eg, ionizing radiation) may have occurred.
- The patient may have experienced a recent viral infection, although such infections are rarely associated with severe neutropenia. Certain bacterial infections may also precede agranulocytosis.
- A history of periodically recurring infections is suggestive of cyclic neutropenia.
- A history of autoimmune diseases may be associated with antineutrophil antibodies. Such antibodies may also be the only manifestation of autoimmune disease. A number of test methods are available, but none is widely used.
- Primary immune neutropenia is uncommon.
- Secondary immune neutropenia may be associated with systemic lupus erythematosus, rheumatoid arthritis, and Felty syndrome.
- A strong family history of recurrent infections, usually beginning in childhood, is strongly indicative of a genetic defect.

## Physical

- Fever (temperature often 40°C or higher)
- Rapid pulse and respiration
- Hypotension and signs of septic shock if infection has been present
- Painful aphthous ulcers may be found in the oral cavity
- Swollen and tender gums
- Usually, purulent discharge is not present because not enough neutrophils exist to form pus
- Skin infections are associated with painful swelling, but erythema and suppuration are usually absent.

## Causes

The most common cause is exposure to drugs or chemicals.

Any chemical or drug that can depress the bone marrow and cause hypoplasia or aplasia is capable of causing agranulocytosis. Some drugs do this to everyone if they are administered in large enough doses. Other agents seem to cause idiosyncratic reactions that affect only certain susceptible individuals.

The mechanisms that cause neutropenia are not completely understood. In many cases, neutropenia occurs after prolonged exposure, resulting in decreased neutrophil production by hypoplastic bone marrow. In other cases, repeated but intermittent exposure is needed. This suggests an immune mechanism, although this idea has not been proven.

A drug may act as a hapten and induce antibody formation. This mechanism operates in cases due to gold, aminopyrine, and antithyroid drugs. The antibodies destroy the granulocytes and may not require the continued presence of the drug for their action. As an alternative, the drug may form immune complexes that attach to the neutrophils. This mechanism operates with quinidine.

Another mechanism is direct inhibition of myelopoiesis. Valproic acid, carbamazepine, and betalactam antibiotics act by this mechanism. In bone marrow cultures, these agents inhibit granulocyte colony formation in a dose-related fashion.

Direct damage to the bone-marrow microenvironment or myeloid precursors plays a role in most other cases.

Many drugs associated with agranulocytosis have been reported to the US Food and Drug Administration (FDA) under its adverse reactions reporting requirement. Many are also reported to a registry maintained by the American Medical Association. The reported drugs were used alone, in combination with another drug known to be potentially toxic, or with another drug without known toxicity.

Several drugs are salient because of their high frequency of association with agranulocytosis. They include the following:

- Phenothiazines
  - Antithyroid drugs (thiouracil and propylthiouracil)
  - Aminopyrine
  - Phenylbutazone
  - Chloramphenicol
  - Sulfonamides
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- Drugs reported to be associated with agranulocytosis include the following:
    - Analgesics
      - Acetaminophen
      - Aminopyrine
      - Dipyrone
    - Cardiovascular drugs
      - Captopril
      - Hydralazine
      - Methyldopa
      - Pindolol
      - Procainamide
      - Propranolol
      - Quinidine
    - Antibiotics
      - Cephalosporins
      - Clindamycin
      - Chloramphenicol
      - Doxycycline
      - Gentamicin
      - Griseofulvin
      - Isoniazid
      - Metronidazole
      - Nitrofurantoin
      - Penicillins
      - Rifampin

- Streptomycin
- Sulfonamides
- Vancomycin
- Diuretics
  - Acetazolamide
  - Bumetanide
  - Chlorothiazide
  - Hydrochlorothiazide
  - Chlorthalidone
  - Methazolamide
  - Spironolactone
- Anticonvulsants
  - Carbamazepine
  - Mephenytoin
  - Phenytoin
  - Primidone
  - Trimethadione
- Hypoglycemic agents
  - Chlorpropamide
  - Tolbutamide
- Antihistamines
  - Brompheniramine
  - Cimetidine
  - Tripeleminamine
  - Ranitidine
  - Thenalidine
- Phenothiazines
  - Chlorpromazine
  - Clozapine
  - Desipramine
  - Prochlorperazine
  - Promazine
  - Thioridazine
  - Trifluoperazine
  - Trimeprazine
- Anti-inflammatory drugs



