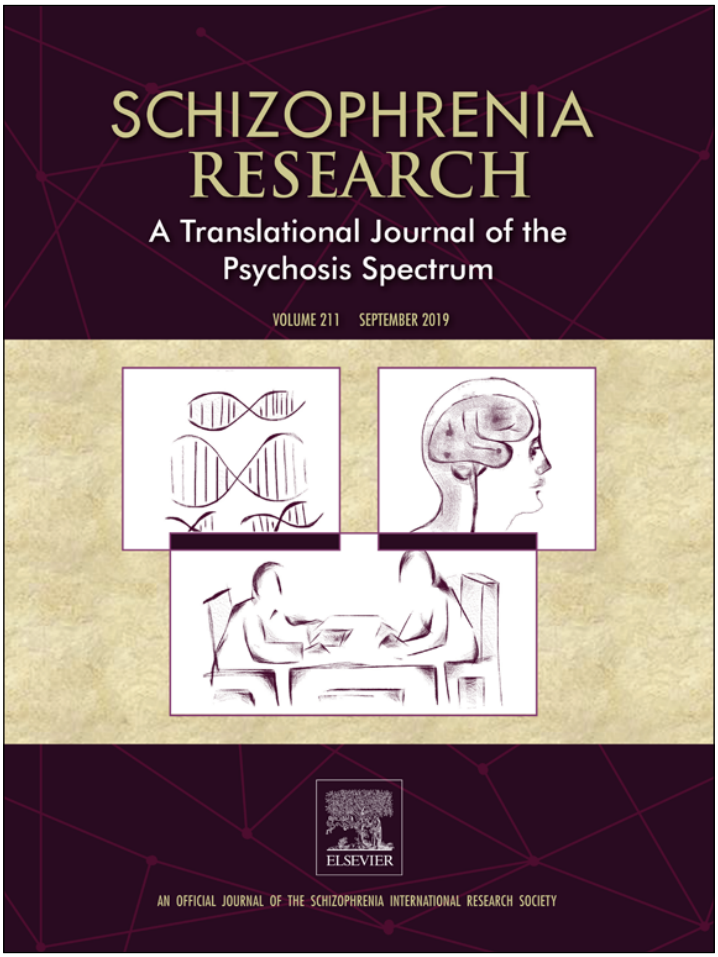

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Clinical determinants of fever in clozapine users and implications for treatment management: A narrative review

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ABSTRACT

Objectives: To identify the clinical determinants of fever in clozapine users and their impact on management of clozapine treatment.
Methods: Articles published in English or French identified with a MEDLINE, Web of Sciences, Cochrane Library and PsycINFO search, from inception through February 2019, using the term "clozapine" in combination with "fever" OR "hyperthermia" OR "body temperature" OR "pyrexia" OR "febrile" OR "heat" OR "thermoregulation". Information extracted for each medical condition were frequency, time to onset after initiation of clozapine treatment, characteristics of fever, associated symptoms, laboratory tests used for diagnosis, course, lethality, discontinuation of clozapine. Data were synthesized narratively.
Results: Our search yielded 394 unique hits published from 1993 to 2018. We included 73 articles in the review: two meta-analyses, 14 reviews, six epidemiological studies, 11 clinical studies and 40 case reports. During clozapine initiation, fever is most frequently benign and transient but should be closely monitored as it may be the first stage of potentially life-threatening adverse drug reactions (ADR) (agranulocytosis, neuroleptic malignant syndrome myocarditis, hepatitis, pancreatitis, nephritis, colitis, etc.). Other ADR associated with fever are independent of duration of exposure to clozapine (heat stroke, pneumonia, pulmonary embolism, necrotizing colitis). If fever is due to intercurrent infection, therapeutic drug monitoring is recommended to adjust clozapine daily dosage.
Conclusion: Benign causes of fever are much more frequent than life-threatening ADR during clozapine treatment. Discontinuation should not be considered as automatic in the event of fever, especially during the early phase of clozapine initiation.

1. Introduction

Fever is a rise in body temperature above of 38 °C (100.4 °F) or greater due to an elevated thermoregulation set-point (Roge et al., 2012; Thompson, 2005). The occurrence of fever in a patient treated by antipsychotics is often a source of concern, as it may be the warning symptom of an incipient life-threatening complication of antipsychotics (Belvederi Murri et al., 2015; Stroup and Gray, 2018). In clinical practice, a key issue is to decide whether antipsychotics should be immediately discontinued or not. This clinical dilemma is particularly complex in the period of clozapine initiation. Short episodes of benign fever may be frequent in this period (Lowe et al., 2007; Rohde et al., 2018), but a range of rare but potentially lethal adverse drug reactions (ADR) associated with fever may also occur (Knoph et al., 2018; Myles et al., 2018; Nielsen et al., 2013; Rohde et al., 2018). The decision to discontinue clozapine or not may have more dramatic short- and long-term consequences than with other antipsychotics, as the patient may lose the chance of benefiting from the sole treatment efficient for his/her disease (Nielsen et al., 2011, 2013; Verdoux and Pambrun, 2014).

Under-prescription or premature discontinuation of clozapine in persons with treatment-resistant schizophrenia is often due to inadequate knowledge about managing ADR, as well as to overestimation of the frequency of life-threatening events (Bachmann et al., 2017; Cohen, 2014; Nielsen et al., 2010; Verdoux et al., 2016, 2018). Since these factors may contribute to prescribers' view of clozapine as a "risky" drug, increasing knowledge about the actual benefit-risk balance of clozapine is essential to promote its use (Carruthers et al., 2016; Netherlands Clozapine Collaboration Group, 2019).

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Fever is an early ubiquitous symptom associated with a wide range of clinical conditions in clozapine users. Hence, it is of interest to have a comprehensive view of the causes needing to be considered in clinical practice, in order to systematize and optimize clinical decision making. The last systematic review on fever during clozapine treatment was published in 2007 (Lowe et al., 2007) and mainly concerned clozapine-induced fever. The aim of the present narrative review was to identify the clinical determinants of fever in clozapine users and their impact on management of clozapine treatment.

2. Materials and methods

2.1. Search strategy

This review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). A protocol was published in the PROSPERO database (CRD42019123890). We performed a MEDLINE, Web of Sciences, Cochrane Library and PsycINFO search from inception through February 2019 using the term "clozapine" in combination with "fever" OR "hyperthermia" OR "body temperature" OR "pyrexia" OR "febrile" OR "heat" OR "thermoregulation". We examined related references of selected papers as well as systematic reviews and meta-analyses on ADR induced by clozapine. We considered articles published in English or French in peer-reviewed journals on medical conditions associated with fever in clozapine users. For each condition, the most recent meta-analyses and systematic reviews, if any, were given precedence over other articles: case reports or case series already included in prior reviews were not considered unless they provided important findings not detailed in those prior reviews.

Titles and abstracts of retrieved citations were screened, selected full-text articles were assessed for eligibility and data were extracted independently by two researchers (HV and CQ); disagreement was resolved by discussion. We extracted the following information: (i) reference: first author's name, journal, year of publication, (ii) study type: meta-analysis, systematic review, review, epidemiological study, clinical study, case report; (iii) medical condition associated with fever: frequency, time to onset after initiation of clozapine treatment, characteristics of fever, associated symptoms, laboratory tests and other exams used for diagnosis, course, lethality, discontinuation of clozapine. As this review was focused on the diagnostic strategies and practical management of clozapine treatment in the event of fever, we did not collect information on (i) pathophysiological hypotheses; (ii) management of the specific medical conditions associated with fever; (iii) clozapine rechallenge strategies. The data were synthesized narratively, since the literature on fever in clozapine users mostly includes cases reports or chart reviews on heterogeneous medical conditions associated with fever, with few quantitative information.

