

Systematic Review: Agranulocytosis Induced by Nonchemotherapy Drugs

Frank Andersohn, MD; Christine Konzen, MD; and Edeltraut Garbe, MD, PhD

Background: Nonchemotherapy drug-induced agranulocytosis is a rare adverse reaction that is characterized by a decrease in peripheral neutrophil count to less than 0.5×10^9 cells/L due to immunologic or cytotoxic mechanisms.

Purpose: To systematically review case reports of drugs that are definitely or probably related to agranulocytosis.

Data Sources: English-language and German-language reports in MEDLINE (1966 to 2006) or EMBASE (1989 to 2006) and in bibliographies of retrieved articles.

Study Selection: Published case reports of patients with nonchemotherapy drug-induced agranulocytosis.

Data Extraction: One reviewer abstracted details about cases and assessed causality between drug intake and agranulocytosis by using World Health Organization assessment criteria.

Data Synthesis: Causality assessments of 980 reported cases of agranulocytosis were definite in 56 (6%), probable in 436 (44%), possible in 481 (49%), and unlikely in 7 (1%). A total of 125 drugs were definitely or probably related to agranulocytosis. Drugs for which more than 10 reports were available (carbimazole, cloza-

pine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine) accounted for more than 50% of definite or probable reports. Proportions of fatal cases decreased between 1966 and 2006. More patients with a neutrophil count nadir less than 0.1×10^9 cells/L had fatal complications than did those with a neutrophil count nadir of 0.1×10^9 cells/L or greater (10% vs. 3%; $P < 0.001$). Patients treated with hematopoietic growth factors had a shorter median duration of neutropenia (8 days vs. 9 days; $P = 0.015$) and, among asymptomatic patients at diagnosis, had a lower proportion of infectious or fatal complications (14% vs. 29%; $P = 0.030$) than patients without such treatment.

Limitations: Case reports cannot provide rates of drug-induced complications, sometimes incompletely assess or describe important details, and sometimes emphasize atypical features and outcomes.

Conclusions: Many drugs can cause nonchemotherapy drug-induced agranulocytosis. Case fatality may be decreasing over time with the availability of better treatment.

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For author affiliations, see end of text.

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Nonchemotherapy drug-induced agranulocytosis is a rare adverse reaction that is characterized by a decrease in peripheral neutrophil count to less than 0.5×10^9 cells/L due to immunologic or cytotoxic mechanisms (1). Discontinuation of treatment with the causative drug is crucial to avoid continuation of hazardous exposure, but its identification may be challenging in patients with polypharmacotherapy. In a subgroup of patients, detection of drug-dependent antineutrophil antibodies can prove drug causality (2), but this method lacks standardization and is not appropriate for drugs that cause agranulocytosis by nonimmunologic mechanisms. The prescribing information is also often not helpful in identifying these drugs because leukopenia and neutropenia are listed as possible adverse drug reactions for many drugs, but no information is provided on the severity of these blood count changes.

Reports on fatal cases of drug-induced acute agranulocytosis differ materially and range from 0% to 23% (3–9). A decrease in the case fatality rate over time has been reported for dipyrone (4), but whether it applies to drug-induced acute agranulocytosis in general is unknown. Granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) are proven treatments for chemotherapy-induced neutropenia, but results on their effectiveness in nonchemotherapy drug-induced agranulocytosis are conflicting.

To establish a comprehensive update of drugs that

cause agranulocytosis, we conducted a systematic review of published case reports. We reevaluated the evidence of causality by applying the standardized World Health Organization criteria for causality assessment of adverse drug reactions to each report. In addition, we analyzed the reports with respect to several clinical characteristics, including the efficacy of therapy with G-CSF or GM-CSF.

METHODS

We followed a set protocol to identify case reports and extract clinical information (all included case reports are listed at www.adverse-effects.com/agranulocytosis/case_reports.html). We plan to update this database every 2 years.

Literature Sources and Search Terms

We searched MEDLINE for case reports of drug-induced agranulocytosis that were published from January

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Context

Drug-induced agranulocytosis is a rare but potentially serious adverse event.

Contribution

This systematic review of case reports involving 980 patients with possible nonchemotherapy drug-induced agranulocytosis found 125 drugs that definitely or probably caused agranulocytosis. More than half of the definite or probable cases involved the following drugs: carbimazole, clozapine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine. More patients with a neutrophil count nadir less than 0.1×10^9 cells/L had fatal complications than did those with a nadir of 0.1×10^9 cells/L or greater (10% vs. 3%).

Caution

Case reports do not describe the frequency of drug-induced complications and sometimes emphasize atypical features and outcomes.