- Fenoprofen
- Gold salts
- Ibuprofen
- Indomethacin
- Phenylbutazone
- Neuropharmacologic agents
  - Chlordiazepoxide
  - Clozapine
  - Desipramine
  - Meprobamate
  - Metoclopramide
  - Prochlorperazine
  - Promazine
- Antimalarials
  - Amodiaquine
  - Dapsone
  - Hydroxychloroquine
  - Pyrimethamine
  - Quinine
- Miscellaneous drugs
  - Allopurinol
  - Colchicine
  - D-Penicillamine
  - Ethanol
  - Levamisole
  - Levodopa
- Antithyroid agents
  - Carbimazole
  - Methylthiouracil
  - Propylthiouracil

Viral infections often lead to mild or moderate neutropenia. Agranulocytosis is uncommon but may occur. The most common organisms are Epstein-Barr virus, hepatitis B virus, yellow fever virus, cytomegalovirus, and influenza.

Many overwhelming infections, both viral and bacterial, may cause severe neutropenia.

Autoimmune neutropenia is the neutrophil analog of autoimmune hemolytic anemia and of idiopathic thrombocytopenic neutropenia. It should be considered in the absence of any of the common causes. Antineutrophil antibodies have been demonstrated in these patients.

Cyclic neutropenia is characterized by periodic bouts of agranulocytosis associated with infection.

- Cyclic neutropenia has a periodicity of about 21 days (range, 12-35 d).
- Granulocyte precursors disappear from the marrow before each neutrophil nadir in the cycle because of accelerated apoptosis of myeloid progenitor cells.
- Some cases may be genetically determined with an autosomal recessive inheritance. Other cases may be due to an autosomal dominant inheritance.

Several uncommon causes of severe neutropenia include Kostmann syndrome, chronic severe neutropenia, and myelokathexis.

- Kostmann syndrome (severe congenital neutropenia) is most often caused by a recessive inheritance and found in remote, isolated populations with a high degree of consanguinity. Autosomal dominant and sporadic cases have also been reported, most often due to mutations in the granulocyte colony-stimulating factor (G-CSF) receptor. A risk of conversion to (M/acute monocytic leukemia (MDS/AML) with monosomy 7 exists after treatment with G-CSF.
- Chronic severe neutropenia has an underlying unknown cause.
- Myelokathexis occurs in early infancy and is associated with recurrent infections. The condition is due to

accelerated apoptosis and decreased expression of *bcl-x* in neutrophil precursors.

## **Acquired Agranulocytosis**

### **Synonyms**

- Agranulocytic Angina
- Granulocytopenia, Primary
- Neutropenia, Malignant

### **General Discussion**

Acquired agranulocytosis is a rare, drug-induced blood disorder that is characterized by a severe reduction in the number of white blood cells (granulocytes) in the circulating blood. The name granulocyte refers to grain-like bodies within the cell. Granulocytes include basophiles, eosinophils, and neutrophils.

Acquired agranulocytosis may be caused by a variety of drugs. However, among the drugs to which a patient may be sensitive are several used in the treatment of cancer (cancer chemotherapeutic agents) and others used as antipsychotic medications (e.g., clozapine). The symptoms of this disorder come about as the result of interference in the production of granulocytes in the bone marrow.

People with acquired agranulocytosis are susceptible to a variety of bacterial infections, usually caused by otherwise benign bacteria found in the body. Not infrequently, painful ulcers also develop in mucous membranes that line the mouth and/or the gastrointestinal tract.

### **Other Problems to be Considered**

- AML
- Acute lymphoblastic leukemia
- Large granular lymphocyte leukemia
- HIV infection

- Shwachman-Diamond syndrome

### **Lab Studies**

- Perform a CBC, including a manual differential. Careful evaluation of the peripheral blood smear provides information about RBC and platelet morphology.
- Examine bone marrow smears and biopsy samples with techniques including flow cytometry.
- Microbiologic cultures of blood, wounds, and body fluids are indicated in febrile patients.
- Tests for antineutrophil antibodies should be performed in patients with a history suggestive of autoimmune neutropenia and in those with no other obvious explanation for the agranulocytosis.
- In congenital neutropenia and cyclic neutropenia, genetic analysis should be done to correctly classify the condition.

### **Imaging Studies**

- No specific imaging study establishes the diagnosis of agranulocytosis.
- As part of the workup for localization of infection, appropriate radiographs (eg, chest images) are indicated.
- Other imaging studies are determined by the specific circumstances of each case.