3. Results

3.1. Literature search

Fig. 1 presents a flow chart of the eligibility process for this review. Ultimately, 73 articles published from 1993 to 2018 were included: two meta-analyses, 11 systematic reviews, three reviews, six epidemiological studies, 11 clinical studies and 40 case reports (Table 1).

3.2. Clozapine-induced blood dyscrasias

In all countries, weekly white blood count (WBC) is required to prevent clozapine-induced agranulocytosis (Nielsen et al., 2016). The incidence of severe neutropenia (absolute neutrophil count <500 cells/mm) is equal to 0.9% (Myles et al., 2018) with more than one third (38%) occurring within the first month of treatment and 89% within the first year. Death from neutropenia is a very rare event (one per 7700 persons exposed to clozapine). The literature on the frequency of fever as the first symptom of agranulocytosis during treatment initiation is very limited (Manfredi and Sabbatani, 2007). During chronic clozapine treatment and after close WBC monitoring has been stopped, the risk of agranulocytosis becomes very low but never disappears (Raja and Raja, 2014). Thus, WBC is required in case of fever with immediate clozapine discontinuation if agranulocytosis is diagnosed (Nielsen et al., 2013). Regarding other blood abnormalities, pancytopenia has been diagnosed in the first month of clozapine treatment in two patients admitted for fever leading to clozapine discontinuation (Pushpakumara et al., 2015; Ziegenbein et al., 2003).

3.3. Impaired thermoregulation

3.3.1. Neuroleptic malignant syndrome (NMS)

The incidence of clozapine-induced NMS is very low (0.2%) during treatment initiation (Rohde et al., 2018). Fever is reported in 50% (Trollor et al., 2012) to 90% (Belvederi Murri et al., 2015) of cases, a frequency comparable to that found in NMS induced by other second-generation antipsychotics (SGA). Characteristics also shared with other SGA include duration (10 days) and fatal outcomes (7%). Differential characteristics for clozapine-induced NMS include early occurrence of fever (2.2 days before NMS diagnosis), low frequency of rigidity (68%) and tremor (44%), delayed elevation of serum creatine-kinase (CK) concentrations (85%), lower severity and higher frequency of history of prior NMS (50%) (Belvederi Murri et al., 2015). If the diagnosis of NMS is confirmed, clozapine must be discontinued immediately (Nielsen et al., 2013).

3.3.2. Heat stroke

Heat stroke during clozapine treatment is probably exceptional and/or underdiagnosed as there are only two published cases (Hoffmann et al., 2016; Kerwin et al., 2004). Both occurred during a heatwave, this fitting with the typical presentation of heat stroke as a major hyperthermia (>40 °C) occurring during or after exposure to high ambient temperature or intense physical exertion. Fever is most often associated with central nervous system symptoms (impaired consciousness, drowsiness, convulsion, or coma), the skin is hot and dry, and dysautonomic symptoms may be observed (tachycardia, hypotension). Both patients showed elevated serum CK concentrations and one patient presented with multiple organ failures. In both cases, clozapine was discontinued at least temporarily and patients survived.

3.4. Concurrent infection

A growing body of evidence suggests that the risk of infection in general (Nielsen et al., 2009; Landry et al., 2003; Ponsford et al., 2018), and of pneumonia in particular, is increased in users of clozapine compared to persons not exposed to antipsychotics or users of other antipsychotics. Pharmacoepidemiological studies showed that current users of clozapine were two times more likely to develop pneumonia than persons not currently exposed (adjusted Risk Ratio, RR = 2.05), especially during the first month of exposure (RR = 9.57). Of all antipsychotics, clozapine exposure was associated with the highest risk of pneumonia, followed by olanzapine (Kuo et al., 2013). In patients with bipolar disorder, this ranking was reversed, olanzapine being associated with the highest risk of pneumonia (RR = 2.97) followed by clozapine (RR = 2.59) (Yang et al., 2013). Patients with schizophrenia exposed to clozapine are also at increased risk of recurrent pneumonia (RR = 1.4) (Hung et al., 2016). A clinical study found that the incidence of pneumonia was higher in clozapine users compared to the general hospital population (adjusted Odds Ratio, OR = 4.1) and to risperidone users (OR = 3.2) (Stoecker et al., 2017). A meta-analysis of studies published up to June 2014 confirmed that the increased risk of pneumonia in SGA users in general (OR = 1.98) is especially marked in clozapine users (OR = 3.11) (Nose et al., 2015).

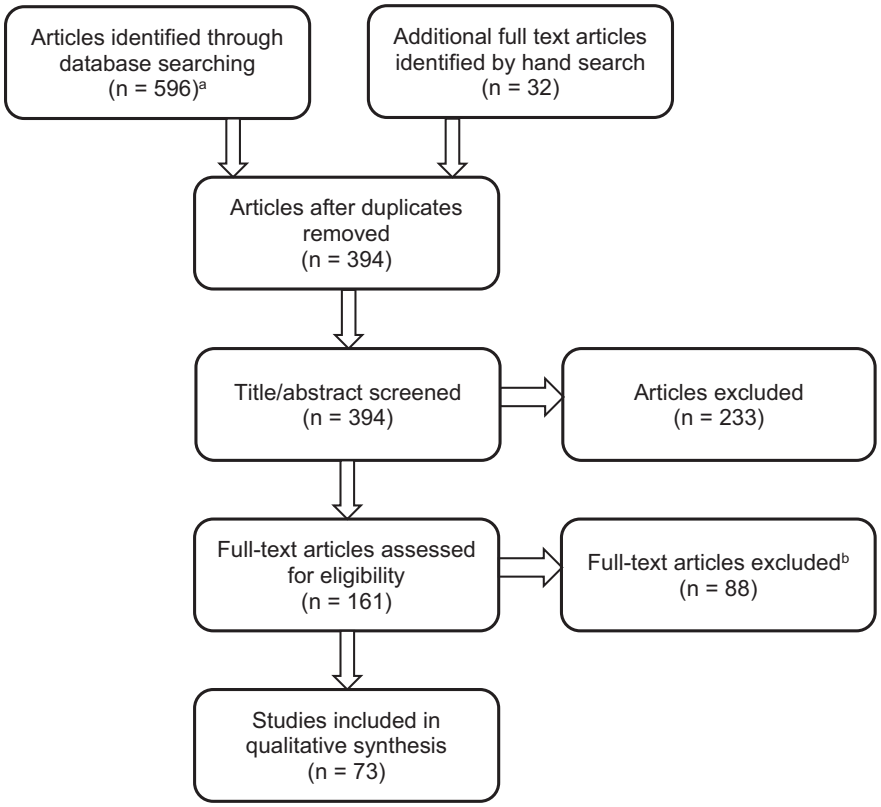

Fig. 1. Study selection. a. MEDLINE n = 225; Web of Sciences n = 208, PsycINFO n = 163; Cochrane Library n = 0. b. Exclusion reasons: case reports included in systematic reviews or not providing new evidence that was already contained in prior reviews (n = 59); oldest reviews or chart series on clozapine or other antipsychotics (n = 17); other unrelated issues (n = 12).