—The Editors

1966 to December 2006 by using the Medical Subject Heading terms “agranulocytosis” and “chemically induced.” The search was limited to articles involving the terms “human” and “case reports” and to articles written in German or English. We searched EMBASE for all articles that were published in German or English between 1989 and December 2006 and were described with the terms “agranulocytosis-side-effect” in the major medical descriptors field and “case-report” in a subheading field. From all articles that were identified in MEDLINE and EMBASE, 1 reviewer selected the reports to be reviewed, and another reviewer conducted the causality assessment and manually checked the references of all retrieved case reports and case series to identify articles that were not found during the primary search.

Selection of Case Reports

Articles were eligible if they reported on a case of nonchemotherapy drug-induced acute agranulocytosis or neutropenia with an absolute neutrophil count less than 0.5×10^9 cells/L. We excluded articles from further review if they fulfilled at least 1 of the following criteria: no individual patient reported; insufficient clinical or laboratory data to permit further evaluation of the report; absolute neutrophil count of 0.5×10^9 cells/L or greater; suppression of bone marrow caused by cytotoxic drugs; diagnosis of aplastic anemia; intentional or accidental drug overdose; congenital agranulocytosis, cyclic neutropenia, or neutropenia due to underlying diseases or causes other than drugs (for example, malignant infiltration of bone marrow); or agranulocytosis in patients younger than 18 years of age (because the spectrum of drugs, comorbid conditions, and

outcome of agranulocytosis in children may differ from that in adults).

Data Abstraction

We extracted several characteristics from the cases, including the patient’s sex, age, medical history, other concomitant cytopenias or immunologic drug reactions (for example, exanthema), and neutrophil count nadir; duration, complications, treatment, and outcome of agranulocytosis; latency between start of treatment and onset of acute agranulocytosis; and results of bone marrow examination, if available. We used the World Health Organization categories “certain,” “probable,” “possible,” and “unlikely” for causality assessments (10) but did not use the category “unclassifiable” because articles that provided insufficient clinical or laboratory data were excluded. We assessed 4 aspects of the suspected drug reaction: 1) the existence of a plausible time relationship to drug administration, 2) the absence of concurrent disease or other drugs that may have caused acute agranulocytosis, 3) the existence of a reasonable response to drug withdrawal (dechallenge), and 4) the existence of a satisfactory rechallenge procedure or of a definitive pharmacologic explanation for acute agranulocytosis (for example, confirmation of causality by detecting drug-dependent antineutrophil antibodies). For a reaction to be rated “certain,” all criteria had to be met. A reaction was rated as “probable” if criteria 1, 2, and 3 were fulfilled and “possible” if only criterion 1 was met and information on criterion 3 was lacking or unclear. A reaction was rated as “unlikely” if criterion 1 was not met and if other drugs, chemicals, or underlying disease provided a plausible explanation for acute agranulocytosis. According to the Council for International Organizations of Medical Sciences criteria of causality assessment of drug-induced cytopenias (11), a plausible time relationship to drug administration was suggested if acute agranulocytosis occurred during current therapy or within 1 month after drug withdrawal and if it did not resolve spontaneously during continuous therapy. This window was extended to 6 months for rituximab-induced, delayed-onset neutropenia, which has repeatedly been reported to occur later than 1 month and up to 6 months after the last rituximab dose. A reasonable response to drug withdrawal was defined as an increase in neutrophil count to more than 1.5×10^9 cells/L within 1 month. After causality assessments, we assigned a level of evidence to each reported drug: Level 1 evidence had to have at least 1 definite case report, level 2 evidence had to have at least 1 probable report but no definite report, and level 3 evidence had to have at least 1 possible report but no definite or probable case report.

Statistical Analysis

We analyzed the proportion of fatal cases reported by time period and tested for trends across 1966 to 1980, 1981 to 1990, and 1991 to 2006. We repeated this analysis after excluding patients who were treated with hematopoietic growth factors. For drugs with more than 3 definite or

probable reports of agranulocytosis and complete information on the investigated variables, we analyzed the median duration of treatment before disease onset and the median time between onset and normalization of neutrophil count. To assess the natural course of the disease, patients who were treated with G-CSF or GM-CSF were excluded in the calculation of the median duration of neutropenia. We compared the proportion of patients who developed localized infections or sepsis or who died in cases with a neutrophil count nadir less than 0.1×10^9 cells/L with those who had a nadir of 0.1×10^9 cells/L or greater. We repeated these comparisons in the subgroup of patients who were asymptomatic at diagnosis and explored relationships between treatment with G-CSF or GM-CSF and duration of neutropenia, infectious complications, and death by using reports published since 1990, when hematopoietic growth factors became widely available.

We used SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina) to perform statistical tests. We compared categorical variables by using the Fisher exact test. We used the Cochran–Armitage test to test for trends in binomial proportions across ordinal-scaled levels of a single explanatory variable and the Student *t*-test to compare a continuous variable (for example, duration of acute agranulocytosis) in different groups. If the data in 1 of the groups were not normally distributed, a Wilcoxon rank-sum test was used. A 2-sided *P* value less than 0.05 was considered statistically significant.

Role of the Funding Source

This study was not funded.

RESULTS

We identified 1135 potentially relevant articles by searching MEDLINE and EMBASE and identified 293 additional articles by checking the bibliographies of retrieved articles (**Figure 1**). Of these articles, 672 reports on 980 patients met the inclusion criteria. Of the 980 reported cases of drug-induced agranulocytosis, 56 (6%) reactions were rated as definite, 436 (44%) were rated as probable, 481 (49%) were rated as possible, and 7 (1%) were rated as unlikely. **Table 1** shows the clinical characteristics of all case reports that were at least possibly related to the suspected drug (*n* = 973). Thirty-six drugs had level 1 evidence and 89 drugs had level 2 evidence for causing acute agranulocytosis (**Table 2**). Fifty-five drugs had level 3 evidence (data not shown). Among patients with agranulocytosis caused by penicillins, more than 50% received high daily doses (data not shown).

The median duration of treatment before onset of acute agranulocytosis ranged from 2 days for dipyrone to 60 days for levamisole and was longer than 1 month for 17 (71%) of 24 drugs (**Figure 2**). The time between onset of acute agranulocytosis and normalization of neutrophil count ranged from 4 to 24 days (**Figure 2**). The proportion of fatal cases decreased between 1966 and 2006 (*P* < 0.001) (**Figure 3**). This decrease remained statistically significant after all patients treated with G-CSF or GM-CSF were excluded (*P* < 0.001). After 1990, agranulocytosis was fatal in 6% of untreated patients and in 5% of patients treated with G-CSF or GM-CSF (**Figure 3**). Patients with a neutrophil count nadir less than 0.1×10^9 cells/L had a

Figure 1. Study flow diagram.

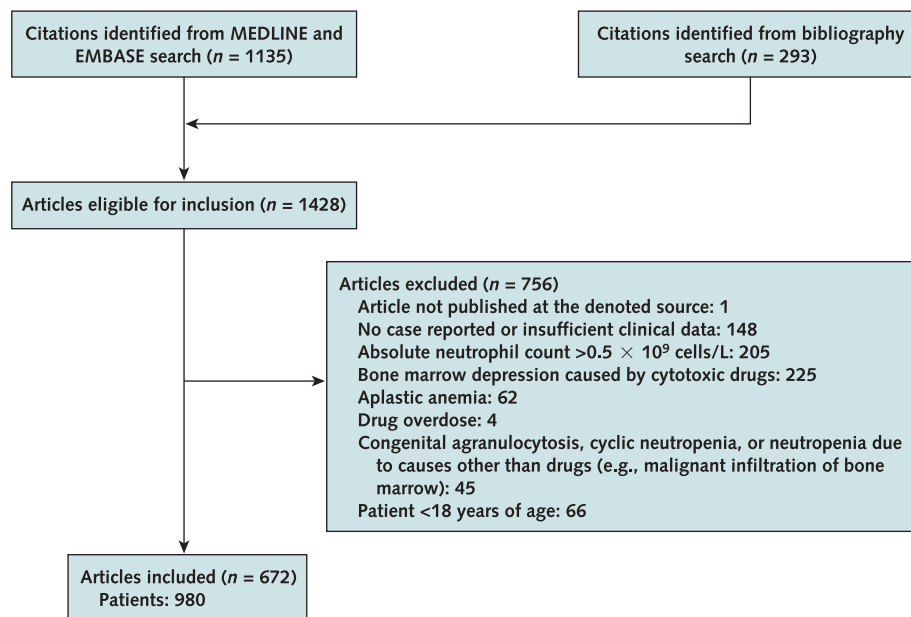


Table 1. Characteristics of Reported Patients with Acute Agranulocytosis*

Variable	Cases of Acute Agranulocytosis†
Sex, n (%)	
Female	483 (50)
Male	469 (48)
Not reported	21 (2)
Mean age (range), y	51.4 (18–92)
Median neutrophil count nadir (range), $\times 10^9$ cells/L	18 (0–499)
Median duration of agranulocytosis (range), d	8 (1–180)
Outcome, n (%)	
Recovery	834 (86)
Recovery with persisting harm‡	22 (2)
Death	97 (10)
Unknown	20 (2)
Infectious complications of agranulocytosis, n (%)	
Sepsis	156 (16)
Nonsystemic infection	508 (52)
Not reported	309 (32)
Bone marrow examination, n (%)	
Normal	15 (2)
Hypoplasia of granulopoietic cells	376 (39)
Hyperplasia of granulopoietic cells	40 (4)
Other abnormalities with normoplastic granulopoiesis	133 (14)
Not reported	409 (42)
Medical history, n (%)	
History of allergic reactions to any antigen	10 (1)
History of adverse drug reactions	60 (6)
Autoimmune disease	158 (16)
Infection preceding acute agranulocytosis	154 (16)
Chronic renal failure	42 (4)
Concomitant adverse drug reactions, n (%)	
Cytopenia other than neutropenia	177 (18)
Immunologic drug reaction§	105 (11)
Other	28 (3)
Therapy for acute agranulocytosis, n (%)	
Glucocorticoids	67 (7)
G-CSF or GM-CSF	238 (24)
Not reported	672 (69)

* G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor.

† There were 973 cases of acute agranulocytosis. Seven reports in which drug causality was assessed as unlikely were excluded.

‡ Irreversible infectious complications, such as necrosis, amputation, and intestinal perforation.

§ For example, exanthema.

higher rate of localized infections (59% vs. 39%; $P < 0.001$), sepsis (20% vs. 6%; $P < 0.001$), and fatal complications (10% vs. 3%; $P < 0.001$) than did those with a neutrophil count nadir of 0.1×10^9 cells/L or greater.

The proportion of patients treated with G-CSF or GM-CSF increased from 35% between 1990 and 1994 to 65% since 1995. Among reports published since 1990, treatment with G-CSF or GM-CSF was associated with a lower median duration of neutropenia (8 days in treated

patients vs. 9 days in untreated patients [$P = 0.015$]). This finding was also evident among patients who were asymptomatic at diagnosis (7.5 days in treated patients vs. 10 days in untreated patients [$P = 0.007$]). In this subgroup, a neutrophil count nadir less than 0.1×10^9 cells/L was associated with more infectious complications or fatal complications than was a nadir of 0.1×10^9 cells/L or greater (34% vs. 13%, respectively; $P = 0.003$). Treatment with G-CSF or GM-CSF seemed to be associated with a lower proportion of patients who developed infectious or fatal complications (14% of treated patients vs. 29% of untreated patients [$P = 0.030$]). In patients with a neutrophil count nadir less than 0.1×10^9 cells/L, the proportions were 22% versus 46% ($P = 0.035$) and in those with a nadir of 0.1×10^9 cells/L or greater, they were 7% versus 17% ($P = 0.30$). Three percent of treated patients and 2% of untreated patients developed sepsis ($P = 0.80$). There were no obvious differences in duration of neutropenia or in the proportion of patients who developed infections among those who were treated with G-CSF or GM-CSF.

DISCUSSION

In this systematic review of case reports with standardized causality assessment, we ascertained 125 drugs that definitely or probably caused acute agranulocytosis. The duration of treatment before diagnosis of acute agranulocytosis ranged from 2 to 60 days and was longer than 1 month for 71% of the drugs. The proportion of reported fatal cases decreased between 1966 and 2006. Treatment with G-CSF or GM-CSF seemed to be associated with a shorter duration of neutropenia and a reduced rate of infectious complications in patients who were asymptomatic at diagnosis.

Several epidemiologic studies have quantified the risk for agranulocytosis for single drugs. To identify and compare these studies with those of our systematic review, we searched MEDLINE by using the terms (“agranulocytosis or neutropenia”) and (“case control” or “case population” or “cohort” or “observational” or “epidemiologic”). We found 4 epidemiologic studies (3, 5, 9, 12–15) that reported statistically significant risk estimates for 25 drugs (Table 3). Our systematic review showed level 1 or level 2 evidence of causality for most drugs that were associated with an increased risk for agranulocytosis in these epidemiologic studies (Table 2). No case report met our eligibility criteria for 4 drugs (acetyldigoxin, cinpezide, digoxin, and dipyridamole) that were associated with an increased risk in the epidemiologic studies.

Most drugs for which we assessed a definite or probable causal relationship to agranulocytosis have not been investigated in observational studies of agranulocytosis (3, 5, 8, 9, 12, 14–17). Risk estimates for only 20 of the 125 drugs with level 1 or 2 evidence were reported in the observational studies. For 31 additional drugs, only the therapeutic chemical class (for example, β -lactam antibiotics)

was investigated, and for the remaining 74 drugs, no information from the epidemiologic studies was available.

In the absence of clinical or epidemiologic data, well-documented case reports of adverse drug reactions are an important source for identifying rare drug risks. A study on the postmarketing discovery of 18 important adverse drug reactions revealed that 13 (72%) of these reactions were initially described in case reports (18). Many of the 11 drugs for which we identified more than 10 definite or probable case reports were associated with a high risk for agranulocytosis in epidemiologic studies, but we found no pertinent data in the epidemiologic studies for some of the drugs (for example, clozapine and rituximab). However, in half of the case reports, the reported causative drug was only possibly, or even unlikely to be, related to agranulocytosis. It is therefore essential to apply causality assessment criteria to case reports before concluding from the report that a particular drug caused agranulocytosis.