### **Procedures**

- Bone marrow aspiration and biopsy

### **Histologic Findings**

- The peripheral blood smear shows a marked decrease or absence of neutrophils.
- The bone marrow may show myeloid hypoplasia or absence of myeloid precursors.

- In many cases, the bone marrow is cellular with a maturation arrest at the promyelocyte stage.
- On occasion, the marrow may be hypercellular.

## Medical Care

Care is based on the etiology of the agranulocytosis. In most cases in which drug exposure is involved, the most important step is to discontinue the offending agent. If the identity of the causative agent is not known, stop administration of all drugs until the etiology is established.

- Start specific antibiotic therapy to combat infections. This often involves the use of third-generation cephalosporins or equivalents.
- Treat areas of Stomatitis and skin infections with local cleaning, antisepsis, and dental care. These infections should be managed by someone who has experience in the treatment of infections in Neutropenic patients.
- Control oral and gingival lesion pain with saline and hydrogen peroxide rinses and local anesthetic gels and gargles.
- The availability of the recombinant neutrophil cytokine, filgrastim (ie, G-CSF), has altered the management of agranulocytosis.
  - When administered before infection is established, filgrastim shortens the period to recovery and the duration of infection.
  - The agent is especially indicated in the management of congenital neutropenia, idiopathic severe chronic neutropenia, and cyclic neutropenia when serious infections are involved.
  - If the condition is mild, with only neutropenia without a serious infection, filgrastim may be withheld.

- Granulocyte transfusions have undergone a cycle of popularity followed by disfavor, though they may be useful in patients with life-threatening infections whose conditions are not responding to antibiotics.
  - These transfusions are accompanied by many complications, including severe febrile reactions.
  - The use of granulocyte transfusions remains controversial.
- In cases caused by heavy metals such as gold, chelation with British antilewisite (dimercaprol) may be needed.

### **Surgical Care**

- Surgical care is generally not indicated.
- Systemic lupus associated with autoimmune agranulocytosis may respond to splenectomy.
- Splenectomy has also been used in Felty syndrome, but the response is often short lived.

### **Consultations**

- Patients with agranulocytosis are seriously ill, and several consultations are indicated.
- A hematologist reviews the bone-marrow slides and peripheral blood smears to confirm the diagnosis and to assist in G-CSF dosing and evaluation.
- An infectious disease specialist advises and assists in the selection of appropriate antibiotics.

### **Diet**

- All foods must be thoroughly cooked. Raw fruits and vegetables may contain large numbers of bacteria and should be avoided.
- In patients with periodontitis and Stomatitis, a soft or full liquid diet is indicated. Spicy and acidic foods should be avoided until recovery is complete.

## Medication

Antibiotics are used to treat infections. The antibiotics of choice are those shown by culture and sensitivity studies to be the most effective for the organism causing the infection. If no causative organism is identified, use empirical broad-spectrum antibiotic coverage. Granulocyte growth factors and general supportive care should also be provided. Cytokines (growth factors) are used to stimulate production of neutrophils by acting on precursor cells.

Drug Category: *Colony-stimulating factors*

These are used to stimulate production of neutrophils by acting on precursor cells.

<b>Drug Name</b>	Filgrastim (Neupogen)
<b>Description</b>	A human G-CSF produced by recombinant DNA technology. Glycoprotein acts on hematopoietic cells in lineage-specific fashion. Stimulates proliferation, differentiation, and some end-cell functional activation.
<b>Adult Dose</b>	5 mcg/kg SC qd; titrate to effect; continue until ANC =1000/ $\mu$ L; continuous administration may be required for chronic conditions
<b>Pediatric Dose</b>	Administer as in adults
<b>Contraindications</b>	Documented hypersensitivity to drug or proteins derived from <i>E coli</i>
<b>Interactions</b>	Do not use 12-24 h before or 24 h after cytotoxic chemotherapy (increases sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy)
<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.
<b>Precautions</b>	MDS or AML in certain patients; leukocytosis; possible tumor growth; confirm diagnosis before use; allergic reactions may occur but not common; bone pain observed in 24% of patients but usually controlled with mild, non-opiate analgesics
<b>Drug Name</b>	Pegfilgrastim (Neulasta)
<b>Description</b>	Long-acting filgrastim created by covalent conjugate of recombinant G-CSF (ie, filgrastim) and