The high frequency of pneumonia in clozapine users is probably related to the increased risk of aspiration pneumonia due to the combination of sedation, hypersalivation and swallowing impairment and co-prescription of benzodiazepines (Cicala et al., 2019; Clark et al., 2018; Schmidinger and Hofer, 2014). Pneumonia may be considered as the most frequent and potentially lethal infectious complication associated with clozapine exposure (Rohde et al., 2018; Ruan and de Leon, 2019; Taylor et al., 2009). The increased mortality of pneumonia in patients using clozapine versus other SGA may be due to inhibition of clozapine metabolism by cytokines released during infection (de Leon and Diaz, 2003; Ruan et al., 2017). Increased of serum clozapine levels may lead to intoxication characterized by sedation, tremor, dizziness, gait disturbance, dysarthria and delirium. Misdiagnosis may occur as these symptoms may be viewed as being due to the pneumonia rather than to clozapine intoxication.

Chest X-ray and urinalysis should be performed in clozapine users presenting without identified cause of fever. Clozapine may be continued in the event of intercurrent infection, with adjustment of dosage by Therapeutic Drug Monitoring (TDM). If TDM is not available, a safe practice is to halve the dosage to prevent clozapine intoxication, particularly when obvious signs of inflammation are present (elevated CRP) (Ruan and de Leon, 2019).

3.5. Clozapine-induced inflammation

We present in a single chapter a wide range of clinical conditions that (i) are not explained by prior described ADR or (ii) any concurrent infection and (iii) are characterized by the presence of an inflammatory process appearing to be directly induced by clozapine (Roge et al., 2012). These conditions can be categorized as presenting with (i) systemic inflammatory process: clozapine-induced fever (3.5.1), fever with isolated CRP elevation (3.5.2), and clozapine-induced lupus (3.5.3); and (ii) localized signs of inflammation: myocarditis (3.5.4), serositis (3.5.5), pneumonitis/alveolitis (3.5.6), hepatitis (3.5.7), pancreatitis (3.5.8), nephritis (3.5.9), colitis (3.5.10) and dermatological disorders (3.5.11). We are aware that this classification is somewhat arbitrary since these disorders may lie on a continuum with no clear-cut boundary between them, and that several conditions may co-occur.

3.5.1. Clozapine-induced fever

Clozapine-induced fever is a defined-by-default condition, i.e. when fever is the single clinical symptom with no other detectable etiology than clozapine exposure. The first case was published in 1997 (Tremeau et al., 1997). The estimation of its frequency (0.5–50%) is difficult due to the lack of a clear-cut definition of temperature threshold (Jeong et al., 2002; Roge et al., 2012). The frequency of clozapine-induced fever during clozapine initiation varied from 14% to 50% in retrospective chart reviews (Lowe et al., 2007; Chung et al., 2008).

Clozapine-induced fever is characterized by mild-to high-grade fever appearing between 5 and 15 days after clozapine initiation and lasting 3–5 days. This diagnosis should be considered only if fever occurs within the first month of clozapine exposure (Lowe et al., 2007; Roge et al., 2012). Mild flu-like or gastro-intestinal symptoms may sometimes be present and do not preclude this diagnosis (Lowe et al., 2007). All laboratory tests should be normal (see Fig. 2), except the presence of eosinophilia, which is compatible with a diagnosis of clozapine-induced fever.

Clozapine-induced fever may motivate treatment interruption (Davis et al., 2014; Legge et al., 2016; Pai and Vella, 2012). However, there is a relative consensus regarding the fact that it is a benign condition and that clozapine should not be discontinued if this diagnosis is confirmed by the negativity of clinical and laboratory exams (Lowe et al., 2007; Nielsen et al., 2013; Roge et al., 2012; Tham and Dickson, 2002). The safety of this strategy has been confirmed by several recently published case reports (Bruno et al., 2015; Driver et al., 2014; Martin and Williams, 2013). As rapid titration may be a risk factor for

Table 1
Articles included in the review.

Topic	Authors, year	Type of articles[a]
Blood dyscrasia		
Agranulocytosis	Myles et al. (2018)	Meta-analysis of incidence studies (up to 2018): 101 samples n = 452,774
	Manfredi and Sabbatani (2007)	Case report: n = 1
Pancytopenia	Ziegenbein et al. (2003) Pushpakumara et al. (2015)	Case reports: n = 2
Impaired thermoregulation		
Neuroleptic malignant syndrome	Belvederi Murri et al. (2015)	Systematic review of case reports (up to 2013): n = 36
	Trollor et al. (2012)	Population-based survey on the Australian Adverse Drug Reaction Advisory Committee database (1994–2010): n = 76
	Rohde et al. (2018)	Population-based survey on Danish registers (1996–2015): n = 7 among 7932 outpatients initiating clozapine
Heat stroke	Kerwin et al. (2004), Hoffmann et al. (2016)	Case reports: n = 2
Concurrent infection	Nose et al. (2015)	Meta-analysis on pneumonia risk in antipsychotic users (up to 2014): 8 observational studies, n = 16,629 cases with pneumonia and n = 14,030 controls
	Clark et al. (2018)	Systematic review of case reports of elevated clozapine levels associated with infection (up to 2016): n = 40
	Cicala et al. (2019)	Review on swallowing difficulties and dysphagia associated with antipsychotics
	Nielsen et al. (2009)	*Population-based studies on antibiotic use in clozapine users on Danish registers (1996–2005): n = 3374* *Population-based studies on the risk of pneumonia in antipsychotics users on the National Health Insurance Research Database in Taiwan*
	Kuo et al. (2013)	Schizophrenia patients (2000–2008): n = 1739 cases with pneumonia and n = 6949 controls
	Yang et al. (2013)	Patients with bipolar disorder (1998–2006): n = 494 cases with pneumonia and n = 1438 controls
	Hung et al. (2016)	Schizophrenia patients (2000–2008): n = 1739 cases with recurrent pneumonia and n = 6949 controls
	Landry et al. (2003)	Chart review of antibiotic use in schizophrenia patients using clozapine: n = 41
	Ponsford et al. (2018)	Clinical study on antibiotic use in schizophrenia patients: n = 123 clozapine users and n = 113 users of other antipsychotics
	Stoecker et al. (2017)	Retrospective clinical study on pneumonia risk in patients admitted to medecine units: n = 155 clozapine users, n = 155 risperidone users and n = 155 not using antipsychotics
	de Leon and Diaz (2003), Ruan et al. (2017), Ruan et al. (2019), Ruan and de Leon (2019)	Case reports of severe infections in clozapine users: n = 6
Clozapine-induced inflammation		
Clozapine-induced fever	Lowe et al. (2007)	Systematic review (up to 2007): 4 clinical studies n = 453 and case reports n = 7
	Jeong et al. (2002)	Chart review of new clozapine users n = 98
	Tham and Dickson (2002)	Chart review of new clozapine users n = 93
	Chung et al. (2008)	Chart review of new clozapine users n = 227
	Tremeau et al. (1997), Martin and Williams (2013), Driver et al. (2014), Bruno et al. (2015)	Case reports n = 4
Isolated elevation of CRP	Roge et al. (2012)	Systematic review (up to 2012) of in vitro and in vivo immunomodulatory effects of clozapine
	Kohen et al. (2009), Stuhec (2013), Buist and Schauer (2016), Davey et al. (2016)	Case reports n = 4
Lupus	Wickert et al. (1994), Wolf et al. (2004), Rami et al. (2006), Buzina and Eterović (2016)	Case reports n = 4
Myocarditis	Ronaldson et al. (2015)	Systematic review of case reports (up to 2014): n = 250
	Bellissima et al. (2018)	Systematic review of case reports (up to 2016): n = 359
	Knoph et al. (2018)	Systematic review (up to 2017): 144 publications on myocarditis or cardiomyopathy (review articles n = 27, research reports n = 31, letters n = 8, cases or case series n = 78 including n = 95 cases)
	Rohde et al. (2018)	Population-based survey on Danish registers (1996–2015): one case among 7932 outpatients initiating clozapine
	Ronaldson et al. (2010)	Chart review of clozapine users with myocarditis n = 38 and without n = 47
	Bandelow et al. (1995), Chopra and de Leon (2016)	Case report n = 2
Serositis	Mouaffak et al. (2009)	Systematic review of case reports (up to 2008): n = 22 (pericarditis n = 6, pleuritis n = 4, polyserositis n = 12)
	Crews et al. (2010), De Berardis et al. (2018)	Case reports n = 2
Pneumonitis/alveolitis	Benning (1998), Aldridge et al. (2013), Hashimoto et al. (2015)	Case reports n = 3
Hepatitis, pancreatitis, nephritis	Lally et al. (2018)	Systematic review of case reports (up to 2017): hepatitis n = 20, pancreatitis n = 11, nephritis n = 11
Colitis	Druss and Mazure (1993), Friedberg et al. (1995), Ginsberg (2005), Karmacharya et al. (2005), Pelizza and Melegari (2007), Marchel et al. (2017)	Case reports n = 10
Dermatological disorders	Bosonnet et al. (1997), Lai et al. (2012), Wu et al. (2015)	Case reports n = 3
Pulmonary thrombo-embolism	Sarvaiya et al. (2018)	Systematic review of case reports (up to 2016): n = 23
	Schmidinger and Hofer (2014)	Case report n = 1
Necrotizing colitis	Cohen (2017)	Review on clozapine and gastrointestinal hypomotility
	Leong et al. (2007)	Case report n = 1
General articles on adverse drug effects	Nielsen et al. (2013)	Systematic review (up to 2012): 81 studies on clozapine adverse effects and grounds for or against clozapine discontinuation

