Blood dyscrasias are a rare, yet extremely serious, adverse effect of drug treatment. Outside of the more predictable bone marrow depression seen with cytotoxic and immunosuppressant agents, drugs in more common use have also been associated with blood disorders. Drug-induced blood disorders have also been the reason for withdrawal for a number of drugs, notably remoxipride in 1994.  

Although anecdotal reports of drug-induced blood disorders are common in the literature, they often have speculative mechanisms and questionable causality. The true incidence of drug-induced dyscrasias is therefore difficult to ascertain, but it is clear that they make a major contribution to the incidence of blood disorders.  

In practice, drug-induced reactions can be difficult to avoid, but knowledge of the propensity of drugs to initiate such reactions does allow prescribers to be both vigilant for early signs of blood disorders and inform patients about signs and symptoms. Early recognition is crucial in mitigating the effects of these serious and sometimes fatal adverse effects.

**Overview of drug-induced blood dyscrasias**

The bone marrow performs the task of providing the body with a balanced supply of all circulating blood cells throughout life. Variability in demand for differing types of blood cells is provided by the self-renewing pluripotential stem cells, from which the fully mature cell lines such as erythrocytes, granulocytes, platelets, macrophages and lymphocytes arise.

Drugs can have differing effects on the various cell types, at differing stages in cell development. Failure of stem cells leading to peripheral blood cytopenia is termed hypoplasia or aplasia. This can take two forms: aplastic anaemia, due to damage sustained by the pluripotential stem cells, or single-cell pancytopenias, where damage is due to a specific committed cell line.

Such diversity of effects leads to a wide spectrum of potential blood disorders depending on where and at what point in the production of the cell line the drug acts upon. The risk for individuals can also vary. The decline in the size of the haemopoietic bone marrow with age increases susceptibility. Certain blood dis-
orders can be more linked to the sex of the individual, or to a genetic propensity to suffer the reaction.4

Aplastic anaemia
A rare failure of haemopoietic stem-cell disorder, aplastic anaemia is characterised by pancytopenia and bone marrow aplasia.5 The fatality rate in a French study from the mid-1980s was 34 per cent one year postdiagnosis.6 The association between drug therapy and aplastic anaemia is long standing, although its relative rarity has made definitive causal associations for particular drugs hard to prove.

An insidious onset, allied to the possibility of delays of up to six months between exposure to the suspected drug and the reaction’s occurrence, also complicates the assessment of a link.

Chloramphenicol
Chloramphenicol was one of the first drugs associated with aplastic anaemia. A relatively common dose-dependent reversible bone marrow depression can appear in the second week of treatment, characterised by an inhibition of erythroid cells and anaemia; this reaction is usually reversible by drug withdrawal.

A more serious idiosyncratic aplastic anaemia can evolve after more sustained usage. Although less common, with wide variations in genetic susceptibility, this is a potentially fatal reaction.

For this reason, chloramphenicol is now reserved for life-threatening conditions and then only with regular monitoring.

The evidence that ocular chloramphenicol is associated with aplastic anaemia is extremely limited, and it remains the agent of choice for superficial eye infections.7

NSAIDs
NSAIDs have also been associated with aplastic anaemia and agranulocytosis. Phenylbutazone, a pyrazole derivative, was withdrawn because of aplastic anaemia, which was fatal in 50 per cent of cases.8 Indomethacin, piroxicam, diclofenac and sulindac are also associated with aplastic anaemia. Other NSAIDs have been linked, but on a more anecdotal basis.

Disease-modifying antirheumatic drugs (DMARDs)
Aplastic anaemia has also been associated with DMARDs, such as gold, sulfasalazine, penicillamine and leflunomide (Arava). Some have recommendations for routine blood monitoring – falling platelet and neutrophil counts can indicate oncoming aplastic anaemia.

The Medicines and Healthcare products Regulatory Agency (MHRA) has received a number of reports of blood disorders associated with methotrexate, including aplastic anaemia.9 It should be noted that error can contribute to blood disorders caused by methotrexate due to prescribing and dispensing errors, in particular the use of a daily instead of a weekly dose. The National Patient Safety Agency (NPSA) has produced guidance to address this issue,10 and patient education is an important method of avoiding these potentially fatal errors.11

Antiepileptic drugs
The use of antiepileptic drugs also appears to be linked to an increased risk of aplastic anaemia. In a retrospective case-control study, the risk of aplastic anaemia had an odds ratio of 9.5 (95% CI 3.0-39.7) compared with no use. Use of multiple antiepileptic agents was more strongly associated with aplastic anaemia, with carbamazepine and valproic acid particularly strongly associated.12

Other drugs associated with aplastic anaemia are listed in Table 1.

