Incidence and Risk Estimate of Drug-Induced Agranulocytosis in Hong Kong Chinese. A Population-Based Case-Control Study.

Running title: Drug-induced agranulocytosis in Hong Kong Chinese

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'Take-home' messages

- The incidence and mortality in Hong Kong Chinese were relatively low compared to Caucasians.
- Antithyroid drugs were the most common class of drugs implicated in agranulocytosis in Hong Kong Chinese.
- Carbimazole had the highest risk of agranulocytosis in the current study.

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Abstract

Purpose Drug-induced agranulocytosis is a rare but life-threatening adverse drug reaction. Its epidemiology in Chinese is largely unknown. This study aimed to estimate the incidence, mortality, and risk of the drugs associated with agranulocytosis in Hong Kong Chinese. *Methods* A population-based case-control study was conducted using the Clinical Data Analysis and Reporting System, a database managed by the Hong Kong Hospital Authority. Patients with drug-induced agranulocytosis from 1 January 2004 to 31 December 2013 were identified. World Health Organization causality assessment was used to evaluate the possible drug aetiology of each case. Odd ratios (ORs) of the drug exposure were calculated using exact conditional logistic regression. *Results* 155 cases of drug-induced agranulocytosis were identified. Mean age was 51.4 years and 95 cases were female. Incidence rate was estimated to be 2.2 cases per million person-years and the all-cause mortality of patients with drug-induced agranulocytosis was 3.9%. Among the cases, the most common associated drug groups were antithyroid drugs (41.9%), antimicrobials (20%), anticonvulsants (10.3%), and antipsychotics (6.5%). Carbimazole had the highest risk of agranulocytosis (adjusted OR 416.7, 95% Confidence Interval (CI) 51.5 – 3372.9) with an incidence of 9.2 (95% CI 6.9 - 12.1) per 10,000 users and 3.6 (95% CI 2.7 - 4.8) per 10,000 user-years. Other drugs with significant risk included cephalosporins, clozapine, penicillins, phenytoin, and propyl thiouracil. *Conclusions* The incidence and mortality in Hong Kong Chinese were relatively low compared to Caucasians. Antithyroid drugs were the most common implicated drug class and carbimazole had the highest risk of agranulocytosis.

Introduction

Drug-induced agranulocytosis is a rare adverse drug reaction, clinically defined as absolute neutrophil count (ANC) lower than 0.5 x 10^9/L in circulating blood.[1, 2] Due to the extremely low neutrophil count, patients with agranulocytosis have a high risk of infection including pneumonia, and life threatening sepsis with non-specific preceding symptoms such as fever and sore throat,. The reported incidence rate of drug-induced agranulocytosis was 2.4-15.4 cases per million per year[3] and the mortality was estimated to be 5-9%.[4-6] Antithyroid drugs, antimicrobials, and antipsychotics have been commonly reported to induce agranulocytosis.[3]

A number of epidemiological studies have been conducted in Europe and different results across the countries have been reported,[4, 5, 7] which could be explained by the differences in drug treatment practice and genetic background of the subjects. Population-based study on drug-induced agranulocytosis has not been reported in Asians and only few case series reports on antithyroid drug-induced agranulocytosis in Chinese[8] and Taiwanese[9] have been published. The epidemiological profile in Chinese is still largely unknown. To fill in this knowledge gap, our study aims to estimate the incidence and mortality of drug-induced agranulocytosis in Hong Kong Chinese and evaluate the drug aetiology profile and their associated risk estimate with agranulocytosis.

Methods

The study protocol has been approved by the institutional review boards of the University of Hong Kong and Hospital Authority Hong Kong.