Table 1 (*continued*)

Topic	Authors, year	Type of articles[a]
	Raja and Raja (2014)	Review on clozapine safety
		Clinical studies on reasons for clozapine discontinuation
	Taylor et al. (2009)	Chart review of clozapine users n = 529 and long-acting risperidone users n = 250
	Pai and Vella (2012)	Chart review of clozapine users discontinuing clozapine n = 151
	Davis et al. (2014)	Chart review of clozapine users n = 320
	Legge et al. (2016)	Chart review of clozapine users n = 316

[a] Case reports including reviews of prior published cases were categorized as case reports.

clozapine-induced fever, clozapine may be temporarily withdrawn and restarted with a slower titration (Chung et al., 2008).

3.5.2. Fever with isolated elevation of C-reactive protein

Clozapine may induce a generalized inflammatory response in the first two weeks of treatment characterized by elevation of pro-inflammatory cytokines and CRP (Buist and Schauer, 2016; Davey et al., 2016; Kohen et al., 2009; Roge et al., 2012; Stuhec, 2013). Isolated CRP elevation without associated symptoms should not lead to treatment discontinuation but to close monitoring for other signs of inflammation, measuring clozapine TDM and considering the slowing of clozapine titration.

3.5.3. Clozapine-induced lupus

Clozapine-induced lupus occurs within the first weeks of treatment (Buzina and Eterović, 2016; Rami et al., 2006; Wickert et al., 1994; Wolf et al., 2004). The clinical picture of drug-induced lupus is characterized by fever, generalized arthralgia and myalgia. The most specific marker is positive antinuclear antibodies titer, associated with elevation of markers of inflammation (CRP). Clozapine was discontinued in three cases. In one case, the benefit/risk ratio of clozapine was considered as greater than discontinuation in spite of the persistence of arthralgia (Wolf et al., 2004). If clozapine is continued, close monitoring of renal function is recommended.

3.5.4. Myocarditis

The first case of clozapine-induced myocarditis was described in a patient titrated extremely fast to 500 mg/day within one week (Bandelow et al., 1995). The highest incidence of clozapine-induced myocarditis has been reported in Australia (around 3%) (Ronaldson et al., 2010, 2015), while a much lower incidence (<0.1%) is found in most other countries. For instance one case (0.03%) of myocarditis was identified in a Danish population-based study carried out on 7932 outpatients initiating clozapine (Rohde et al., 2018). Rapid titration might be a contributing factor for clozapine-induced myocarditis in general and for the differences between Australia and other countries in particular (Chopra and de Leon, 2016; Rohde et al., 2018; Ronaldson et al., 2015).

The onset of myocarditis is typically within the first three weeks after clozapine initiation, with 87% of cases occurring within 30 days (Bellissima et al., 2018). Fever, the most frequent symptom of myocarditis, is reported in at least two out of three patients. It may be the single symptom before the emergence of more specific symptoms of cardiac lesion (tachycardia, dyspnea, chest-pain, hypotension, narrowed pulse