Agranulocytosis
Profound reductions in granulocytes and a neutrophil count of less than 0.5x10^9 per litre indicate agranulocytosis. Drug-induced agranulocytosis can be caused by direct marrow toxicity or be immune mediated.

The antithyroid drugs carbimazole (Neo-Mercazole) and

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Table 1. Drugs associated with aplastic anaemia

<table>
<thead>
<tr>
<th>Antibacterials</th>
<th>Chloramphenicol, co-trimoxazole, sulphonamides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory agents</td>
<td>Fenbufen, diclofenac, gold, indomethacin, penicillamine, piroxicam</td>
</tr>
<tr>
<td>Antithyroid drugs</td>
<td>Carbimazole, propylthiouracil</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Pyrimethamine</td>
</tr>
<tr>
<td>Antidepressants and antipsychotics</td>
<td>Chlorpromazine, dosulepin</td>
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<tr>
<td>Antihypertensives</td>
<td>Lisinopril</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Chlorpropamide, tolbutamide</td>
</tr>
<tr>
<td>Other</td>
<td>Acetazolamide</td>
</tr>
</tbody>
</table>

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The antithyroid drugs carbimazole (Neo-Mercazole) and
propylthiouracil carry a relatively high risk of haematological dysfunctions including agranulocytosis.\textsuperscript{13} Females and those aged over 65 may have an increased risk. Although some have argued for routine blood monitoring, the balance of opinion is that monitoring is not considered worthwhile due to the rapid onset of the adverse effect that monitoring would not capture. Recurrence of agranulocytosis has also been reported when switching from carbimazole to propylthiouracil.\textsuperscript{14}

Approximately half the fatalities caused by carbimazole and propylthiouracil reported to the Yellow Card scheme result from agranulocytosis and neutropenia.\textsuperscript{15} Patients taking antithyroid drugs should be told to notify their doctor at once if they experience fever, a sore throat, mouth ulcers, bruising, malaise or non-specific illness. Such reports should be treated as medical emergencies.\textsuperscript{16}

The atypical antipsychotic clozapine is a known cause of agranulocytosis. It is associated with a 2-3 per cent incidence of neutropenia\textsuperscript{4} and a case fatality rate of between 4 and 16 per cent.\textsuperscript{17} For this reason, its use is restricted to patients enrolled in strict blood-monitoring programmes, although it has been argued that the risk of agranulocytosis after six months is sufficiently reduced to challenge the continued necessity for such strict monitoring.\textsuperscript{17}

Other psychotropic drugs and antidepressants have also been associated with agranulocytosis.\textsuperscript{18} Chlorpromazine is associated with a delayed-onset agranulocytosis, with severe cases occurring in 0.1 per cent of patients taking standard doses.\textsuperscript{4}

Antibiotic agents have been associated with agranulocytosis including co-trimoxazole, which has a variety of serious haematological effects.\textsuperscript{19}

Table 2 lists other drugs associated with agranulocytosis.

### Pure red cell aplasia

Pure red cell aplasia (PRCA) is characterised by anaemia with a marked reduction in reticulocytes, and leads to weakness, pallor and lethargy in patients. Around 5 per cent of cases are drug induced and many of the drugs associated with aplastic anaemia can cause PRCA. Phenytoin, azathioprine, and isoniazid have been implicated in several case reports.\textsuperscript{4}

In 2002, the UK CSM reported on 40 confirmed cases of PRCA associated with epoetin alfa (Eprex).\textsuperscript{20}

### Thrombocytopenia

Severe reductions in platelet count to less than 150x10\textsuperscript{9} per litre are indicative of thrombocytopenia. Less serious signs, such as petechiae (see Figure 1) and purpura, can also give way to more severe haemorrhage in the GI and genitourinary tracts. Cerebral haemorrhage is a common cause of death.\textsuperscript{4} Drug-induced thrombocytopenia can either be due to direct effects on the bone marrow, or through an autoimmune mechanism.