Data source

Clinical data in this study were obtained from the Clinical Data Analysis and Reporting System (CDARS), a database managed by the Hong Kong Hospital Authority (HA).[10] HA is a publicly funded healthcare provider, offering services to all residents in Hong Kong (>7 million people). CDARS contains patients' data, including demographic information, diagnosis, procedures, prescription, laboratory tests, admission and discharge information. The database has captured data since 1993 from all public hospitals, institutions and outpatient clinics under HA, and has been used to conduct high-quality local and multinational pharmacoepidemiological studies.[11, 12]

In addition to the clinical data from CDARS, medical notes written by clinicians were also reviewed to evaluate the drug causality of the cases. The medical notes were obtained from the electronic database in HA, which contains scanned copies of the written medical notes.

Case identification and selection

Potential cases of agranulocytosis, from 1 January 2004 to 31 December 2013, were first identified in CDARS by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 288.0 Neutropenia. Neutropenia was defined as ANC less than 1.5 x 10^9/L and was subdivided into Grade 1 to 4 by the Common Terminology Criteria for Adverse Events Ver. 4.0.[13] Agranulocytosis was defined as Grade 4 neutropenia (ANC less than 0.5 x 10^9/L). To confirm the cases of agranulocytosis, laboratory test records were reviewed. Only patients who had a record of ANC less than 0.5 x 10^9/L with a normal hemoglobin level (≥10 g/dL) and platelet count (100 x 10^9/L) were selected. The index day was deemed to be the day on which ANC<1.5 x 10^9/L, a threshold of abnormal neutrophil count in circulating blood. We excluded patients who met at least one of the following criteria: 1) receiving chemotherapy, radiotherapy, or the use of drugs for malignant disease and immunosuppression (British National Formulary 8.1 to 8.3) within 6 months

of index day; 2) having systemic diseases that could lower the neutrophil count (lymphoma, leukemia, myelodysplastic syndromes, hepatitis, HIV, systemic lupus erythematosus, rheumatoid arthritis, vitamin B12 deficiency, aplastic anemia, myelofibrosis, Crohn's disease, hypersplenism, infection, Kikuchi's disease, Sjogren's syndrome, chronic neutropenia, cyclic neutropenia, and congenital neutropenia); 3) age of onset younger than 3; 4) insufficient laboratory records and clinical data for evaluation.

Incidence rate and mortality

Incidence rate was calculated by dividing the number of cases by the total person-year during the study. The total person-year was estimated by summation of person-year of each year, which is calculated by the mid-year population data from the Census and Statistics Department, Hong Kong (http://www.censtatd.gov.hk/). We further calculated age- and sex- specific incidence to investigate any increased rate in subgroup populations. All-cause mortality of patient with a validated diagnosis of agranulocytosis during hospitalization was calculated.

Drug exposure and incidence

All prescription records and medical notes written by clinicians were reviewed to evaluate the causality between the drug intake and disease occurrence. We applied the World Health Organization causality assessment[14] and categorised the cases into "certain", "probable", "possible", "unlikely" according to 4 aspects: 1) a plausible time relationship to drug intake; 2) the absence of other causes or other drugs that induced the disease; 3) a reasonable response to the withdrawal of drug (positive dechallenge); 4) an existence of rechallenge or a positive result of drug dependent antibody testing against neutrophil granulocytes. A plausible time relationship was defined as the occurrence of disease during the drug therapy, or within 1 month after drug

withdrawal. A reasonable response to the withdrawal of drug was defined as neutrophil count returned to 1.5 x 10^9/L or higher. Cases categorized into certain and probable were selected for analysis. Cases with more than one suspected drug were grouped as multiple drugs and were not included in the drug analysis.

For each associated drug, the total number of patients prescribed the drug from 2004 - 2013 were obtained to calculate the drug-specific incidence of agranulocytosis.

Case-Control analysis

A case-control analysis was conducted to estimate the risk of drug that is associated with agranulocytosis. Controls were selected from patients visiting the out-patients clinics. For each case, four controls were matched on sex, exact age, and calendar year of the index day. The index day of control was the day visiting out-patient clinic. Same exclusion criteria as cases were applied to controls. Controls were considered as exposed to a drug if the drug had been prescribed in a window of 30 days preceding index day.

Statistical analysis

Continuous variables were presented as mean with S.D. or median with range and categorical variables were showed as frequency with percentage. The incidence rate with 95% confidence interval (CI) was estimated using Poisson distribution. Given the small number of cases, the exact method for conditional logistic regression was used to calculate odd ratios (ORs) and 95% CI. Age, sex, and any concurrent drugs with significant crude OR were adjusted. All calculations were performed with R statistical software package (version 3.0.1, www.R-project.org). A two-tailed p value < 0.05 was considered significant.

Results

Overall, 10,062 patients with a new diagnosis of neutropenia were identified in CDARS. Of these, 4,879 patients were confirmed to have agranulocytosis. After exclusion screening, 311 patients were remained for drug causality assessment. Of these, 154 patients with agranulocytosis were considered to be certain or probable drug-induced cases. As one patient had two episodes of agranulocytosis induced by two different antithyroid drugs (carbimazole and propyl thiouracil), a total of 155 cases were included in the analysis (The case screening flow chart is shown in Figure 1).The mean age of the cases was 51.4 years and over 60% of cases were female. Median length of stay was 9 days (range 1 - 123 days). The comorbidity of the cases was reviewed and cardiovascular disease (34.8%) was the most common chronic disease found in the cases, followed by diabetes (14.2%) and chronic renal diseases (7.1%). (Table 1)

Incidence rate and mortality

The age- and sex- specific incidence rate of drug-induced agranulocytosis were shown in Table 2. Based on total person-year of 69,875,600 during the study period, the overall incidence rate of drug-induced agranulocytosis was estimated to be 2.2 (95% CI 1.9-2.6) cases per million person-years. Women (incidence rate 2.6, 95% CI 2.1-3.2) were more likely to have the disorder than men (incidence rate 1.8, 95% CI 1.4-2.4). In both sexes, the incidence rate increased with age. The incidence rate per million person-years in people aged over 65 was 4.6 (95% CI 3.4-5.9), which was at least twice higher than people in other age groups (incidence rate 0.5, 95% CI 0.2-1.0 in people aged 0-19; 2.1, 95% CI 1.5-2.8 in people aged 20-39; 2.1, 95% CI 1.6-2.8 in people aged 40-64). The trend of incidence rate was significantly increased from 2004 - 2013 ($p = 0.028$, Figure 2).

Among the cases, 6 patients (2 female and 4 male) died during hospitalization. 5 of the patients (83.3%) were aged over 60 and all patients had at least one chronic disease. The all-cause mortality in patients with drug-induced agranulocytosis was calculated to be 3.9%.

Drug aetiology

A total of 59 drugs were identified to have a certain or probable association with agranulocytosis (Table 3). Of these, a majority of cases were induced by antithyroid drugs (41.9%), with carbimazole (33.5%) to be the most common implicated drug. Antimicrobials (20%) and anticonvulsants (10.3%) were the second and third common group of drugs. Among the group of antimicrobials, over one-third (41.9%) of the cases were induced by penicillins. Other associated drugs included antipsychotics (6.5%), antigout dugs (1.9%), antiplatelet drugs (1.9%), antidepressants (1.3%), iron-chelating drugs (1.3%), calcium channel blockers (0.7%), and nonsteroidal anti-inflammatory drugs (0.7%). Notably, two cases were associated with traditional Chinese medicine (TCM).

Out of the 134 cases (excluded cases induced by TCM, over-the-counter drug, or multiple suspected drugs), agranulocytosis occurred within the first 30 days of drug exposure in 46.3% of cases; 46.3% within 31-60 days and 5.2% within 61-90 days. The median (range) exposure time to drugs was 33 days (0-1201). Antipsychotics had the longest median exposure duration of 48.5 days (27-1201), in which one clozapine-induced case had agranulocytosis after 3 years of treatment. Antithyroid drugs and anticonvulsants had the median exposure time of 35.5 days (0-106) and 32 days (13-74), respectively. The duration was the shortest for antimicrobials, at 20 days (2-48).

The incidence of agranulocytosis for each specific drug was shown in table 3. Although methimazole has the highest incidence proportion of 47.2 cases per 10,000 users (95% CI 1.2 - 262.8), and incidence rate of 22.9 cases per 10,000 patient-years (95% CI 0.6-127.8), estimation was based on one case only. For drugs with at least 3 cases reported, carbimazole, propyl thiouracil, and clozapine have a higher incidence (incidence proportion 9.2 - 19.8 cases per 10,000 users; incidence rate 3.6 - 4.9 cases per 10,000 user-years), compared to phenytoin, penicillins, cephalosporins, and rifampicin (incidence proportion 0.7 - 1.4; incidence rate 0.1 - 0.8).

The four most common drug classes (antithyroid drugs, antimicrobials, anticonvulsants, and antipsychotics) were included in the case-control analysis. 488 controls were matched with 122 cases. As expected, carbimazole had the highest risk (adjusted OR 416.7, 95% CI 51.5-3372.9) of agranulocytosis, and followed by clozapine (adjusted OR 154.6 (95%CI 12.9-1853.9), and propyl thiouracil (adjusted OR 40.7, 95% CI 5.2–316.8). Other drugs with significant increased risk included penicillins, cephalosporins, and phenytoin. (Table 4)

Discussion

Our study evaluated the epidemiological profile, including incidence, drug aetiology, and mortality of drug-induced agranulocytosis, in Hong Kong Chinese using a population-based health database in Hong Kong. Our data were consistent with previous studies in other populations showing a relatively low incidence and mortality.

In the early 1980s, the International Aplastic Anemia and Agranulocytosis Study (IAAAS) has estimated the incidence of agranulocytosis in European countries to be 6.2 cases per million per year with a large difference across the regions, ranging from 1.7 in Milan, Italy to 9.0 in Budapest, Hungary.[5] Over the years, several population-based studies conducted in Caucasians have reported

similar incidence, ranging from 2.0 - 9.2 cases per million per year.[4, 15-18] Compared to these studies, we observed a relatively lower incidence with slight increase over the years. The low incidence of agranulocytosis was also reported in Thai population (0.7 cases per million per year),[19] suggesting that Asians may have a lower incidence of drug-induced agranulocytosis compared to Caucasians.

Old age was commonly reported as a risk factor for agranulocytosis as the incidence rates reported in the literature were consistent in the age group of 20-39 and 40-59, while the rate in the group aged over 60 was reported to be twice higher. A Thai study by Shapiro et al estimated an incidence rate of 3.6 cases per million per year at aged over 60, which was three times higher than other age groups[19]. Studies suggested that the high risk in older patients could be attributed to the increased number of concurrent drugs patients might be taking. We investigated this potential association with our data and found that the mean±sd number of concurrent drugs in patients at age over 60 was 10.7±5.0 while at age below 60 was 5.1±4.4. A significant difference ($p<0.001$) was observed. It is possible that polypharmacy may increase the potential of drug-drug interactions and hence increase the risk of agranulocytosis. A case report described a patient with 3-year treatment of clozapine developed agranulocytosis after the addition of valproic acid, an anticonvulsant.[20] Although currently there are limited studies on exploring the potential impact of drug-drug interactions on the occurrence of agranulocytosis, clinicians should be aware of the higher risk of adverse drug events in patients with multiple drug exposures.

The ratio of women to men in our study was 1.6 to 1 and a higher incidence rate was estimated in women, which was similar to previous studies.[3, 15] More women were observed to have the higher incidence probably due to the drug aetiology profile, as antithyroid drugs were the most common

drugs associated with agranulocytosis in our population, and hyperthyroidism is predominantly present in women.[21]

A broad-spectrum of drug aetiology profile was observed in the current study, which was generally comparable with other populations. In our study, we found that antithyroid drugs were the most common drugs to be associated with a high risk of agranulocytosis, which is a phenomenon that has been well-documented in the literature. The IAAAS estimated a relative risk of 102 (95% CI 38 - 275) in antithyroid drugs,[22] whereas study by van der Klauw et al reported a relative risk of 114.8 (95% CI 60.5 – 218.6).[15] In accordance with these studies, we reported large ORs of 416.7 and 40.7 in carbimazole and propyl thiouracil respectively.

Antimicrobials were the second most common drug class but only penicillins and cephalosporins, both belong to the group of beta-lactams, had an elevated risk of agranulocytosis. Several studies reported the association of beta-lactams and agranulocytosis and the ORs were estimated to be 3.1 - 4.7 cases per million.[4, 15, 17] Compared with previous studies, we observed a higher risk (penicillins, adjusted OR 8.1; cephalosporins, adjusted OR 21.4). However, an important point to note is that beta-lactams can be prescribed for the treatment of potential infections associated with agranulocytosis, without the data on the date of onset of infection which possibly prompted the prescribing of penicillin, some of the cases identified may actually have the exposure to penicillin after the onset of agranulocytosis. We therefore cannot exclude the possibility of overestimating the risk of agranulocytosis associated with the use of beta-lactams in our study.

One case of oxcarbazepine-induced agranulocytosis was identified in this study. Oxcarbazepine, a 10-keto analogue of carbamazepine, is one of the newer antiepileptic drugs. Like carbamazepine, the major adverse event of oxcarbazepine is cutaneous adverse reactions such as Stevens-Johnson

Syndrome. To date, only seven cases were reported in the literatures to be oxcarbazepine-induced blood dyscrasias[23-29] but none of the cases was agranulocytosis. Thus, our study reported the first oxcarbazepine-induced agranulocytosis in the literature. Interestingly, among eight oxcarbazepine-induced blood dyscrasias (including our case), four occurred in Asians[24, 26, 27] (including 3 Chinese and 1 Asian-American), suggesting that genetic predisposition may play a role on the pathogenesis of oxcarbazepine-induced blood dyscrasias, warranting further investigation.

The exposure period of each drug groups were comparable with other studies.[2] Over 90% of our cases developed agranulocytosis within the first three months of drug treatment, with half of the cases having exposed to the drug for more than one month. However, there were few reports of late onset of agranulocytosis after prolonged treatment of clozapine[30, 31] and antithyroid drugs[32]. In our study, we also found one case with delayed onset after three years of clozapine treatment. In view of the long exposure period before onset of agranulocytosis, debate over the effectiveness of routine blood monitoring has been discussed for years. Tajiri et al showed that 43 out of 55 antithyroid drug-induced cases were asymptomatic and detected during routine blood monitoring, supporting the need of regular monitoring.[33] In contrast, study by Nakamura et al reported that more than half of the antithyroid drugs-associated cases had normal blood count in two weeks before onset of agranulocytosis, arguing that routine monitoring of blood cell count had little value in predicting the disease.[34] In our cases, all nine patients with clozapine-induced cases had blood monitoring on a weekly basis. However, only three cases showed a gradual decrease in ANC while four cases had a sharp drop compared to the last record. For antithyroid drug-induced case, over 80% of them did not have blood monitoring during the exposure period. Even if the blood counts were monitored, the intervals were so long that any gradual decrease could hardly be detected. It

seems that routine blood monitoring to detect agranulocytosis is not promising but whether it can allow early detection and hence lower the severity of the disease, in terms of infection rate, length of stay and complications, are worth investigating.

The mortality of drug-induced agranulocytosis in European populations was reported to be 4.8 - 9.1%[4-6, 15, 35] and has a decreasing trend in recent years.[2] Risk factors associated with mortality in agranulocytosis cannot be investigated in current study due to small number of deaths but we found that most of them were older patients (aged over 65) with at least one chronic disease. Compared to European populations, our study estimated a lower mortality which may be due to a couple of reasons. First of all, some European studies were conducted 20-30 years ago when treatment for agranulocytosis was not as advanced as nowadays, possibly resulting in poorer treatment outcomes for the patients. Furthermore, drug aetiology profiles were different and it seems that some drugs, particularly metamizole, induced more severe cases than the others. The IAAAS reported a 9% fatality rate among cases associated with analgesics (mainly metamizole)[5] but only 2% in antithyroid drug-associated cases.[22] Similarly, a German study on metamizole-associated agranulocytosis reported a high fatality rate of 23%.[36] Our cases may be less severe as none was induced by metamizole and most of them were induced by antithyroid drugs.

Apart from old age and the female gender, genetic predisposition is also a risk factor of agranulocytosis. Study by Goldstein et al had reported that two human leukocyte antigen (HLA) alleles in HLA-DQB1 and HLA-B were associated with clozapine-induced agranulocytosis.[37] A Taiwanese study identified strong markers HLA-B*38:02 and HLA-DRB1*08:03 in antithyroid drugs-induced agranulocytosis.[38] Another study in Hong Kong Chinese population also reported a strong association between HLA-B*38:02 and antithyroid drugs-induced agranulocytosis.[39] In

European population, another marker, HLA-B*27:05, was found in antithyroid drugs-induced agranulocytosis.[40] Given the effectiveness of genetic screening in preventing rare adverse drug reactions,[41, 42] it is worth considering the incorporation of genetic screening in future clinical guidelines.

Our study has several strengths and limitations. First, the database CDARS contains a comprehensive clinical data and it captures patients from all the publicly-funded hospitals and ambulatory clinics, allowing a population-based analysis of the disorder. Second, the controls were matched with age, sex, and index day for a comparable characteristics and drug exposure period to the cases, minimising the confounding bias. Limitations in the study included the small sample size, given a rare disease, which leaded to a wide CI in the risk estimate. In addition, we cannot exclude the possibility of under diagnosis and recording. Nevertheless, as CDARS is used for clinical management, it is believed that such an important clinical diagnosis is unlikely to be missed. Furthermore, during the drug causality assessment, cases were excluded due to limited drug exposure records. These patients may have the prescription of the associated drug from the private clinics or hospitals, which were not covered by CDARS. As a result, an underestimation of incidence cannot be ruled out.

In conclusion, the incidence and mortality in Hong Kong Chinese was relatively lower compared with Caucasians. The drug aetiology profile was comparable with those in literatures, and carbimazole, clozapine, and propyl thiouracil had been associated with the highest risk of agranulocytosis.

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Table 1 Characteristics of patient with drug-induced agranulocytosis

Characteristics	**Case (n=155)**
Female, n (%)	95 (61.3)
Age	
Mean ± SD.	51.4 ±20.5
>60, n (%)	56 (36.1)
Chronic disease, n (%)	
Cardiovascular diseases	54 (34.8)
Diabetes	22 (14.2)
Chronic renal disease	11 (7.1)
Community acquired, n (%)	84 (54.2)
Length of stay, median (range)	9 (1-123)
Death, n (%)	6 (3.9)

Table 2 Age- and Sex- specific incidence rate^ of drug-induced agranulocytosis from 2004 to 2013.

Age	Women			Men			Total		
	Cases (n)	Incidence rate	(95% CI)	Cases (n)	Incidence rate	(95% CI)	Cases (n)	Incidence rate	(95% CI)
0 - 19	3	0.5	(0.1–1.4)	3	0.4	(0.1-1.3)	6	0.5	(0.2-1.0)
20 - 39	33	2.8	(1.9–3.9)	11	1.2	(0.6-2.1)	44	2.0	(1.5-2.8)
40 - 59	30	2.5	(1.7-3.5)	19	1.7	(1.0-2.7)	49	2.1	(1.6-2.8)
≥60	29	4.5	(3.0-6.5)	27	4.6	(3.0-6.7)	56	4.6	(3.4-5.9)
Total	95	2.6	(2.1-3.1)	60	1.8	(1.4-2.4)	155	2.2	(1.9-2.6)

^incidence rate per million person-years

Table 3 Drug aetiology profile and incidence from 2004 – 2013 for specific drug

Drug class	Drug	Cases, n	No. of drug users	Incidence proportion per 10,000 users (95% CI)		Incidence rate per 10,000 user-years (95% CI)	
Antithyroid drugs	Carbimazole	52	56,249	9.2	(6.9-12.1)	3.6	(2.7-4.8)
	Propyl thiouracil	12	10,441	11.5	(5.9-20.1)	4.9	(2.5-8.6)
	Methimazole	1	212	47.2	(1.2-262.8)	22.9	(0.6-127.8)
Antimicrobials	Penicillins^	13	124,294	1	(0.6-1.8)	0.1	(0.1-0.2)
	Cephalosporins$^{\Delta}$	8	112,973	0.7	(0.3-1.4)	0.1	(0.1-0.2)
	Rifampicin	4	41,401	1	(0.3-2.5)	0.8	(0.2-1.9)
	Vancomycin	2	56,825	0.4	(<0.1-1.3)	0.3	(<0.1-1.1)
	Meropenem	2	45,078	0.4	(0.1-1.6)	0.4	(0.1-1.4)
	Doxycycline	1	76,095	0.1	(<0.1-0.7)	0.1	(<0.1-0.6)
	Cotrimoxazole	1	93,239	0.1	(<0.1-0.6)	0.1	(<0.1-0.5)
Anticonvulsants	Phenytoin	9	62,473	1.4	(0.7-2.7)	0.6	(0.3-1.2)
	Lamotrigine	2	5,079	3.9	(0.5-14.2)	1.2	(0.1-4.1)
	Carbamazepine	2	28,399	0.7	(0.1-2.5)	0.2	(<0.1-0.7)
	Oxcarbazepine	1	1,256	8	(0.2-44.4)	2.5	(0.1-14.0)
	Topiramate	1	2,907	3.4	(0.1-19.2)	1.0	(<0.1-5.6)
	Gabapentin	1	60,573	0.2	(<0.1-0.9)	0.1	(<0.1-0.5)
Antipsychotics	Clozapine	9	4,551	19.8	(9-37.5)	3.6	(1.6-6.8)
	Quetiapine	1	41,296	0.2	(<0.1-1.3)	0.1	(<0.1-0.6)
Antigout drugs	Allopurinol	2	100,285	0.2	(<0.1-0.7)	0.1	(<0.1-0.2)
	Colchicine	1	19,5458	0.1	(<0.1-0.3)	<0.1	(<0.1-0.1)
Traditional Chinese Medicine	-	2	-	-		-	
Others†	-	5	-	-		-	
Multiple drugs	-	18	-	-		-	

^Penicillins include piperacillin/piperacillin+tazobactam (9), cloxacillin (3), and Ticarcillin/clavulanic acid (1).

$^{\Delta}$Cephalosporins include ceftriaxone (6), cefuroxime (1), and cefotaxime (1).

†Others include clopidogrel (3), mirtazapine (2), deferiprone (2), diclofenac (1), amlodipine (1), over-the-counter drug with unknown ingredient (1)

Table 4 Risk estimate of drug associated with agranulocytosis

Drug class	Drug	Cases (n=122)	Control (n=488)*	Crude odd ratio (95%CI)	Adjusted odd ratio (95%CI)^
Antithyroid drugs	Carbimazole	52	5	198.1 (27.4 – 1433.6)	416.7 (51.5 – 3372.9)
	Propyl thiouracil	12	1	48.0 (6.2 – 369.2)	40.7 (5.2 – 316.8)
	Methimazole	1	0	-	-
Antimicrobials	Penicillins	13	20	3.0 (1.4 – 6.5)	8.1 (2.8 – 23.4)
	Cephalosporins	8	4	8.0 (2.4 – 26.6)	21.4 (3.9 – 116.0)
	Rifampicin	4	0	-	-
	Vancomycin	2	1	8.0 (0.7-88.2)	-
	Meropenem	2	0	-	-
	Cotrimoxazole	1	0	-	-
	Doxycycline	1	0	-	-
Anticonvulsants	Phenytoin	9	5	8.5 (2.6 – 27.7)	31.6 (4.9 - 201.9)
	Carbamazepine	2	3	2.7 (0.5 – 16.0)	-
	Lamotrigine	2	1	8.0 (0.7 – 88.2)	-
	Gabapentin	1	6	0.7 (0.1 – 5.5)	-
	Oxcarbazepine	1	0	-	-
	Topiramate	1	0	-	-
Antipsychotics	Clozapine	9	1	36.0 (4.6 – 284.2)	154.6 (12.9 - 1853.9)
	Quetiapine	1	3	1.3 (0.1 – 12.8)	-

*drug that was not exposed in control group were excluded in the analysis

^adjusted for age, sex, and any concurrent drugs with significant OR in the crude model

Figure 1 Case screening flow chart

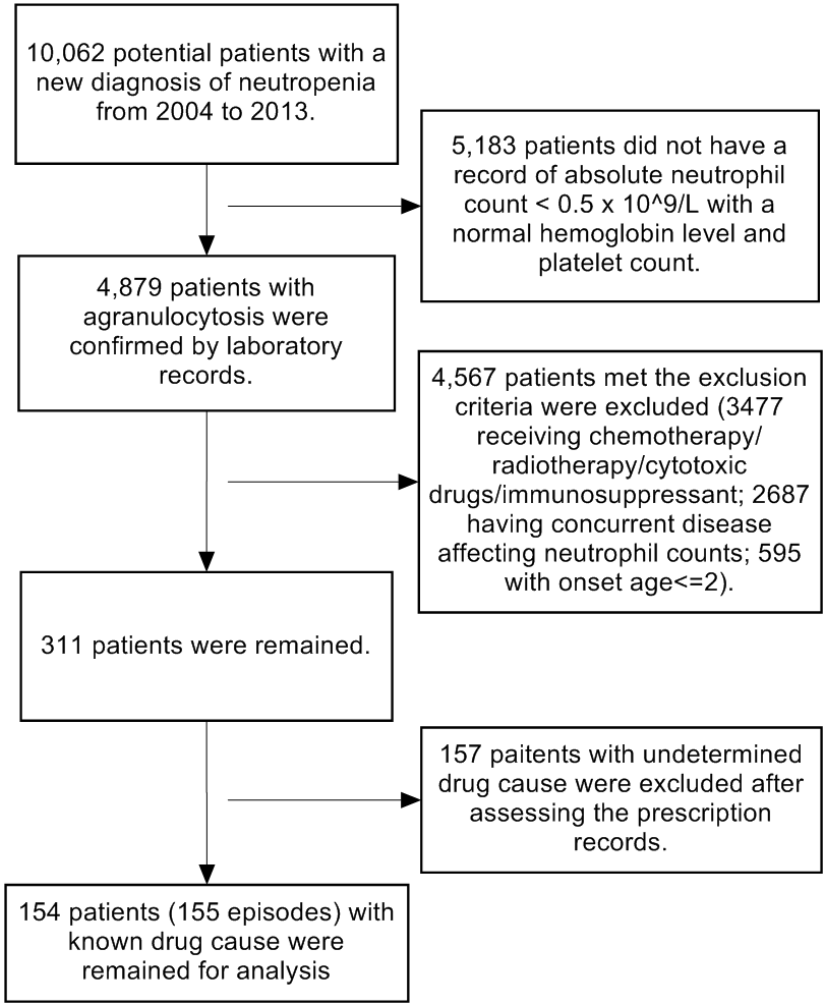

Figure 2 Annual incidence rate of drug-induced agranulocytosis from 2004 - 2013