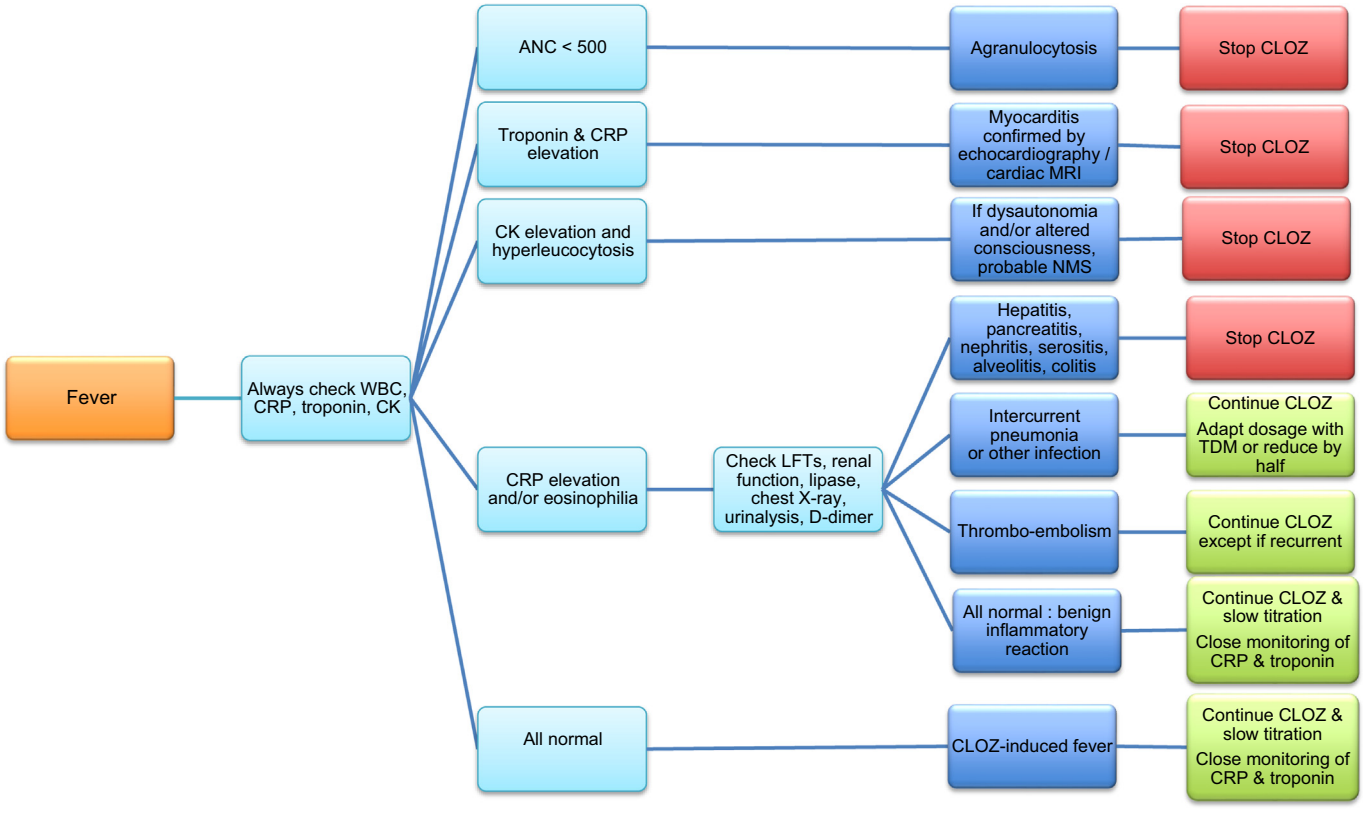

Fig. 2. Main medical causes of fever occurring within the first months of clozapine (CLOZ) treatment: synthesis of practical clinical guidelines. WBC: white blood count; CRP C-reactive protein; CK: creatine-kinase; ANC: absolute neutrophil count; MRI: magnetic resonance imaging; NMS: neuroleptic malignant syndrome; LFTs: liver function test; TDM: Therapeutic Drug Monitoring.

pressure or peripheral edema) (Bellissima et al., 2018; Knoph et al., 2018; Rohde et al., 2018; Ronaldson et al., 2010, 2015). Other unspecific symptoms may be present (fatigue, malaise, flu-like symptoms, diarrhea or neck pain). Elevation of both CRP and troponin is a highly sensitive indicator of myocarditis (Knoph et al., 2018; Raja and Raja, 2014; Ronaldson et al., 2010). ECG changes and eosinophil count are not specific enough to be helpful in clinical practice: myocarditis is confirmed by echocardiography, cardiac magnetic resonance imaging or endomyocardial biopsy (Bellissima et al., 2018; Knoph et al., 2018; Raja and Raja, 2014). Myocarditis is associated with a high mortality rate (15–24%) (Bellissima et al., 2018; Rohde et al., 2018). If this diagnosis is suspected based on CRP and troponin elevation, clozapine must be discontinued immediately (Nielsen et al., 2013; Rohde et al., 2018; Ronaldson et al., 2015).

3.5.5. Serositis

Serositis is defined as the inflammation of serous membranes (pericarditis, pleuritis, and ascites) (Crews et al., 2010; De Berardis et al., 2018; Mouaffak et al., 2009). The incidence of clozapine-induced serositis seems to be very low. A population-based study carried out on 7932 outpatients initiating clozapine did not find any case of pericarditis (Rohde et al., 2018). In most reported cases, the onset took place shortly (8 to 70 days) after clozapine initiation. Fever or flu-like symptoms were frequently observed (32%) (Mouaffak et al., 2009). Associated symptoms varied according to the site of serositis: dyspnea, tachycardia, fatigue, precordial pain, and diarrhea. Inflammation of other organs (pancreatitis, hepatitis, colitis, lupus-like syndrome) is often reported (41%) (Mouaffak et al., 2009). The most frequent laboratory abnormalities were elevation of CRP and eosinophilia with a diagnosis confirmed by echography. No death was reported. Clozapine was discontinued in 20 of 22 patients; the symptoms remitted in one patient and were “tolerated” in the last one.

3.5.6. Pneumonitis/alveolitis

In all reported cases, the symptoms of clozapine-induced pneumonitis/alveolitis appeared within the first three weeks of treatment (Aldridge et al., 2013; Benning, 1998; Hashimoto et al., 2015). Fever was associated with tachycardia, cough, dyspnea or fatigue. Laboratory tests showed elevation of CRP, leukocytosis, eosinophilia. The diagnosis was confirmed by Chest X-ray or high-resolution computed tomography. The symptoms always disappeared after discontinuation of clozapine.

3.5.7. Hepatitis

In the reported cases of clozapine-induced hepatitis (Lally et al., 2018), the mean time to onset after clozapine initiation was 34 days and all but three cases occurred over the first 8 weeks of clozapine treatment. Fever was present in 89% of cases, associated with unspecific symptoms (abdominal pain, nausea, lethargy). Jaundice was less frequent (22%). CRP and transaminase levels were always significantly elevated (>3-fold above the upper limit). Hypereosinophilia (100%) and elevation of serum bilirubin (50%) were also observed. Three deaths were reported. Moderate elevation of transaminases (up to twice the upper limit) is frequent during clozapine treatment (Nielsen et al., 2013; Raja and Raja, 2014) and clozapine may be continued with close monitoring of other hepatitis symptoms, transaminases levels and WBC. If the diagnosis of clozapine-induced hepatitis clozapine is confirmed, clozapine must be discontinued immediately (Nielsen et al., 2013).

3.5.8. Pancreatitis

The mean delay between initiation of clozapine and onset of pancreatitis was 18 days with all cases occurring within 5 weeks (Lally et al., 2018). Fever, present in 75% of cases, was associated with unspecific symptoms (abdominal pain or distension, nausea, vomiting). All cases showed elevated CRP, serum amylase and/or lipase levels, and eosinophilia was present in 60% of cases. No fatal outcome was reported. As elevation of serum lipase or amylase levels may be delayed, imaging is useful to rule out the diagnosis of pancreatitis (transabdominal or endoscopic ultrasound, magnetic resonance cholangiopancreatography) (Lally et al., 2018). Sodium valproate may increase the risk of clozapine-induced pancreatitis through drug-drug interactions (Lally et al., 2018; Raja and Raja, 2014). Only one patient was co-prescribed valproate among the 11 cases identified in the systematic review. As only 2% of pancreatitis cases are drug-induced, other risk factors should be seriously considered such as alcohol misuse, hyperglycemia and hypertriglyceridemia. Clozapine must be discontinued immediately if the diagnosis of clozapine-induced pancreatitis is confirmed.

3.5.9. Nephritis

The mean delay between initiation of clozapine and onset of nephritis was 28 days and within 3 weeks in 73% of cases (Lally et al., 2018). Fever was always present and associated with unspecific symptoms like tachycardia, nausea, vomiting, and diarrhea, and less frequently with urinary difficulties. Elevated CRP and creatinine were always present, eosinophilia in 86% and proteinuria in 73%. Rash, a classical symptom of nephritis, was never observed. No fatal outcome was reported. Clozapine must be discontinued immediately if the diagnosis of clozapine-induced nephritis is confirmed.

3.5.10. Colitis

The typical clinical picture of inflammatory colitis associates spiking fever, intense watery or bloody diarrhea and abdominal pain (Druss and Mazure, 1993; Friedberg et al., 1995; Ginsberg, 2005; Karmacharya et al., 2005; Marchel et al., 2017; Patterson and Jennings, 1993; Pelizza and Melegari, 2007). Most cases occurred within the first month after initiation of clozapine. In some cases, fever was absent (Marchel et al., 2017) or not reported (Friedberg et al., 1995). Elevation of WBC and hypereosinophilia were reported in most cases. The diagnosis is confirmed by biopsy of colon showing eosinophilic infiltrates (Karmacharya et al., 2005; Marchel et al., 2017) or lymphocytic infiltrates (Pelizza and Melegari, 2007). Clozapine should be stopped if the diagnosis of clozapine-induced colitis is confirmed.

3.5.11. Dermatological disorders

There are a few reports of fever associated with dermatological lesions in the literature. They are limited by their heterogeneity and in several cases, by the lack of clearly established imputation of the disorder to clozapine. Serositis may be associated with dermatological disorders (Mouaffak et al., 2009). In three cases, dermatological lesions associated with fever were the most prominent symptoms (Bosonnet et al., 1997; Lai et al., 2012; Wu et al., 2015). The diagnoses were: (i) acute generalized exanthematic pustulosis with erythematopustular skin reaction six weeks after the initiation of clozapine; (ii) Stevens-Johnson syndrome/toxic epidermal necrosis with multiple mucous ulcers and erythematous skin rashes over the entire body and extremities, CRP elevation and leukocytosis occurring two years after the initiation of clozapine; and (iii) pityriasis rosea-like eruption confirmed by histopathological examination with generalized skin rashes 4 weeks after the onset of clozapine. Clozapine was discontinued in all the cases.

3.6. Pulmonary thrombo-embolism

More than half (58%) of the published cases occurred within the first month of treatment (5 days to 4 years) (Sarvaiya et al., 2018; Schmidinger and Hofer, 2014). Fever may be associated with other unspecific symptoms such as tachycardia, fatigue or elevated C-reactive protein (CRP). The frequency of fever was not specified in the systematic review. More specific symptoms are dyspnea, chest pain or hemoptysis. The diagnosis is based upon determination of fibrin D-dimer level and chest X-ray, and confirmed by computed tomography pulmonary

angiography. A fatal outcome was reported in 25% of cases. Clozapine discontinuation may be justified if thrombo-embolism recurs (Nielsen et al., 2013).

3.7. Necrotizing colitis

Fever associated with abdominal pain and distension may reveal ischemic bowel necrosis (Raja and Raja, 2014), a complication of severe constipation induced by the anticholinergic properties of clozapine (Cohen, 2017). We identified one case report occurring after 4 months of clozapine treatment: the diagnosis was confirmed by abdominal radiography showing large bowel dilatation (Leong et al., 2007). Partial colectomy may be required and clozapine should be discontinued at least temporarily.

4. Discussion

4.1. Fever occurring within the first two months of treatment

Practical guidelines synthesizing the principles of the clinical management of fever occurring during the first month of treatment and clozapine treatment are presented in Fig. 2. If fever occurs in the weeks following treatment initiation, the priority is to eliminate agranulocytosis, NMS and myocarditis. Irrespective of the clinical picture, laboratory tests should at least include WBC, CRP, troponin and CK. As fever may be the single symptom in the early course of clozapine-NMS, other clinical (altered consciousness, autonomic instability) and laboratory (CK, WBC) indicators of NMS should be monitored repeatedly. Clinical (tachycardia, dyspnea, chest pain) and laboratory (CRP, troponin) indicators of myocarditis should also be monitored repeatedly (Knoph et al., 2018). Slow titration of clozapine is recommended to prevent myocarditis, especially in East Asians, in patients taking inhibitors and in poor metabolizers who can be identified by weekly assessment of clozapine TDM during titration (Ruan et al., 2019).

In the presence of dyspnea, tachycardia, chest pain or cough, several diagnoses other than myocarditis should be considered including pericarditis (diagnosed by echocardiography), pulmonary embolism (D-dimer level, chest X-ray, computed tomography pulmonary angiography) or alveolitis (chest X-ray, high-resolution computed tomography).

In the presence of gastro-intestinal signs and/or increased CRP or eosinophilia, a low threshold should be used for initiating checks of liver function tests, renal function and serum lipase, in order to rule out hepatitis, pancreatitis or nephritis (Lally et al., 2018). Intense diarrhea may be due to inflammatory colitis, this diagnosis being confirmed by a colon biopsy.

If no cause of fever is identified, a diagnosis of clozapine-induced fever can be considered (Nielsen et al., 2013; Roge et al., 2012). Although eosinophilia and elevated CRP may be important warning signs of severe ADR, they have little specificity and may be transient signs of the immunomodulatory effects of clozapine. In this event, more specific markers and clozapine TDM should be closely monitored. Waiting to increase clozapine dosage until of the abnormalities have normalized may be recommended.

4.2. Fever occurring during maintenance treatment

The risk of inflammatory ADR may be considered as negligible after treatment initiation. NMS and agranulocytosis are also much more frequent at treatment initiation but may occur anytime over the course of treatment (Belvederi Murri et al., 2015; Raja and Raja, 2014). As the risk of pneumonia does not decrease over time in clozapine users (Kuo et al., 2013), fever should alert clinicians about the possibility of potentially-lethal pneumonia. Clozapine users should be warned about this risk and should consult in the event of fever in order to rule out pneumonia and to adapt clozapine dosage. Other conditions associated with fever are also independent from duration of exposure to clozapine: pulmonary embolism, heat stroke or necrotizing colitis may occur anytime during the course the clozapine treatment. If fever occurs during clozapine maintenance treatment, it is necessary to systematically monitor WBC, CRP and CK, and depending on the associated signs to perform the relevant exams: abdominal radiography, urinalysis, abdominal or chest X-ray, fibrin D-dimer level or computed tomography pulmonary.

4.3. Methodological limitations

The findings of the present systematic review should be considered in the light of potential limitations. First, this review should not be considered as exhaustive regarding the possible causes of fever in clozapine users as we cannot exclude that our search may have missed some articles, or that other causes of fever in clozapine users, if any, may have been observed but not published. Second, the management strategies were drawn from empirical clinical practices proposed by experienced clinicians and are not evidence-based. Third, standardized criteria and scales to assess the clozapine causality of ADR are rarely mentioned in the articles included in the review. Hence, some of these cases of ADR associated with fever may have not been caused by clozapine exposure.

4.4. Conclusion

Three key points with concrete implications for clinical practice emerged from this narrative review on medical conditions associated with fever during clozapine treatment. First, most life-threatening ADR associated with fever occur at initiation of clozapine. Second, ADR induced by immunomodulation lie on a continuum of severity ranging from the most benign condition i.e. clozapine-induced fever, to life-threatening complications such as myocarditis. If there is the possibility of a life-threatening ADR, even if uncommon, cessation is most often appropriate. However, as benign causes of fever are much more frequent than life-threatening ADR, discontinuation should not be considered as automatic in the event of intercurrent fever during clozapine treatment during the phase of clozapine initiation. Third, even if fever is not attributable to clozapine exposure, it may lead to clozapine intoxication. TDM is recommended to adjust clozapine daily dosage, especially in the event of pneumonia.

Contributors

All authors contributed to the systematic review and to the interpretation of the results. HV wrote the first draft of the manuscript. All authors contributed and have approved the final manuscript.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest in relation to the subject of this study.

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References

Aldridge, G., Collins, C., Croucher, M., 2013. Clozapine-induced pneumonitis. Aust NZ J Psychiatr 47, 1215–1216.

Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., Coma Fuste, A., Furu, K., Garuoliene, K., Hoffmann, F., Hollingworth, S., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., Lopez, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Piovani, D., Reutfors, J., Saastamoinen, L.K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.C., Siskind, D., Skurtveit, S., Verdoux, H., Wang, L.J., Zara Yahni, C., Zoega, H., Taylor, D., 2017. International trends in clozapine use: a study in 17 countries. Acta Psychiatr. Scand. 136 (1), 37–51.

Bandelow, B., Degner, D., Kreusch, U., Ruther, E., 1995. Myocarditis under therapy with clozapine. Schizophr. Res. 17 (3), 293–294.

Bellissima, B.L., Tingle, M.D., Cicovic, A., Alawami, M., Kenedi, C., 2018. A systematic review of clozapine-induced myocarditis. Int. J. Cardiol. 259, 122–129.

Belvederi Murri, M., Guaglianone, A., Bugliani, M., Calcagno, P., Respino, M., Serafini, G., Innamorati, M., Pompili, M., Amore, M., 2015. Second-generation antipsychotics and neuroleptic malignant syndrome: systematic review and case report analysis. Drugs in R&D 15 (1), 45–62.

Benning, T.B., 1998. Clozapine-induced extrinsic allergic alveolitis. Br. J. Psychiatry 173, 440–441.

Bosonnet, S., Dandurand, M., Moati, L., Guillot, B., 1997. Acute generalized exanthematic pustulosis following administration of clozapine (Leponex(R)). First case. Annales Dermatologie Venereologie 124 (8), 547–548.

Bruno, V., Valiente-Gomez, A., Alcoverro, O., 2015. Clozapine and fever: a case of continued therapy with clozapine. Clin. Neuropharmacol. 38 (4), 151–153.

Buist, N.C.L., Schauer, C.K.M.W., 2016. Fever and elevated CRP-related to clozapine dose. Aust NZ J Psychiatry 50 (2), 182–183.

Buzina, N., Eterović, M., 2016. Life-threatening lupus-like syndrome associated with clozapine. J. Clin. Psychopharmacol. 36 (5), 532–534.

Carruthers, J., Radigan, M., Erlich, M.D., Gu, G., Wang, R., Frimpong, E.Y., Essock, S.M., Olfson, M., Castillo, E.G., Miller, G.A., Sederer, L.I., Stroup, T.S., 2016. An initiative to improve clozapine prescribing in New York state. Psychiatr. Serv. 67 (4), 369–371.

Chopra, N., de Leon, J., 2016. Clozapine-induced myocarditis may be associated with rapid titration: a case report verified with autopsy. Int J Psychiatr Med 51 (1), 104–115.

Chung, J.P.Y., Chong, C.S.Y., Chung, K.F., Dunn, E.L.W., Tang, O.W.N., Chan, W.F., 2008. The incidence and characteristics of clozapine-induced fever in a local psychiatric unit in Hong Kong. Can. J. Psychiatr. 53 (12), 857–862.

Cicala, G., Barbieri, M.A., Spina, E., de Leon, J., 2019. A comprehensive review of swallowing difficulties and dysphagia associated with antipsychotics in adults. Exp Rev Clin Pharmacol 12 (3), 219–234.

Clark, S.R., Warren, N.S., Kim, G., Jankowiak, D., Schubert, K.O., Kisely, S., Forrester, T., Baune, B.T., Siskind, D.J., 2018. Elevated clozapine levels associated with infection: a systematic review. Schizophr. Res. 192, 50–56.

Cohen, D., 2014. Prescribers fear as a major side-effect of clozapine. Acta Psychiatr. Scand. 130 (2), 154–155.

Cohen, D., 2017. Clozapine and gastrointestinal hypomotility. CNS Drugs 31 (12), 1083–1091.

Crews, M.P.K., Dhillon, G.S., MacCabe, J.H., 2010. Clozapine rechallenge following clozapine-induced pericarditis. J Clin Psychiatry 71 (7), 959–961.

Davey, P., Gee, S., Shergill, S.S., 2016. Inflammatory response to clozapine in the absence of myocarditis: case report. Br J Psychiatry Open 2 (3), 244–246.

Davis, M.C., Fuller, M.A., Strauss, M.E., Konicki, P.E., Jaskiw, G.E., 2014. Discontinuation of clozapine: a 15-year naturalistic retrospective study of 320 patients. Acta Psychiatr. Scand. 130 (1), 30–39.

De Berardis, D., Fornaro, M., Orsolini, L., Olivieri, L., Nappi, F., Rapini, G., Vellante, F., Napoletano, C., Serroni, N., Giannantonio, M.D., 2018. Clozapine-related sudden pericarditis in a patient taking long acting aripiprazole and valproate: a case report. Clin Psychopharmacol Neurosci 16 (4), 505–507.

de Leon, J., Diaz, F.J., 2003. Serious respiratory infections can increase clozapine levels and contribute to side effects: a case report. Progress Neuro-psychopharmacol & Biol Psychiatry 27 (6), 1059–1063.

Driver, D.I., Anvari, A.A., Peroutka, C.M., Kataria, R., Overman, J., Lang, D., Tietcheu, M., Parker, R., Baptiste, K., Rapoport, J.L., Gogtay, N., 2014. Management of clozapine-induced fever in a child. Am. J. Psychiatry 171 (4), 398–402.

Druss, B.G., Mazure, C.M., 1993. Transient fever and hematologic abnormalities during clozapine use. J. Clin. Psychopharmacol. 13 (2), 155–156.

Friedberg, J.W., Frankenburg, F.R., Burk, J., Johnson, W., 1995. Clozapine-caused eosinophilic colitis. Ann. Clin. Psychiatry 7 (2), 97–98.

Ginsberg, D.L., 2005. Clozapine-induced eosinophilic colitis. Primary Psychiatry 12 (8), 27–28.

Hashimoto, N., Maeda, T., Okubo, R., Narita, H., Kusumi, I., 2015. Simple pulmonary eosinophilia associated with clozapine treatment. J. Clin. Psychopharmacol. 35 (1), 99–101.

Hoffmann, M.S., Oliveira, L.M., Lobato, M.I., Belmonte-de-Abreu, P., 2016. Heat stroke during long-term clozapine treatment: should we be concerned about hot weather? Trends Psychiatr Psychother 38 (1), 56–59.

Hung, G.C., Liu, H.C., Yang, S.Y., Pan, C.H., Liao, Y.T., Chen, C.C., Kuo, C.J., 2016. Antipsychotic reexposure and recurrent pneumonia in schizophrenia: a nested case-control study. J Clin Psychiatry 77 (1), 60–66.

Jeong, S.H., Ahn, Y.M., Koo, Y.J., Kang, U.G., Kim, Y.S., 2002. The characteristics of clozapine-induced fever. Schizophr. Res. 56 (1–2), 191–193.

Karmacharya, R., Mino, M., Pirl, W.F., 2005. Clozapine-induced eosinophilic colitis. Am. J. Psychiatry 162 (7), 1386–1387.

Kerwin, R.W., Osborne, S., Sainz-Fuertes, R., 2004. Heat stroke in schizophrenia during clozapine treatment: rapid recognition and management. J. Psychopharmacol. 18 (1), 121–123.

Knoph, K.N., Morgan III, R.J., Palmer, B.A., Schak, K.M., Owen, A.C., Leloux, M.R., Patel, M., Leung, J.G., 2018. Clozapine-induced cardiomyopathy and myocarditis monitoring: a systematic review. Schizophr. Res. 199, 17–30.

Kohen, I., Afzal, N., Hussain, S., Manu, P., 2009. Increases in C-reactive protein may predict recurrence of clozapine-induced fever. Ann. Pharmacother. 43 (1), 143–146.

Kuo, C.J., Yang, S.Y., Liao, Y.T., Chen, W.J., Lee, W.C., Shau, W.Y., Chang, Y.T., Tsai, S.Y., Chen, C.C., 2013. Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. Schizophr. Bull. 39 (3), 648–657.

Lai, Y.W., Chou, C.Y., Shen, W.W., Lu, M.L., 2012. Pityriasis rosea-like eruption associated with clozapine: a case report. Gen. Hosp. Psychiatry 34 (6) 703.e705-707.