The best-known drug associated with thrombocytopenia is heparin, which can cause mild to moderate thrombocytopenia (platelet count 50-150x10\textsuperscript{9} per litre). Occurring in the first 5-10 days, this reaction involves a complex immune reaction; the diagnosis is made by one or more clinical events and antibody detection. Heparin should be immediately discontinued, and expert advice sought on management.\textsuperscript{4}

A more severe and serious heparin-induced thrombocytopenia, which occurs in around 2 per cent of patients, is linked to thrombotic events such as myocardial infarction (MI) and strokes.

Glycoprotein IIb/IIIa inhibitors, such as abciximab (Reopro), have also been associated with thrombocytopenia.\textsuperscript{21}

Beta-lactam antibiotics have been associated with a seven-fold increase in risk for thrombocytopenia, by either an immune-mediated mechanism or bone marrow suppression.\textsuperscript{22} However,
other authors have suggested this may be a result of confounding by indication – where the infection that the antibiotic is used to treat is an early manifestation of a blood disease.23

A number of other drugs have been associated with thrombocytopenia, including co-trimoxazole, acetazolamide, chlorpropamide, furosemide, diazepam, methyl dopa, sodium valproate, thiazide diuretics, tolbutamide and trimethoprim.4

### Haemolytic anaemia

Drug-associated haemolytic anaemia is thought to occur in approximately one in a million people, with four distinct mechanisms proposed for the majority of cases: immune complex formation, hapten formation, autoantibody production and, in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency, oxidative red cell damage.2 Immune complexes seem to be the major cause, with quinine, quinidine, rifampicin, methotrexate, sulphonureas and anti-histamines among those associated.

Penicillin has been associated with hapten formation – around 3 per cent of patients receiving high doses will develop a positive antiglobulin test, of which a small proportion will develop haemolytic anaemia. A positive Coombs’ test can distinguish immune reactions from other causes of haemolytic anaemia.

Haemolysis caused by G6PD deficiency is dose dependent and increases with cumulative doses. Drugs with a definite risk of haemolysis include nitrofurantoin, primaqamine, quinolones and sulphonamides. The BNF includes advice on G6PD deficiency and further information on drugs to be avoided.24

### Reporting of blood disorders

Given the seriousness of iatrogenic blood disorders, any cases should be reported on a Yellow Card to the MHRA. A study based in French and Spanish hospitals showed that 70 per cent of drug-induced agranulocytosis was not reported to regulatory authorities.25 Rare blood disorders are unlikely to arise within the relatively small sample of patients who take a drug within clinical trials, and therefore the vigilance and suspicion of prescribers is essential.

### Mitigation and prevention of drug-induced blood disorders

The most important part of management is the prompt recognition that a problem exists. This is done by two mechanisms: firstly, vigilance for signs and symptoms that may indicate a blood disorder and, secondly, patient education about the warning symptoms that should alert them to the need to urgently contact their GP or emergency services if a prompt GP appointment is not possible.

Treatment of blood dyscrasias requires specialist expertise. Any drugs suspected of being involved in the reaction should be discontinued immediately and short-term supportive treatments given to aid a potential spontaneous recovery. Such support can include blood and platelet products, antibiotic or antifungal agents and recombinant human haemopoietic growth factors.4

Aplastic anaemia may require immunosuppressive therapy and bone marrow or stem cell transplant. Modern treatments for blood dyscrasias, such as granulocyte colony-stimulating factor (G-CSF), have significantly reduced mortality rates. Haemolytic anaemia normally recovers within two to three weeks of drug withdrawal, although corticosteroid therapy may be beneficial.

### Conclusion

Drug-induced blood disorders are a rare adverse effect, whose deleterious effects can be mitigated by the vigilance of both health professionals and patients. Although many are idiosyncratic effects, some drugs with a well-known risk of blood dyscrasias are widely used due to a lack of alternative agents with similar effects. In the case of these, following specific monitoring advice may help avert adverse effects, but specific advice to patients on how to spot symptoms indicative of blood dyscrasias is important.

In the case of new drugs, any suspected case of blood dyscrasias should be reported to regulatory bodies.

### References


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### Table 3. Important clinical signs that may indicate a blood disorder19

- bleeding gums
- chest pain
- ‘cold symptoms’
- dry cough
- dyspnoea
- fatigue
- lassitude
- lymphadenopathy
- malaise
- pallor
- petechiae
- pharyngitis
- purpura
- rash
- stomatitis
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Anthony Cox is pharmacovigilance pharmacist at the West Midlands Centre for Adverse Drug Reaction Reporting, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham