

SEMINAR

Drug fever: a narrative review

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ABSTRACT

Drug fever is an adverse drug reaction accompanied by a febrile response and is a common problem among clinicians, hence an updated knowledge of drug fever is important. A consensus regarding the definition of drug fever is lacking. Thus, descriptions of drug fever in previous literature are often inconsistent. In this narrative review, we summarized various features of drug fever, including its definition, epidemiology, risk factors, clinical presentation, diagnosis, treatment and prognosis, based on the earliest literature. Recent advances in information technology have encouraged researchers to use pharmacovigilance databases for clinical and pharmacological research. We outlined how a pharmacovigilance database, along with recently developed research methods, could be used to research drug fever.

KEY WORDS

drug fever, drug adverse reactions, narrative review

INTRODUCTION

Fever is a condition in which patients manifest elevated body temperatures, and a body temperature of above 37.3°C is usually considered abnormal [1]. Although the precise mechanism is yet to be elucidated, the human body temperature is regulated by a thermoregulatory center located in the anterior hypothalamus [2]. When exogenous pyrogens, such as bacteria or viruses, enter the human body, they are phagocytosed by lymphocytes and activated. Activated lymphocytes release cytokines, such as interleukin-1, that stimulate the thermoregulatory center, and the stimulated thermoregulatory center raises the “set point” of the body temperature. The human body responds to elevated body temperature (e.g., by shivering); thus, the patient manifests with an elevated body temperature.

Heat stroke also accompanies elevated body temperature but the “set point” of the body temperature is not changed. In this situation, excessive heat increases body temperature beyond the thermoregulatory center. This condition is called “hyperthermia” and is distinguished from fever. In adverse drug reactions (ADRs), both fever and hyperthermia can occur, depending on the type of culprit drug.

Drug fever is an adverse reaction that accompanies fever. Drug fever is a common problem for clinicians because drugs are used for treatment, prevention, and even diagnosis. As all clinicians may prescribe drugs that can cause drug fever and treat patients who present with drug fever, clinicians must be familiar with the diagnosis and treatment of drug fever.

The main pathophysiology of drug fever is hypersensitivity to drugs, such as an immune response. Among the

four classical classifications of allergic reactions [3], drug fever is classified as a type III reaction [4]. This finding originated from the observation of patients with serum sickness, which is considered an entity similar to drug fever. The pathophysiology of serum sickness was speculated to be a type III reaction because the patients had decreased serum C3 and C4 levels, and skin biopsy revealed immune deposits in the blood vessels of some patients.

Although previous narrative reviews of drug fever outlined the diagnosis and treatment of drug fever [5], several new agents have emerged in the past decade. Some of the diseases are known to cause drug fevers. In addition, a recent study on drug fever using a pharmacovigilance database, along with several methods, such as the proportional reported ratio, provided new insights into drug fever [6].

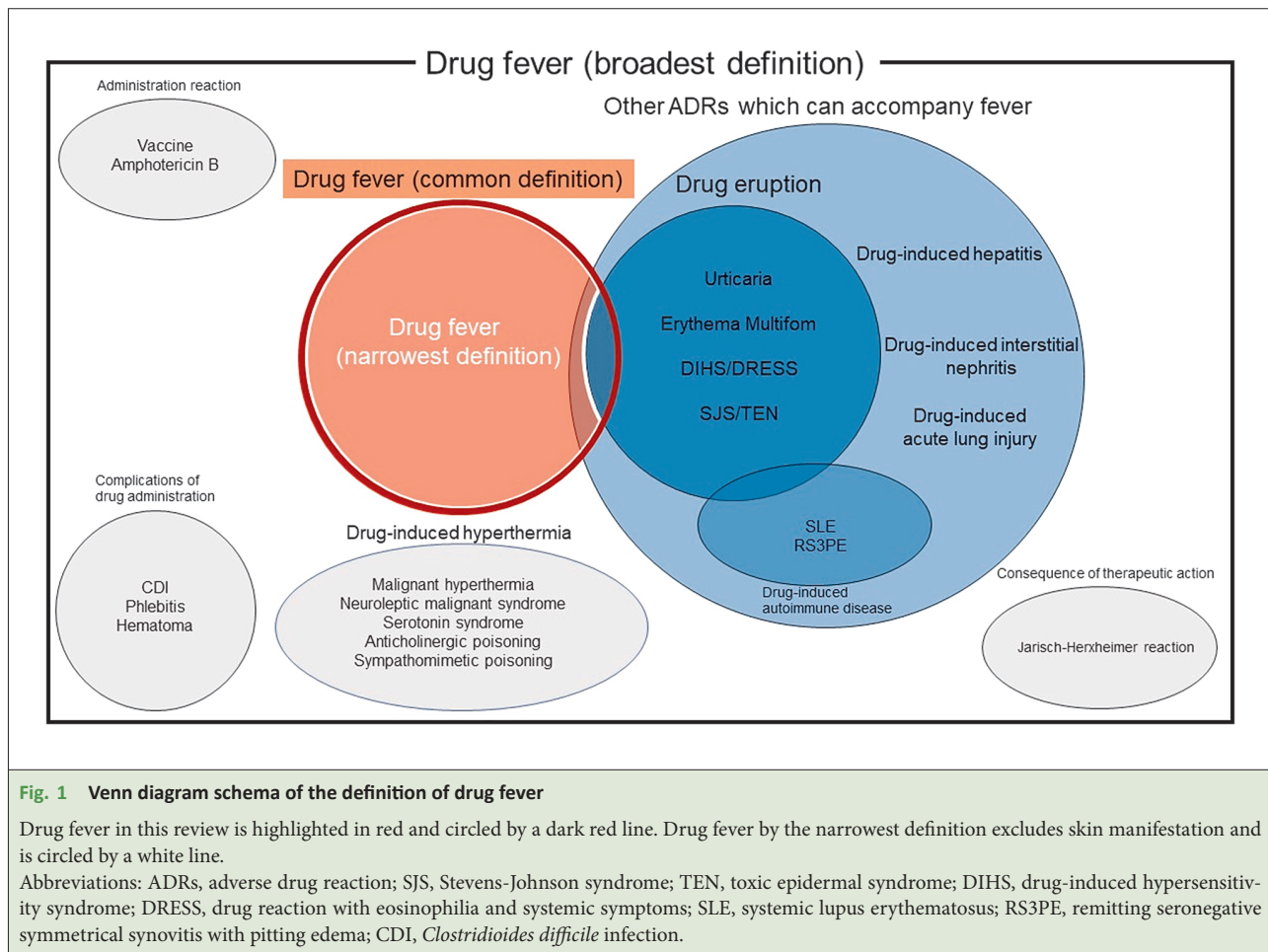
In this seminar article, we provide an updated review of the clinical aspects, such as epidemiology, diagnosis, and treatment of drug fever.

METHOD

We searched Pubmed and Embase on November 26, 2022. We used the terms “drug fever” and “drug-induced fever.” We included all English-language review articles and cohort studies without any restrictions on publication year. For case reports, we included articles published after 2010 because a previous narrative review [5] summarized case reports published between 1950 and 2009. We checked the references in the included articles and assessed their relevance. In addition, we checked the articles that cited our included articles in the Citation Chaser [7]. Google Scholar was used for articles that were not indexed in the citation chaser.

DEFINITION

To date, there is no unified definition for drug fever. Many specific types of ADRs accompany febrile reactions (**Fig. 1**); however, there is a disagreement among researchers regarding which diseases should be considered part of drug fever.



The broadest definition of drug fever includes complications of drug administration, such as phlebitis, hematoma, chemical meningitis, *Clostridioides difficile* infection, drug-induced hyperthermia (malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, anticholinergic poisoning, and sympathomimetic poisoning), administration reactions (e.g., amphotericin B or vaccine-related reactions), and consequences of therapeutic action (Jarisch-Herxheimer reaction) [8]. However, we have excluded these entities from this review.

In this review, we define drug fever as a febrile response that fulfills all the following criteria: i) initiation after drug administration; ii) resolution within 72 h after discontinuation of the drug without specific therapy; iii) no other cause identified by history, physical examination, laboratory, or imaging investigation; and iv) no relapse of fever 72 h after defervescence. Some researchers have excluded febrile ADR with skin manifestation [6, 9]; however, this definition may be too strict. We included ADR with fever and skin rash in drug fever, but severe forms of drug eruption, such as Stevens-Johnson syndrome and drug-induced hypersensitivity syndrome, were excluded. Although other febrile ADRs, such as drug-induced hepatitis, drug-induced interstitial nephritis, and drug-induced acute lung injury, can be included in the above definition, it is impossible to distinguish these entities from drug fever.

EPIDEMIOLOGY

Compared to ADR, few reports have described the incidence of drug fever. A national health insurance claims data-based study in Korea estimated that the annual incidence of drug fever is approximately 0.001% [10]. An old single-center retrospective cohort study reported that among 1,000 consecutive patients treated in a general internal medicine ward, 42 (4.2%) developed some type of ADR, and two (0.2%) had fever and rash [11]. A three-year prospective single-center cohort study reported that among the 7,765 included patients, 122 (1.6%) experienced major antibiotic-induced disease and 9 (0.1%) had fever [12]. We found no available data on the incidence of drug fever in a population receiving multiple types of drugs. Single-center retrospective cohort studies revealed that 0.7–13.1% of patients who received antibiotics developed drug fever [16–18]. Retrospective cohort studies revealed that 2.8–8.7% of patients who received anti-neoplastic agents developed drug fever [19, 20]. Recent studies based on pharmacovigilance data have reported that drug fever in ADR is 2–10% [13–15].

Drug fever is an important differential diagnosis among patients admitted to investigating the cause of the fever. Japanese single-center retrospective cohort studies reported that drug fever accounted for 1.8–5.7% of all causes of fever in patients who were admitted for investigating the causes of fever [21, 22].

Drug fever is an important differential diagnosis of fever of unknown origin. Fever of unknown origin was defined as a temperature of $\geq 38.3^{\circ}\text{C}$ for at least 3 weeks without a definite diagnosis despite 3 inpatient days or at least three outpatient visits [23]. A few single-center retrospective cohort studies have reported that drug fever accounts for approximately 2% of cases with fever of unknown origin [24–26].

It is commonly believed that drug fever is a common cause of nosocomial fever yielding about 10% [23, 27, 28]. However, this number may have been misquoted to include all types of ADR, not just drug fever [11]. A prospective cohort study of nosocomial fever in Thailand reported that among 86 patients with nosocomial fever, only 3 (3.5%) were diagnosed with drug fever [29].

RISK FACTORS

Risk factors for drug fever have not yet been determined. A previous narrative review discussed the risk factors for drug fever using an old study [5]. However, the cited study was a case series of drug fever [30]. The study had no comparator and, thus, could not estimate the quantitative risk. Previous narrative reviews reported that older age and women are risk factors for drug fever [27, 31, 32]. However, this description may have been misquoted to include all types of ADR, not just drug fever [11]. No studies have investigated the risk factors of drug fever in a population receiving multiple types of drugs.

There are few reports on the risk factors of drug fever induced by specific drugs. A single-center retrospective cohort study revealed that age was negatively associated with carboplatin-associated drug fever (adjusted odds ratio, 0.126; 95% confidence interval, 0.025–0.628) [19]. In other words, younger patients are more likely to develop drug fever. Patient sex was not investigated because the study was conducted in a hospital with female patients. Other factors, such as body mass index, allergy history, disease type or stage, and carboplatin history, were not associated with carboplatin-induced drug fever. Another single-center retrospective cohort study revealed that female sex (adjusted odds ratio, 3.162; 95% confidence interval, 1.264–7.914) and concomitant use of clarithromycin (adjusted odds ratio, 4.834; 95%

confidence interval, 2.165–10.794) were associated with furazolidone-induced drug fever [33]. Age was not associated with furazolidone-induced drug fever. However, these findings are related to specific agents and have no assurance of generalizability.

CLINICAL PRESENTATION

Time Between Initiation of the Culprit Drug and Development of Fever

A case series of drug fever due to various drugs reported that the median time between the initiation of the culprit drug and the development of fever was 2–8 days [6, 30]. However, it is well known that the time interval can vary widely depending on the type of drug [6, 30]. For example, the time interval for antibiotics is 1–5 weeks (most commonly within 1–2 weeks) [16, 18, 30, 34–40]. The time interval between the administration of anti-neoplastic agents is 3–4 days [20].

The time interval for drug fever may be shortened if patients have previously received the same class of agents. A single-center retrospective cohort study reported that the median time interval of piperacillin-induced drug fever in patients without a history of administration of some kind of β -lactams was 22.5 days, whereas it was 13 days in patients with a history of administration of some kind of β -lactams [16].

Fever Pattern

No specific patterns were observed for drug fever. This knowledge is common in old textbooks and recent literature [6, 8, 30]. Similar to other febrile illnesses, such as infectious diseases, drug fever can develop into various fever patterns [1]. Therefore, fever patterns cannot be used as diagnostic indicators of drug fever.

Associated Symptoms of Drug Fever

Bradycardia is the most common symptom of drug fever. The pulse rate increases in proportion to high body temperature in many infectious diseases, which is known as Liebermeister's rule [41]. The pulse rate at 102 degrees Fahrenheit (around 39) is estimated to be 110 beats per minute, from which the pulse rate increases by 10 beats per minute for every 1 degree Fahrenheit (approximately 0.55°C) increase in body temperature. However, this correlation between fever and pulse rate has not been observed in a few diseases. A constant or decreasing pulse rate with an elevated body temperature is referred to as pulse-temperature dissociation (deficit), Faget's sign, or, most commonly, relative bradycardia [42]. It is

defined as a pulse rate lower than that expected from the body temperature [42]. In some case series of antibiotic-induced drug fever, the incidence of relative bradycardia in drug fever was reported to be 83–100% [37, 38]. Another case series reported that the incidence of relative bradycardia in patients with drug fever was 11%; however, the authors used a different definition for relative bradycardia (pulse rate 100/min or lower during fever) [30]. Based on these results, relative bradycardia in the correct definition may be a common symptom of drug fever. Although the diagnostic accuracy of relative bradycardia for drug fever in febrile patients has not been fully investigated, the absence of relative bradycardia may help rule out drug fever.

Some clinicians believe that one of the characteristic findings of drug fever is the “inappropriate sense of well-being” of the patient despite the fever [35]. A case series of antibiotics-induced fever reported that “reduced general condition” was observed in 3 out of 11 patients with drug fever. However, the definition of “reduced general condition” was not described in detail in their research. Whether an “inappropriate sense of well-being” can help to diagnose drug fever remains to be determined.

Skin manifestations are a common symptom of drug fever. Although the reported incidence is highly variable according to the type of causative drug, it is reportedly 15–31% [16, 30, 34, 36–38]. The most common type of skin rash in drug fever is maculopapular rash, which is also called morbilliform (which means ‘measles-like’) or exanthematous rash [43]. Patients with maculopapular rashes typically exhibit symmetrical rashes consisting of red macules and papules on the entire body. Urticaria is a possible type of skin rash associated with drug fever.

Shaking chills, defined as chills accompanied by shaking of the generalized body (rigor) despite wearing a thick blanket, are strongly associated with bacteremia [44]. However, shaking chills can also occur in drug fevers, yielding 36–51% [30, 36]. Therefore, the presence of shaking chills does not exclude a diagnosis of drug fever.

Other symptoms such as nausea, headache, and arthralgia are known to cause drug fever [30].

Laboratory Findings

Although there are no specific laboratory findings for drug fever, some laboratory findings have been observed in patients with drug fever.

Eosinophilia is the most common laboratory finding associated with fever. The reported incidence of eosinophilia and its definition vary greatly among studies,

yielding 0.9–25% [6, 16, 30, 34, 38–40]. Some authors define eosinophilia as eosinophils 300 or greater [30], 500 or greater [16], or 5% or greater [39]. Other studies have not reported a definition of eosinophilia [6, 34, 38].

Leukopenia is also associated with drug fever. Although the definition is not always clear, the reported incidence of leukopenia is 0.9–90% [6, 16, 36].

Elevated C-reactive protein levels are also observed in drug fever [36, 40]. A case series of antibiotics-induced drug fever reported that C-reactive protein levels increase in 10 out of 11 cases of drug fever, with a median value of 5 mg/dL (range: 3.2–22.9 mg/dL) [36].

Procalcitonin, a precursor peptide of calcitonin, is a predictive marker of bacteremia [45]. A case series of antibiotics-induced drug fever reported that among patients with drug fever and procalcitonin examined, it was lower than 0.25 ng/dL in 10 out of 11 patients [38].

Other laboratory findings included elevated liver enzyme levels, renal failure, or anemia [39, 46].

DRUGS ASSOCIATED WITH DRUG FEVER

Numerous drugs have been associated with fever (Table 1). Clinicians should be aware that some of these

drugs are not only prescribed in hospitals or clinics but may also be included as one of the ingredients of over-the-counter drugs (e.g., ibuprofen is included in many over-the-counter painkillers). Since the publication of a previous review [5], several new drugs have been reported to cause drug fever. These include acitretin [47], bendamustine [48], celecoxib [49], dalteparin [50], dexmedetomidine [51], doxycycline [52], enoxaparin [53, 54], ertapenem [55], favipiravir [56–59], imipenem/cilastatin [60], mesalamine [61], olanzapine [62, 63], pantoprazole [64, 65], propofol [66], S-carboxymethyl-L-cysteine [67], sorafenib [68], teicoplanin [69], tigecycline [70], and vildagliptin [71].

DIAGNOSIS

An essential point in the diagnosis of drug fever is suspected. There are two main situations in which drug fever should be considered as a differential diagnosis. One is new-onset fever, in which patients develop a fever that is afebrile for more than 48 h [72]. The other is prolonged fever, where patients' fever persists for more than 72 h despite appropriate treatment for febrile illnesses [73]. Clinicians should be aware that there are no single signs

Table 1 Drugs associated with drug fever (adopted from Patel et al. [5]).

Drugs reported after 2010 are highlighted in bold font, while those listed in the review by Patel et al. are written in standard font.

Category	Drug
Antimicrobials	Penicillins: Ampicillin, carbenicillin, cloxacillin, mezlocillin, nafcillin, oxacillin, penicillin, piperacillin, staphicillin, ticarcillin Cephalosporins: Cefazolin, cefotaxime, ceftazidime, cephalixin, cephalothin Other antimicrobials: Acyclovir, amphotericin B, aureomycin, declomycin, doxycycline , ertapenem , erythromycin, furadantin, imipenem/cilastatin , isoniazid, minocycline, nitrofurantoin, novobiocin, rifampicin, streptomycin, teicoplanin , terramycin, tetracycline, tigecycline , trimethoprim-sulfamethoxazole, vancomycin
Anti-neoplastic agents	Bendamustine , bleomycin, chlorambucil, cisplatin, cytosine arabinoside, daunorubicin, hydroxyurea, interferon, L-asparaginase, mercaptopurine, procarbazine, streptozocin, vincristine
Cardiovascular agents	Clofibrate, dalteparin , diltiazem, dobutamine, enoxaparin , furosemide, heparin, hydrochlorothiazide, methyldopa, oxprenolol, procainamide, quinidine and quinine, triameterene
Immunosuppressants	Azathioprine, everolimus, mycophenolate mofetil, sirolimus
NSAIDs	Celecoxib , ibuprofen, naproxen, tolmetin
Sympathomimetic and hallucinogenic agents	Amphetamine, lysergic acid, 3,4-methylene dioxymethamphetamine
Anticonvulsants	Carbamazepine, phenytoin
Antidepressants	Doxepin, nomifensine
Others	Acitretin , allopurinol, cimetidine, dexmedetomidine , favipiravir , folate, iodide, mebendazole, methalamine , metoclopramide, olanzapine , pantoprazole , piperazine adipate, propofol , propylthiouracil, prostaglandin E2, ritodrine, sorafenib , sulfasalazine, theophylline, thyroxine, vildagliptin

or symptoms that can diagnose or exclude drug fever (e.g., the absence of a cutaneous region cannot be a reason for excluding drug fever).

When clinicians obtain a history of fever from a patient, care must be taken to include all medications, including those prescribed by other doctors or OTC drugs, within one month. A single administration of a drug can induce drug fever [64, 74], and hence a history of the used-as-needed drug should be obtained.

There is no method to provide a definitive diagnosis of drug fever when a patient is febrile. A tentative diagnosis of drug fever should be established after excluding other critical diseases. Therefore, the evaluation of patients with suspected drug fever should include a thorough history and physical examination to explore the focus of the fever. If laboratory testing or imaging studies are performed, clinicians should be cautious again that no single finding can diagnose or exclude drug fever (e.g., the absence of eosinophilia cannot be a reason for excluding drug fever). If clinicians are confident of a tentative diagnosis of drug fever after a fever workup, they should stop the drug that is considered the culprit. Determining the culprit drug may be difficult when various drugs are administered orally or parenterally. In such cases, stopping the drugs individually every two to three days, beginning with the drug suspected to be the culprit, may be reasonable [8]. If the diagnosis is correct, the fever will usually alleviate within 24–48 h, and the diagnosis will be confirmed [6, 18, 30, 34–39].

If a patient's fever persists for more than 72 h after discontinuing the presumed culprit drug, four possibilities should be considered.

i) Wrong diagnosis. The patient may have diseases completely different from ADR, such as abscesses, collagenous disease, or malignant disease. Clinicians should rule out other diseases before tentatively diagnosing drug fever. However, if a patient's fever persists after drug discontinuation, clinicians should consider tentative diagnoses other than ADR.

ii) Complication from other forms of drug events. Patients with a more severe form of ADR, such as drug-induced interstitial nephritis, may have a fever longer than 72 h after discontinuation of the drug [75]. Clinicians should cautiously evaluate patients for organ-specific symptoms other than fever, such as liver injury, renal failure, and rashes. If a patient experiences severe organ failure, clinicians should consider administering corticosteroids [76, 77].

iii) Wrong drug. Although the diagnosis of drug fever is correct, the fever will not resolve if the clinician's

assumption about the causative drug is incorrect. If clinicians maintain a tentative diagnosis of drug fever after reviewing the patient's history and physical examination, they should consider discontinuing other drugs.

iv) Rare cases of prolonged drug fever. A case series of antibiotic-induced fever reported that 36% of patients with drug fever had a fever for >3 days after discontinuing the drug [35]. One patient had a persistent fever for as long as 7 days. However, this was a rare case. Clinicians should seek other possibilities for prolonged fever rather than adhere to the first tentative diagnosis and optimistically observe patients.

After the patient is defervesced, physicians should consider whether the suspected drug is truly the culprit. Criteria for assessing causality in individual cases were developed by the Council for International Organizations of Medical Sciences (CIOMS) [78]. These include:

- Positive rechallenge (discussed in detail below)
- Causality established in previous studies
- Time to onset of plausibility
- Symptom resolution after stopping the drug (dechallenge positive)
- Lack of confounding risk factors
- Amount and duration of exposure consistent or plausible with the cause and effect
- Corroborating the accuracy of the case history
- Comedication is unlikely to play a significant role
- Lack of alternative explanations

Not all the criteria must be met to prove causality. The priority of each criterion may depend on the case and can be determined by the clinicians. A more objective scale with attributed weights for each item is available for drug-induced liver injury (CIOMS scale) [79]. However, this has not yet been validated for drug fever. Scales that can be used for ADRs include the Naranjo scale [80], World Health Organization global introspection method [81], and Karg and Lasagna's method [82]. Among these, the Naranjo scale seems to be the most frequently used in previous reports on drug fever [6]. The Naranjo scale consists of 10 questions answered as "yes", "no", or "do not know". A different value (from 1 to 2) was assigned to each answer. The probability of a drug adverse event can be estimated as "doubtful," "possible," "probable," or "definite" depending on the total score. The drug is likely the cause if the result is "possible," "probable," or "definite" [6].

The reappearance of fever with drug rechallenge can be one of the components of the diagnosis of drug fever and assessment of causality [6]. If the causative drugs are re-administered, the patient will develop a fever shortly

(usually within a day); thus, clinicians can confirm the diagnosis [39]. Drug rechallenge has long been controversial because it may be harmful to patients, and some reviews recommend extreme caution if clinicians decide to perform it [5, 8, 9, 83]. A previous review discouraged clinicians from utilizing this tool [5]. A case series reported that one of nine patients with drug rechallenge developed myocardial infarction during rechallenge with quinidine sulfate [30]. However, a more recent case series of 167 patients with drug fever reported that 38% of the patients received drug rechallenge, and no patients experienced serious adverse events [6]. Because drug rechallenge involves some risks, it may not be necessary if discontinuation of the possible causative drug does not affect the patient's outcome. However, withholding all drugs that are suspected to cause drug fever may harm the patient, especially if the possible causative drugs are the key drugs of treatment (e.g., anti-neoplastic drugs). If the key drugs of treatment are possible causative drugs, clinicians should consider drug rechallenge and identify the causative drug.

The drug-induced lymphocyte stimulation test (DLST), also called the lymphocyte transformation test, is a reliable test for determining the culprit drug in drug hypersensitivity reactions [84]. Although no studies have investigated the diagnostic significance of DLST only in patients with drug fever, DLST positivity may help to determine the culprit drug in drug fever. However, clinicians must be cautious that the DLST has limited sensitivity, and the negative result of the DLST does not deny the possibility that the testing drug is the culprit. Clinicians should perform the DLST only in cases in which it is difficult to identify the culprit drug from the clinical course.

TREATMENT

If clinicians strongly suspect drug fever, they usually discontinue the suspected culprit drug to confirm the diagnosis. Drug discontinuation is both a diagnostic and treatment procedure. However, no specific treatments were necessary.

PROGNOSIS

The prognosis of drug fever is usually favorable. A recent case series on drug fever reported that 154 of 167 (97%) patients recovered without sequelae [6]. They reported that one patient died of myocardial infarction, but this was not related to ADR. An older case series reported

that 6 of 148 patients (4%) died, and drug fever was one of the contributing factors [30]. However, according to this narrow definition, some of these cases were not cases of drug fever. One case was neuroleptic malignant syndrome induced by haloperidol [85] and two cases were bleomycin-induced fulminant hyperpyrexia [86, 87], which rarely occurs when bleomycin is administered to febrile patients with lymphoma and is considered to be one of the infusion reactions [88].

Therefore, the mortality rate of drug fever in the narrow definition is considered very low.

RESEARCH METHODOLOGY

The cited articles in case series or cohort studies were mostly based on chart reviews (**Table 2**). One study used the pharmacovigilance database of France [6].

The pharmacovigilance database is a database of individual ADR reports [89]. Reports are typically collected using spontaneous reporting systems. The World Health Organization has an international database called Vigibase [90], but some countries have national databases such as the Food and Drug Administration Adverse Event Reporting System (the United States) [91], Canada Vigilance Adverse Reaction Online Database [92], French Pharmacovigilance Database, and Japanese Adverse Drug Event Report database [93].

Researchers can make assumptions about the association between a certain drug and ADR by analyzing these databases. For example, if researchers want to determine whether there is an association between azathioprine and drug fever, the best way is to observe the overall population after drug administration and create a two-by-two contingency table. However, it is difficult to obtain this data. Instead, they can create a two-by-two contingency table to display the number of cases with azathioprine and other drug administration and with drug fever and other ADRs from the database (**Fig. 2**). The association between azathioprine use and drug fever can be discussed by calculating the proportional reporting ratio [94]. The proportional reporting ratio is a method of disproportionality analysis and is often used to analyze spontaneous ADR databases [95].

Notably, when analyzing drug fever using these databases, researchers should be cautious about the inherent limitations of pharmacovigilance databases based on spontaneous reports. First, ADRs tend to be underreported in spontaneous reporting systems and are easily affected by external factors such as media coverage [96]. Thus, the signals in these databases are vulnerable to

Table 2 List of previous studies of drug fever					
Study	Definition of drug fever	Causative drug	Study period	Number of cases	Data
Foster 1963	(1) Fever followed the administration of the antibiotic in question, and disappeared soon after it was discontinued. (2) Fever was not accounted for other causes	Antibiotics	1952–1963	25	Chart review
Young 1982	(1) temperatures were taken and recorded at least four times each day during the febrile period and after its resolution; (2) no infection or other cause of fever was detected from results of physical examination, appropriate cultures, and other studies (x rays, scans, etc.); (3) there was no underlying condition that might itself have caused a febrile state; (4) fever coincided temporally with the administration of the offending drug; (5) fever disappeared promptly, within <96 hr and usually <48 hr after discontinuation of the drug without other therapeutic measures; and (6) the temperature remained normal thereafter for at least three and usually more than five days.	Various drugs	1975–1980	12	Chart review
LeRoy 1986	A temperature greater than or equal to 100.4°F for which there was no cause other than administration of the drug, which disappeared within 48 hours of discontinuing the drug, and which did not return for at least 72 hours	Various drugs	1984–1985	36	Chart review
Mackowiak 1987	Fever coinciding the administration of a drug and disappearing after discontinuation of the drug when no other cause for the fever could be ascertained after a careful physical examination and appropriate laboratory study	Various drugs	Chart review; 1959–1986 Case report review: 1966–1986	148	Chart review and case report review
Mikasa 1989	Fever without other systemic symptoms followed the administration of the antibiotic and lasted for 2 days or more, and disappeared soon after it was discontinued.	Antibiotics	Jan 1986–Dec 1986	22	Chart review
Oizumi 1989	(1) A fever of 37.5°C or above which lasted for more than two days during treatment with an antibiotic; (2) The fever was associated neither with other clinical manifestations nor with laboratory findings suggestive of an infectious exacerbation; (3) The fever could not be ascribed to any other measures that were instituted for the management of infections; and (4) The fever subsided immediately after cessation of a suspected antibiotic (“dechallenge”).	Antibiotics	Not reported	56	Chart review
Kuwabara 1990	Fever without skin manifestation followed the administration of the antibiotic and disappeared soon after it was discontinued. Fever was not accounted for other causes	Antibiotics	1983–1988	8	Chart review
Vodovar 2012	(1) an oral or rectal body temperature above 38°C; (2) the absence of other causes of fever as determined by physical examination and appropriate biological and microbiological tests (i.e. absence of any infection); (3) the absence of any underlying condition causing fever by itself; (4) the absence of skin reactions; (5) the coincidence of fever onset with drug administration; (6) disappearance of the fever within 72 h following drug discontinuation without any other intervention; (7) no recurrence of fever within at least 72 h after normalization of temperature; and 8)- exclusion of other differential diagnoses for hyperthermia including antipsychotic malignant syndrome, serum sickness-like reactions, serotonin syndrome, and malignant hyperthermia.	Various drugs	1986–2007	167	French national pharmacovigilance database
Fang 2016	body temperature reduced rapidly after taking suspected drugs was stopped and rose when the same drug was used again. Otherwise, it is considered as drug fever when the patients suffered from allergic reaction (with or without rashes) in combination with any one of the following conditions: (1) for patients with infectious fever, the body temperature reduced when antibiotics were used but rose again in continue medication; (2) after the treatment of antibiotics, body temperature became higher and cannot be explained by original infection and other reasons for the other normal conditions; and (3) patients with non-febrile illnesses suffered from fever after dosing that cannot be explained by secondary infections	Antituberculous drugs	Apr 2006–Mar 2013	94	Chart review
Ogawara 2016	Not reported	Anti-neoplastic drugs	Apr 2004–Mar 2007, or Apr 2007–Dec 2008.	88	Chart review
Yaita 2016	was defined by clinical characteristics that met all of the following criteria: (1) an axial temperature above 37.5°C (in Japan, an oral or rectal temperature is generally not measured); (2) no other origin of fever can be detected by detailed ID consultation (including appropriate imaging tests and microbiological tests); (3) any underlying febrile illness, the improvement of which can be confirmed by the ID physician; and (4) after the discontinuation of drugs, the fever is alleviated.	Antibiotics	Apr 2014–May 2015	16	Chart review
Peng 2017	Unexplained fever due to other reasons, recurrence of fever after re-medication	Antibiotics	Feb 2011–Feb 2014	20	Chart review
Labbus 2018	If all of the following criteria were fulfilled: (1) central (ear) body temperature >38.0°C measured on two occasions; (2) intravenous antibiotic treatment for > 3 days; (3) exclusion of infectious or other non-infectious causes of fever; and (4) defervescence after discontinuation of antibiotic treatment.	Antibiotics	2014–2017	11	Chart review
Zhang 2021	Hypersensitivity was classified according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0	Carboplatin	Jan 2017–Dec 2018	27	Chart review
Zhang 2022	Fever had been caused by the medication if it cleared rapidly after the suspected drug was discontinued	Furazolidone	Jul 2018–Sep 2018.	45	Chart review

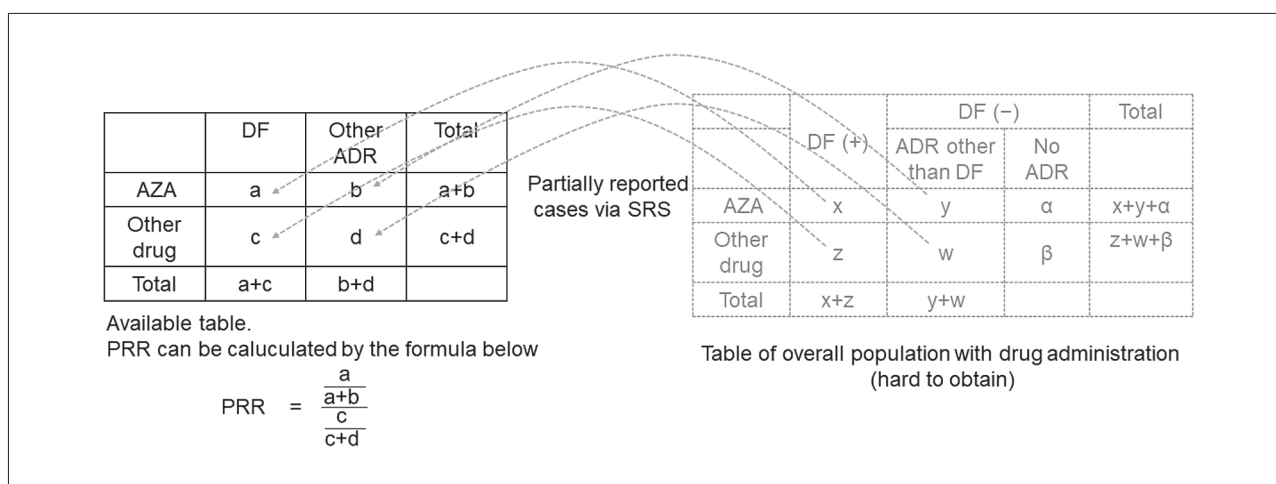


Fig. 2 An example of two-by-two contingency table in disproportionality analysis

To calculate the risk of azathioprine (AZA)-induced drug fever and compare the risk with other drugs, data of the whole population with AZA and other drug administrations are necessary; however, such data are unavailable. However, the number of spontaneously reported cases of AZA and other drug administrations with drug fever and ADR other than drug fever is available in the pharmacovigilance database. Researchers can create a two-by-two contingency table from these data. The proportional reporting ratio (PRR) can be calculated from the table using the formula. If the PRR exceeds a certain value, AZA and drug fever may occur.

reporting biases. Second, these databases lack information on the total number of people receiving the drug and therefore cannot calculate the risk ratio of ADRs. Researchers cannot draw any conclusions regarding the risk or prevalence of ADRs from studies using these databases. Third, the definition of drug fever in these databases may not be accurate. When researchers create a two-by-two contingency table, cases with ADR of interest and cases with other ADR must be separated according to the researchers' definition. ADRs are usually classified using the Medical Dictionary for Regulatory Activities (medDRA) [97]. Drug fever was included in medDRA. However, other classifications such as drug-induced hepatitis or drug-induced renal disease may be included in the definition of drug fever. Disease classification was performed using an ADR reporter. The definition of drug fever used by reporters is often unknown. Precise clinical information, such as laboratory or imaging findings, was not available. In the above example, when separating cases with drug fever from cases with other ADR, there is no guarantee that the cases identified as drug fever in the database use the same definition as the researchers' definition of drug fever.

To overcome these limitations, the validation of diagnostic codes is necessary. In addition, confirmation studies must be performed after detecting the signal using pharmacovigilance databases. Researchers should keep in mind that signal detection is not necessarily a side effect of the drug. We present two examples of validation study types. The first is the use of post-market surveillance for

new drugs. In Japan, all patients administered new drugs were surveyed. Researchers can create a two-by-two contingency table by setting the reporters' diagnosis of ADR as the reference standard, and the diagnostic code extracted from the administrative claims data as the comparator. Diagnostic algorithms based on administrative claims data can also be used for comparison. The sensitivities and specificities of the diagnostic codes and algorithms were calculated from the tables. Researchers should be cautious when using this method for frequent ADR. Therefore, it may not be suitable for the treatment of drug-induced fever. The second involves the use of pharmacovigilance databases. Researchers extract the cases classified as "drug fever" from a certain pharmacovigilance database and obtain relevant clinical information. If there are too many reports classified as "drug fever," researchers can select the reports randomly (about 100 reports). Using clinical information, the researchers assessed whether the extracted cases could be truly classified as drug fever based on their definition. There will be true positives (cases classified as drug fever in medDRA and the researcher's definition) and false positives (cases classified as drug fever in medDRA but not in the researcher's definition). The positive predictive value can be calculated from these numbers, and researchers can determine whether the medDRA classification of drug fever is appropriate. The most important thing is the confirmation study of the association between drugs and fever. To confirm the presumption or signal of drug fever, establishment of a definition of drug fever is warranted.

CONCLUSIONS AND FUTURE DIRECTIONS

Drugs are essential in clinical practice. All clinicians can treat patients with drug fever and should be familiar with its diagnosis and treatment of drug fever. Clinicians should always consider drug fever in the differential diagnosis when treating patients with fever.

Although the accumulation of knowledge over the last decade has led to a better understanding of the diagnosis and treatment of drug fever, some areas remain unresolved. First, there is a disagreement among researchers regarding the definition of drug fever. When researchers use databases to study drug-related fever, diagnostic codes or algorithms must be validated unless they review the medical records of all patients directly. Second, there is a lack of means to estimate the pre-test probability of drug fever before drug discontinuation in patients with fever. Clinical signs such as relative bradycardia should

be verified and validated to help differentiate drug fever from other febrile illnesses. Third, although rechallenge is the gold standard for diagnosing drug-induced fever, its safety has only been confirmed in a few studies. Large population studies are necessary to confirm the safety of this treatment.

As new drugs are introduced into the market, the types of drugs causing drug fever are likely to become more diverse, and it is necessary to closely monitor information about drug fever.

CONFLICT OF INTEREST

The authors have nothing to declare.

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