The median duration of drug exposure before onset of acute agranulocytosis ranged from 19 to 60 days in most cases; for dipyrrone, a median drug exposure of only 2 days was observed. For almost three quarters of the drugs that we analyzed, the duration of drug exposure before disease onset was greater than 1 month. It has been suggested that agranulocytosis caused by a nonimmunologic mechanism

may have a later onset than agranulocytosis caused by an immune-mediated mechanism (19). However, factors other than the disease mechanism (for example, the frequency of blood count monitoring in asymptomatic patients) may also have influenced the duration of drug exposure before disease onset.

We found a decrease in case fatality in reports of drug-induced agranulocytosis over time even after excluding patients who were treated with hematopoietic cell growth factors. Earlier studies on nonchemotherapy drug-induced agranulocytosis also reported higher case-fatality rates (9% to 16%) (3, 6), whereas more recent studies indicate that fatality rates have decreased to approximately 5% (4, 20, 21). Improved intensive care treatment, availability of efficient broad-spectrum antibiotics, and increased alertness of physicians to drug-induced agranulocytosis with prompt cessation of use of the suspected drug may have contributed to improved outcomes in patients with agranulocytosis.

Treatment with hematopoietic cell growth factors has been reported to decrease fatality in patients with nonchemotherapy drug-induced agranulocytosis (22). Although limited by a small number of patients, we did not observe statistically significant associations between decreased case-fatality rates and use of G-CSF or GM-CSF. Approximately

Table 2. Drugs with Definite or Probable Causality

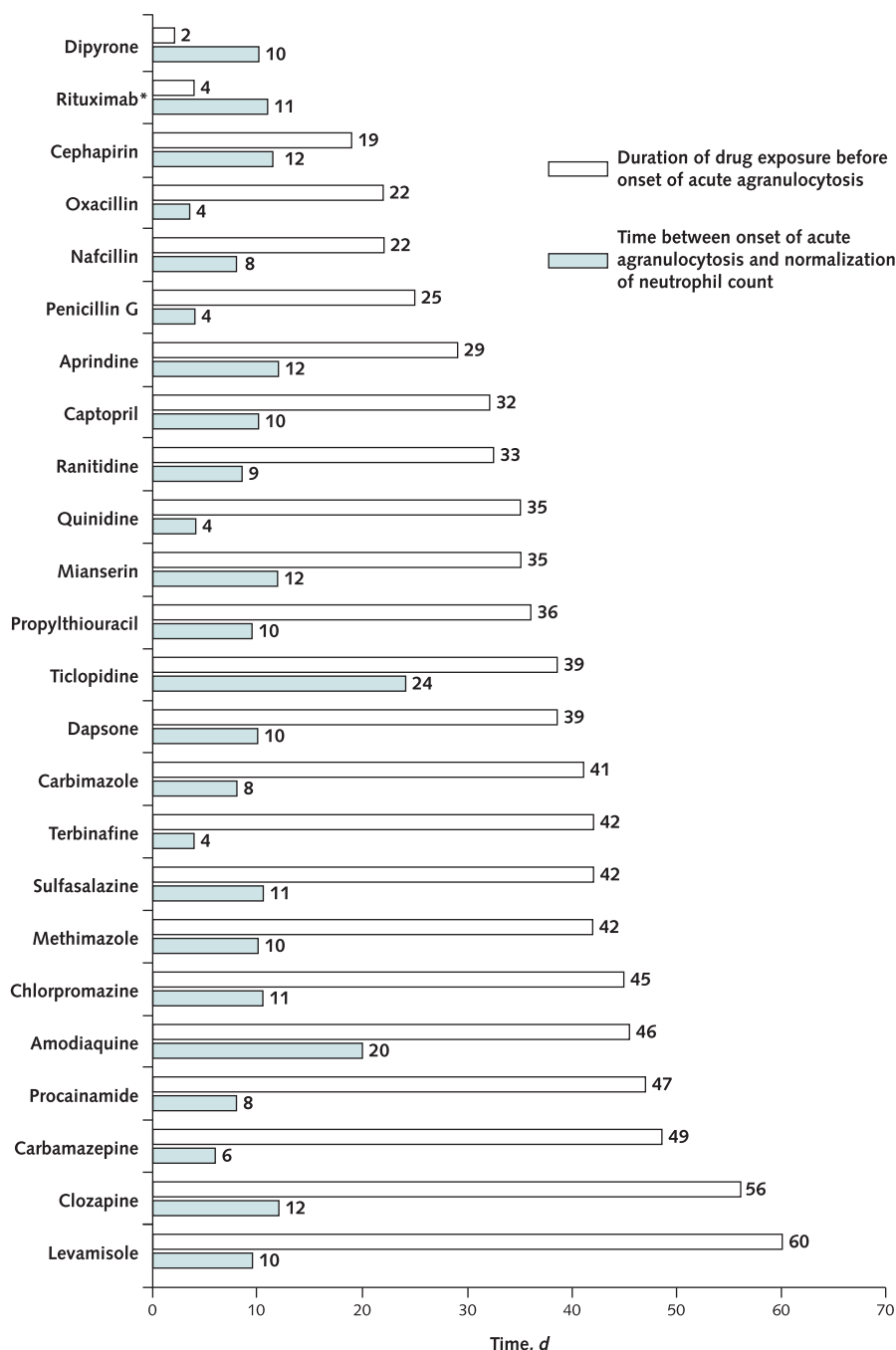
Drug Category	Level 1 Evidence*	Level 2 Evidence†
Analgesics and nonsteroidal anti-inflammatory drugs	Aminopyrine (2/0), diclofenac (1/0), diflunisal (1/0), dipyrrone (6/5), ibuprofen (1/1)	Acetaminophen (1), bucillamine (1), fenoprofen (1), mefenamic acid (1), naproxen (2), pentazocine (2), phenylbutazone (1), piroxicam (1), sulindac (2)
Antiarrhythmics	Disopyramide (1/0), procainamide (3/19), quinidine (3/4)	Ajmaline (4), amiodarone (1), aprindine (4)
Anti-infective drugs	Ampicillin (1/1), carbenicillin (1/0), cefotaxime (1/1), cefuroxime (1/0), flucytosine (1/0), fusidic acid (1/0), imipenem–cilastatin (1/1), nafcillin (1/4), oxacillin (2/4), penicillin G (4/7), quinine (2/2), ticarcillin (1/0)	Abacavir (2), amodiaquine (10), amoxicillin–clavulanic acid (1), cefamandole (1), cefepime (2), ceftriaxone (6), cephalexin (1), cephalothin (3), cephradine (4), cephradine (1), chloroguanide (1), clarithromycin (1), cloxacillin (1), dapsone (17), hydroxychloroquine (2), indinavir (1), isoniazid (1), mebendazole (1), nifuroxazide (1), nitrofurantoin (1), norfloxacin (1), penicillin G–procaine (1), piperacillin (1), terbinafine (5), trimethoprim–sulfamethoxazole (3), vancomycin (5), zidovudine (2)
Anticonvulsants	Phenytoin (1/2)	Carbamazepine (4), lamotrigine (3)
Antineoplastics	Amygdalin (1/0)	Aminoglutethimide (2), flutamide (1), imatinib (3), nilutamide (1), rituximab‡ (25)
Antirheumatics	Infliximab (1/0), levamisole (2/6)	Gold (5), penicillamine (2), sulfasalazine (12)
Antithyroid drugs	Propylthiouracil (1/10)	Carbimazole (21), methimazole (55)
Cardiovascular drugs	Clopidogrel (1/0), methyldopa (1/0), ramipril (1/0), spironolactone (1/2)	Bepidil (1), bezafibrate (1), captopril (9), metolazone (1), ticlopidine (15), vesnarinone (2)
Gastrointestinal drugs	Cimetidine (1/2), metoclopramide (1/0)	Famotidine (3), mesalazine (1), metiamide (4), omeprazole (2), pirenzepine (1), ranitidine (4)
Psychotropic drugs	Chlorpromazine (2/6), clozapine (4/49), fluoxetine (1/0)	Amoxapine (1), clomipramine (1), cyanamide (1), desipramine (1), dothiepin (1), doxepin (1), imipramine (1), indalpine (1), maprotiline (1), meprobamate (1), methotrimeprazine (1), mianserin (9), olanzapine (1), thioridazine (1), ziprasidone (1)
Other drugs	Calcium dobesilate (1/0), mebhydrolin (1/0)	Acetosulfone (1), acitretin (1), allopurinol (1), chlorpropamide (2), deferiprone (2), prednisone (1), promethazine (1), riluzole (2), ritodrine (1), tolbutamide (1), yohimbine (1)

* At least 1 report with a definite relationship. The numbers in parentheses are the number of definite/probable reports.

† At least 1 report with a probable relationship, but no report with a definite relationship. The numbers in parentheses are the number of probable reports.

‡ For rituximab-induced, delayed-onset agranulocytosis, a plausible time relationship to drug administration was assumed if the last rituximab infusion was given within 6 months before onset of agranulocytosis.