	monomethoxypolyethylene glycol. As with filgrastim, acts on hematopoietic cells by binding to specific cell-surface receptors, activating and stimulating production, maturation, migration, and cytotoxicity of neutrophils.
<b>Adult Dose</b>	6 mg SC once
<b>Pediatric Dose</b>	<45 kg: Not established >45 kg: Administer as in adults
<b>Contraindications</b>	Documented hypersensitivity to <i>E coli</i> derived proteins PEG, or filgrastim
<b>Interactions</b>	Do not administer between 14 d before and 24 h after cytotoxic chemotherapy or irradiation (increases sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy); lithium may potentiate release of neutrophils
<b>Pregnancy</b>	C - Safety for use during pregnancy has not been established.
<b>Precautions</b>	Splenic rupture reported rarely; ARDS secondary to influx of neutrophils to sites of inflammation in lungs may occur; may precipitate sickle cell crisis; may cause bone pain; risk of MDS or AML in certain patients; leukocytosis; possible tumor growth

### Further Inpatient Care

- If septic shock occurs, move the patient to the ICU.
- Intubation may be required.

### Further Outpatient Care

- Observation and CBC monitoring at increasing intervals after recovery

### Deterrence/Prevention

- Caution patients to avoid any drug that was previously implicated in causing them agranulocytosis.
- When prescribing new drugs to a patient with a history of a relatively high incidence of associated agranulocytosis, frequently obtain CBCs in the initial period.
  - The exact frequency depends on the specific drug and the time course of neutropenia association.



- At the first sign of a drop in the ANC, the drug should be discontinued.

## **Complications**

A metastatic abscess formation may result from infections, even if the infection was successfully resolved.

## **Prognosis**

- If treated promptly and vigorously, patients with drug-induced agranulocytosis have a good prognosis.
- Agranulocytosis secondary to viral infections is usually self-limited, and patients with such conditions have a good prognosis.

## **Patient Education**

- Patients should be educated to avoid drugs that have caused them agranulocytosis.
- Patients should be educated about the importance of follow-up CBC testing when a new drug with a high propensity to cause neutropenia is introduced.
- In the workplace, people must be educated to follow regulations from the Occupational Safety and Health Administration (OSHA) that covers safety precautions when they deal with toxic substances.

## **Special Concerns**

- Obtain a detailed history with particular emphasis on medication use. The inquiry must extend back in time to include discontinued medications.
- Over-the-counter drugs must be included in the inquiry because patients often do not consider them to be medications.
- Any possible occupational or accidental exposure to toxic chemicals or physical agents must be excluded.

- Agranulocytosis should be differentiated from other syndromes of bone-marrow failure, including pancytopenia and aplastic anemia. Leukemia should be excluded

Medication causes list:

The list of medications or substances mentioned in sources as possible causes of Agranulocytosis includes:

Acetophenazine Maleate  
 Aminosalicylate Sodium  
 Amobarbital  
 Amobarbital and Secobarbital  
 Amytal  
 Apo-Chlorpropamide  
 Aquatag  
 Avlosulfon

Benzthiazide  
 Butalan  
 Butarbital Sodium  
 Buticaps  
 Butisol Sodium

Certain antibiotics  
 Certain tranquillisers  
 Chemotherapy - some types affect bone marrow production of granulocytes  
 Chlorpromazine Hydrochloride  
 Chlorpropamide  
 Chlorprothixine  
 Cosmegen

Dactinomycin  
 Dapsone  
 Deavynfar

Diabinese

Exna

Hydrex

Insogen

Marazide

Metaxalone

Novo-Propamide

Ormazine

Proaqua

Radiation therapy

Salofalk

Skelaxin

Sodium P.A.S

Taractan

Thorazine

Tindal

Tubasal

Tuinal

### **Drug interactions causing Agranulocytosis:**

Many drugs can cause agranulocytosis and neutropenia. The mechanism of neutropenia can be varied depending on the drug. Many anti- neoplastic drugs cause agranulocytosis and neutropenia by bone marrow suppression. Neutropenia and agranulocytosis can also result from antibody or compliment mediated damage to the stem cells. Some drugs may cause increased peripheral destruction of white cells. About three fourth of all agranulocytosis in the United States is