Figure 2. Median duration of treatment and neutropenia.



Only drugs with more than 3 definite or probable reports of the time between onset of acute agranulocytosis and normalization of neutrophil count and the duration of treatment before onset of acute agranulocytosis were considered. Patients treated with hematopoietic growth factors were excluded in the calculation of the median duration of neutropenia. *For rituximab, the white bar represents the median number of infusions before onset of agranulocytosis.

65% of patients described in the case reports since 1995 received treatment with G-CSF or GM-CSF. It is unclear whether this high proportion of patients represents common clinical practice or is attributable to preferential publication of reports on patients who received the best care in the opinion of the physicians submitting the case reports.

We found statistically significant associations between shorter duration of neutropenia and treatment with G-CSF or GM-CSF, regardless of whether patients had an infection at the time of diagnosis. A decreased duration of neutropenia has been shown in other retrospective studies of the effect of treatment with G-CSF or GM-CSF (20, 22).

A small prospective, randomized trial of treatment with G-CSF versus treatment without growth factors in 24 patients with antithyroid drug–induced agranulocytosis failed to show a statistically significant effect (23), possibly because the dose of G-CSF (24) was insufficient. A neutrophil count nadir less than 0.1×10^9 cells/L has been suggested as a criterion for a poor prognosis and an indication for treatment with growth factors in patients with nonchemotherapy drug–induced agranulocytosis (20). In our study, patients with an absolute neutrophil count less than 0.1×10^9 cells/L had more localized infections, sepsis, and fatal complications than did those with a nadir of 0.1×10^9 cells/L or greater. In patients who were asymptomatic at diagnosis and had a neutrophil count less than 0.1×10^9 cells/L, treatment with growth factors was associated with a statistically significantly lower rate of infectious complications and fatal complications, although this was not the case for patients with a neutrophil count nadir of 0.1×10^9 cells/L or greater. Our findings thus support previous recommendations (20) to treat patients with a neutrophil count nadir less than 0.1×10^9 cells/L with hematopoietic growth factors.

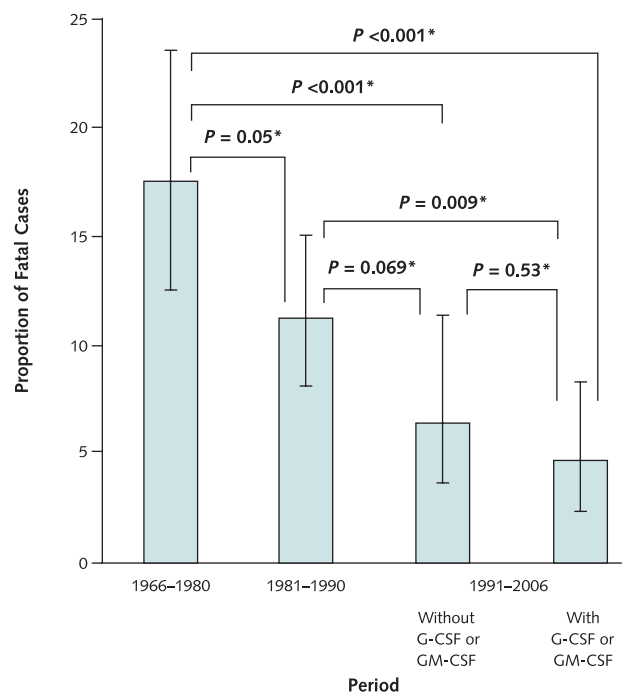
Mature neutrophil granulocytes and their bone marrow precursors may be affected in nonchemotherapy drug–induced agranulocytosis (25, 26). Of the reported bone marrow examinations in our case reports, 67% revealed signs of decreased generation of neutrophil granulocytes. This proportion is similar to that reported in other studies of nonchemotherapy drug–induced agranulocytosis, which showed impaired granulopoiesis in 65% (6) and 68% (25) of patients. The observation of impaired generation of granulocyte precursor cells in the bone marrow indicates an important difference in the pathogenesis of acute agranulocytosis and other blood dyscrasias (for example, drug-induced immune thrombocytopenia or drug-induced immune hemolytic anemia), in which peripheral cells are the main target of the immune reaction (27, 28).

One must be cautious when interpreting data from case reports because of several limitations. Case reports cannot provide a quantitative estimate of the risk for complications or death associated with a drug. Many patients with drug-induced adverse events are never reported in the literature, and we may have missed some case reports by limiting our searches to English-language and German-language studies indexed in MEDLINE or EMBASE and to bibliographies of retrieved articles. Some cases lacked important details about comorbid conditions, therapy, and outcomes and were difficult to evaluate for eligibility and causality. In 26 of 56 reports (46%) in which the drug was assessed as the definite cause of the agranulocytosis, the rating of “definite” was based on confirmation of drug-dependent antineutrophil antibodies, a positive result on the lymphocyte transformation test, or immune inhibition of granulocyte macrophage progenitors in the bone marrow. These tests lack standardization, which may have led to some misclassification in our causality assessment. Fi-

nally, published case reports sometimes emphasize atypical features and outcomes and do not provide unbiased estimates of treatment efficacy.

In conclusion, we identified an important number of drugs that definitely or probably cause nonchemotherapy drug–induced agranulocytosis and have not been investigated in previous epidemiologic studies. The proportion of fatal cases has decreased over the past decades. Treatment with hematopoietic growth factors seemed to be associated with a shorter duration of nonchemotherapy drug–induced agranulocytosis and a reduction in the number of infectious and fatal complications in patients who were asymptomatic at presentation. We also identified 11 drugs with more than 10 definite or probable reports, many of which had been associated with a high risk for agranulocytosis in epidemiologic studies. The manufacturers recommend routine blood count monitoring for 9 of these drugs (carbimazole, clozapine, dapsone, dipyrrone, long-term high-dose penicillin G, procainamide, rituximab, sulfasalazine, and ticlopidine) and monitoring in case of infection for methimazole and propylthiouracil. Patients receiving these drugs should be informed about the importance of such symptoms as fever, sore throat, or other infections, and

Figure 3. Proportion of fatal cases over time and treatment with granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF).



$P < 0.001$ for trends over time for 1966 to 1980, 1981 to 1990, and 1991 to 2006. Patients who were treated and those who were not treated with hematopoietic growth factors were included. Error bars represent 95% CIs. *Fisher exact test.

Table 3. Single Drugs Associated with an Increased Risk for Acute Agranulocytosis in Observational Studies*

Drug	Odds Ratio (95% CI)	Reference*	Evidence Level according to Systematic Review of Case Reports
Acetaminophen	2.4 (1.1–5.2)	9	2
Acetyldigoxin	9.9 (2.3–42.0)	14	No case report available
Aprindine	Increased†	14	2
Calcium dobesilate	77.8 (4.5–1346.2)	5	1
Carbamazepine	11.0 (1.2–102.6)	5	2
	5.9 (1.0–24.4)	9	
	16.9 (1.2–238.2)	15	
Carbimazole	16.7 (2.6–69.7)	9	2
Cinepazide	Increased†	14	No case report available
Clomipramine	20.0 (6.1–57.6)	9	2
Chlorpromazine	15.7 (1.3–182.1)	15	1
Diclofenac	3.9 (1.0–15.0)	5	1
Digoxin	2.5 (1.1–5.4)	14	No case report available
	5.9 (2.8–12.6)	9	
Dipyridamole	3.8 (1.3–11)	14	No case report available
Dipyrone	23.7 (8.7–64.4)	3	1
	25.8 (8.4–79.1)	5	
Erythromycin	7.6 (1.1–51.1)	5	3
Indomethacin	8.9 (2.9–27.8)	3	3
Methimazole	230.9 (120.4–453.5)	9	2
Phenytoin	11.6 (3.1–43.5)	5	1
Prednisone	19.9 (10.1–49.7)	9	2
Procainamide	Increased†	14	1
Propranolol	2.5 (1.1–6.1)	14	3
Pyrithylidione	200.11 (22.62–∞)	13	3
Spironolactone	20.0 (2.3–175.9)	5	1
Sulfasalazine	74.6 (36.3–167.8)	9	2
	24.8 (2.2–282.8)	15	
Ticlopidine	103.2 (12.7–837.4)	5	2
Trimethoprim-sulfamethoxazole	14 (4.9–42.0)	12	2
	25.1 (11.2–55.0)	9	
	10.4 (3.0–36.2)	15	

* Population-based case–control study done in Europe, Scandinavia, and Israel (International Agranulocytosis and Aplastic Anemia Study) (3, 12, 14); case–control study with data from a health care database done in Saskatchewan, Canada (15); case–control study done in the Netherlands using data from the PHARMO Record Linkage System health care database (9); population-based case–control study done in Spain (5, 13).

† Statistically significant increased risk without specification of the odds ratio.

blood counts should be obtained immediately if symptoms occur.

From Charité—Universitätsmedizin Berlin, Berlin, Germany, and Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany.

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Request for Single Reprints: Frank Andersohn, MD, Department of Clinical Pharmacology and Toxicology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; e-mail, frank.andersohn@charite.de.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Drs. Andersohn and Konzen: Department of Clinical Pharmacology and Toxicology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.

Dr. Garbe: Department of Clinical Epidemiology, Bremen Institute for Prevention Research and Social Medicine, Linzer Strasse 10, 28539 Bremen, Germany.