related to drugs. Procainamide, anti-thyroid drugs and sulfasalazine are at the top of the list of drugs causing this problem. Most agranulocytosis is related to the direct effect related to its dose. Phenothiazines, semi-synthetic penicillins, non-steroidal anti-inflammatory drugs (NSAIDs), aminopyrine derivatives, benzodiazepines, barbiturate, gold compounds, sulfonamides, and anti-thyroid medications are the most common causes of neutropenia and agranulocytosis. The neutropenia manifests in about one two weeks after exposure to these drugs. Degree of neutropenia depends upon the dose and duration of exposure. Recovery usually occurs within few days of stopping the drug. The marrow recovery may take 10 to 14 days. Some time a rebound leukocytosis may occur. If the neutropenia is not very severe and the medication is an essential drug for the patient, some times the drug may be continued with under close monitoring. As long as absolute neutrophil count is above 500 to 700 and there is no active infection the drug may be continued if needed. If a bone marrow biopsy is done and it shows cellular bone marrow this might suggest peripheral destruction of white cells and this may be clinically less relevant.

Drug-induced agranulocytosis is a life-threatening disorder that leads to a selective profound granulocytopenia. Many drugs including neuroleptics, anti-thyroid medications, analgesics, phenothiazine derivatives and anti-inflammatory drugs are known to induce agranulocytosis.

Drug-induced agranulocytosis has been defined as a severe selective neutropenia due to an unpredictable adverse drug reaction (neutrophils  $< 200 \text{ ml}^{-1}$ ). It is a serious disorder that is associated with a high risk of mortality due to life-threatening infection. A variety of drugs, including analgesics, anticonvulsants, antimicrobials and antithyroid drugs, have been associated with agranulocytosis. In this case, granulocytes were gradually reduced

after the start of vinpocetine, and it did not continue without vinpocetine, suggesting that vinpocetine induced agranulocytosis.

To our knowledge, this is the first report that either a cerebral vasodilator or cerebral metabolism activator can cause agranulocytosis. Toxic and immune mechanisms are suggested to underlie drug-induced agranulocytosis. The immune type is mediated by drug-induced auto-antibodies or drug-dependent antibodies with rapid destruction of mature circulating granulocytes and hyperplastic bone marrow. With the toxic type, cell production in the proliferative compartments of the bone marrow is impaired. Direct toxicity to haematopoietic cells is suggested by the rather slow decline of the leukocytes.

Toxicity is also not strictly limited to granulopoietic precursors, but may include transient hypoplasia of erythroblasts (and even megakaryocytes). Aspiration biopsy in this case showed a reduced number of myelocytic cell types as well as erythroblasts in the bone marrow, although erythrocytes were not decreased during clinical course probably because of longer peripheral life span, suggesting that toxicity of haemopoietic precursors may be the predominant cause of agranulocytosis in this case. It is also suggested that the development of totipotent stem cells are inhibited by vinpocetine, as not only myelocytic cell types but erythroblasts are reduced. The other explanation for this is that the recovery of WBC, myelocytic cell types and erythroblasts is slower than expected even with the induction of G-CSF. It is generally thought that bone marrow suppression at the committed stem cell level or more subsequent stages is transient because undamaged uncommitted stem cells may feed into this system to initiate rapid recovery.

Megakaryocytes are intact in this case, but bone marrow suppression might develop into aplastic anemia when vinpocetine was continued. Although agranulocytosis related to vinpocetine was slow to develop in this case, frequent hematologic evaluation is recommended during

treatment with cerebral vasodilators and cerebral metabolism activators. Although agranulocytosis is detected early and drug therapy is withdrawn, patients are vitally endangered by infectious diseases for a longer period of time until hematologic recovery. To lower the risk of severe infection, G-CSF administration is recommended in such cases. In the case reported here, though recovery was not rapid, G-CSF may help induce the recovery of myelocytic proliferation; subsequently the patient was rescued from severe infectious diseases. The lack of a suitable assay for predicting the occurrence of drug-induced agranulocytosis mandates the need for monitoring for this adverse effect.

When combined, certain drugs, medications, substances or toxins may react causing Agranulocytosis.

The list below is incomplete and various other drugs or substances may cause the symptoms. Always inform your doctor of any medications or treatments you are using, including prescription, over-the-counter, supplements, herbal or alternative treatments.

Clozapine and Carbamazepine interaction

Pentazine VC with Codeine Liquid and oral antithyroid drug interaction

Phenameth DM Syrup and oral antithyroid drug interaction

Phenergan and oral antithyroid drug interaction

Phenergan VC Syrup and oral antithyroid drug interaction

Phenergan VC with Codeine Syrup and oral antithyroid drug interaction

Phenergan with Codeine Syrup and oral antithyroid drug interaction

Phenergan with Dextromethorphan Syrup and oral antithyroid drug interaction

Pherazine DM Syrup and oral antithyroid drug interaction

Pherazine VC with Codeine Syrup and oral antithyroid drug interaction

Pherazine with Codeine Syrup and oral antithyroid drug interaction  
Prometh Plain and oral antithyroid drug interaction  
Prometh VC Plain Liquid and oral antithyroid drug interaction  
Prometh VC with Codeine Liquid and oral antithyroid drug interaction  
Prometh with Codeine Syrup and oral antithyroid drug interaction  
Prometh with Dextromethorphan Syrup and oral antithyroid drug interaction  
Promethacon and oral antithyroid drug interaction  
Promethazine and oral antithyroid drug interaction  
Promethazine VC Plain Syrup and oral antithyroid drug interaction  
Promethegen and oral antithyroid drug interaction  
Promethist with Codeine Syrup and oral antithyroid drug interaction

### **About medication causes:**

Another misdiagnosis possibility is that a particular medication or substance may be the real cause of the disease. Certain medications, chemicals, toxins or substances may possibly be underlying causes of Agranulocytosis. Side effects of medications or exposure to toxins, chemicals, or other substances may cause a symptom or condition. Hence, they become possible underlying causes of Agranulocytosis but are often misdiagnosed or overlooked as a cause. For a general overview of this misdiagnosis issue see *Medication Underlying Cause Misdiagnosis*.

List of drugs that causes agranulocytosis or neutropenia sorted as per probability.

(Anti-neoplastic drugs are not included)

- **Dipyron**
- **Mianserin**
- **Sulfasalazine**
- **Co-trimoxazole**
- **Anti-arrythmic agents**
  - **Procainamide**
  - **Ajmaline**

- Tocainide
- Aprindine
- Amiodarone
- **Penicillins**
  - Amoxicillin
  - Aziocillin
  - Benzylpenicillin
  - Phenethicillin
  - Cloxacillin and penicillin
- **Thiouracil derivatives**
  - Methyl thiouracil
  - Propyl thiourcil
- **Phenylbutazone**
- **Cimetidine**
- **Penicillamine**
- **Diclofenac**
- **Carbamazepine**
- **ACE-Inhibitors**
  - Captopril
  - Enalapril
- **Hydrochlorothiazide with potassium sparing diuretics**
- **Indomethacine**
- **Cephalosporins**
  - Cephalexin
  - Cepahazolin
  - Cefuroxime
  - Cefitaxime
  - Cephradine
- **Oxyphenbutazone**
- **Nitrofurantoin**
- **Salicylic acid derivatives**
- **Clozapine**
- **Carbimazone**
- **Sulphonylurea derivatives**
  - Glibenclamide
  - Tolbutamide
- **Methyldopa**
- **Thiamazole**
- **Nucleosides**
- **Aminoglutethimide**
- **Ibuprofen**



- **Pentazocine**
- **Levamisole**
- **Promethazine**
- **Chloramphenicol**
- **Acetaminophen and combinations**
- **Perazine**
- **Mebhydrolin**
- **Ranitidine**
- **Imipramine**
- **Miscellaneous drugs (relatively lower probability)**
  - **Phenytoin**
  - **Chlorthalidone**
  - **Sulphamethizole**
  - **Norfloxacin**
  - **Naproxen**
  - **Clomipramine**
  - **Trazodone**
  - **Omeprazole**
  - **Alimemazine**
  - **Pirenzepine**
  - **Ticlopidine**
  - **Ibopamine**
  - **Hydralazine**
  - **Nifedipine**
  - **Nalidixic acid**
  - **Doxycycline**
  - **Clindamycin**
  - **Gentamycin**
  - **Fusidic acid**
  - **Dapsone**
  - **Azapropazone**
  - **Propyphenazone**
  - **Sulindac**
  - **Piroxicam**
  - **Pirprofen**
  - **Niflumic acid**
  - **Allopurinol**
  - **Glafenine**
  - **Valproate**
  - **Levodopa with carbidopa**
  - **Chlorpromazine**

- **Haloperidol**
- **spironolactone**
- **Zuclopenthixol**
- **Zopiclone**
- **Cinnarizine**
- **Metronidazole**
- **Pyrimethamine combinations**
- **Thophylline**