Lally, J., Al Kalbani, H., Krivoy, A., Murphy, K.C., Gaughran, F., MacCabe, J.H., 2018. Hepatitis, interstitial nephritis, and pancreatitis in association with clozapine treatment: a systematic review of case series and reports. J. Clin. Psychopharmacol. 38 (5), 520–527.

Landry, P., Benaliouad, F., Tessier, S., 2003. Increased use of antibiotics in clozapine-treated patients. Int. Clin. Psychopharmacol. 18 (5), 297–298.

Legge, S.E., Hamshere, M., Hayes, R.D., Downs, J., O'Donovan, M.C., Owen, M.J., Walters, J.T.R., MacCabe, J.H., 2016. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. Schizophr. Res. 174 (1–3), 113–119.

Leong, Q.M., Wong, K.S., Koh, D.C., 2007. Necrotising colitis related to clozapine? A rare but life threatening side effect. World J Emerg Surg 2, 21.

Lowe, C.M., Grube, R.R.A., Scates, A.C., 2007. Characterization and clinical management of clozapine-induced fever. Ann. Pharmacother. 41 (10), 1700–1704.

Manfredi, R., Sabbatani, S., 2007. Clozapine-related agranulocytosis associated with fever of unknown origin, protective hospitalisation, and multiple adverse events related to the administration of empiric antimicrobial treatment. Pharmacoepidemiol. Drug Saf. 16 (12), 1285–1289.

Marchel, D., Hart, A.L., Keefer, P., Vredeveld, J., 2017. Multiorgan eosinophilic infiltration after initiation of clozapine therapy: a case report. BMC Res Notes 10 (1), 316.

Martin, N., Williams, R., 2013. Management of clozapine-induced fever: a case of continued therapy throughout fever. JPN 38 (4), E9–10.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097.

Mouaffak, F., Gaillard, R., Burgess, E., Zaki, H., Olie, J.P., Krebs, M.O., 2009. Clozapine-induced serositis: review of its clinical features, pathophysiology and management strategies. Clin. Neuropharmacol. 32 (4), 219–223.

Myles, N., Myles, H., Xia, S., Large, M., Kisely, S., Galletly, C., Bird, R., Siskind, D., 2018. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta Psychiatr. Scand. 138 (2), 101–109.

Netherlands Clozapine Collaboration Group, 2019. Guideline for the use of clozapine. http://wwwclozapinepluswerkgroepnl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013pdf, Accessed date: March 2019.

Nielsen, J., Foldager, L., Meyer, J.M., 2009. Increased use of antibiotics in patients treated with clozapine. Eur. Neuropsychopharmacol. 19 (7), 483–486.

Nielsen, J., Dahm, M., Lublin, H., Taylor, D., 2010. Psychiatrists' attitude towards and knowledge of clozapine treatment. J. Psychopharmacol. 24 (7), 965–971.

Nielsen, J., Damkier, P., Lublin, H., Taylor, D., 2011. Optimizing clozapine treatment. Acta Psychiatr. Scand. 123 (6), 411–422.

Nielsen, J., Correll, C.U., Manu, P., Kane, J.M., 2013. Termination of clozapine treatment due to medical reasons: when is it warranted and how can it be avoided? J Clin Psychiatry 74 (6), 603–613 (quiz 613).

Nielsen, J., Young, C., Ifteni, P., Kishimoto, T., Xiang, Y.T., Schulte, P.F., Correll, C.U., Taylor, D., 2016. Worldwide differences in regulations of clozapine use. CNS drugs 30 (2), 149–161.

Nose, M., Recla, E., Trifiro, G., Barbui, C., 2015. Antipsychotic drug exposure and risk of pneumonia: a systematic review and meta-analysis of observational studies. Pharmacoepidemiol. Drug Saf. 24 (8), 812–820.

Pai, N.B., Vella, S.C., 2012. Reason for clozapine cessation. Acta Psychiatr. Scand. 125 (1), 39–44.

Patterson, B.D., Jennings, J.L., 1993. Spiking fever and profuse diarrhea with clozapine treatment. Am. J. Psychiatry 150 (7), 1126.

Pelizza, L., Melegari, M., 2007. Clozapine-induced microscopic colitis: a case report and review of the literature. J. Clin. Psychopharmacol. 27 (6), 571–574.

Ponsford, M., Castle, D., Tahir, T., Robinson, R., Wade, W., Steven, R., Bramhall, K., Moody, M., Carne, E., Ford, C., Farewell, D., Williams, P., El-Shanawany, T., Jolles, S., 2018. Clozapine is associated with secondary antibody deficiency. Brit J Psychiatr 1–7.

Pushpakumara, J., Karunarathna, P., Sivathiran, S., Liyanage, A., Indrakumar, J., 2015. Clozapine induced pancytopenia leading to severe sepsis: an unusual early complication. BMC Research Notes 8, 792.

Raja, M., Raja, S., 2014. Clozapine safety, 40 years later. Curr. Drug Saf. 9 (3), 163–195.

Rami, A.F., Barkan, D., Mevorach, D., Leitersdorf, E., Caraco, Y., 2006. Clozapine-induced systemic lupus erythematosus. Ann. Pharmacother. 40 (5), 983–985.

Roge, R., Moller, B.K., Andersen, C.R., Correll, C.U., Nielsen, J., 2012. Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far? Schizophr. Res. 140 (1–3), 204–213.

Rohde, C., Polcwiartek, C., Kragholm, K., Ebdrup, B.H., Siskind, D., Nielsen, J., 2018. Adverse cardiac events in out-patients initiating clozapine treatment: a nationwide register-based study. Acta Psychiatr. Scand. 137 (1), 47–53.

Ronaldson, K.J., Taylor, A.J., Fitzgerald, P.B., Topliss, D.J., Elsik, M., McNeil, J.J., 2010. Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. J Clin Psychiatry 71 (8), 976–981.

Ronaldson, K.J., Fitzgerald, P.B., McNeil, J.J., 2015. Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatr. Scand. 132 (4), 231–240.

Ruan, C.J., de Leon, J., 2019. Thirty years of both ignorance and clinical experience suggest that clozapine intoxication during co-occurring infections and inflammation may have higher morbidity and mortality than is currently believed. Psychosomatics 60 (2), 221–222.

Ruan, C.J., Zhen, X.Y., Ge, X.L., Wang, C.Y., Guo, W., Tang, Y.L., Li, W.B., de Leon, J., 2017. Pneumonia can cause clozapine intoxication: a case report. Psychosomatics 58 (6), 652–656.

Ruan, C.J., Zang, Y.N., Wang, C.Y., Cheng, Y.H., Sun, C., Spina, E., de Leon, J., 2019. Clozapine metabolism in East Asians and Caucasians: a pilot exploration of the prevalence of poor metabolizers and a systematic review. J. Clin. Psychopharmacol. 39 (2), 135–144.

Sarvaiya, N., Lapitskaya, Y., Dima, L., Manu, P., 2018. Clozapine-associated pulmonary embolism: a high-mortality, dose-independent and early-onset adverse effect. Am. J. Ther. 25 (4), e434–e438.

Schmidinger, S., Hofer, A., 2014. Pulmonary embolism and aspiration pneumonia after reexposure to clozapine: pulmonary adverse effects of clozapine. J. Clin. Psychopharmacol. 34 (3), 385–387.
Stoecker, Z.R., George, W.T., O'Brien, J.B., Jancik, J., Colon, E., Rasimas, J.J., 2017. Clozapine usage increases the incidence of pneumonia compared with risperidone and the general population: a retrospective comparison of clozapine, risperidone, and the general population in a single hospital over 25 months. Int. Clin. Psychopharmacol. 32 (3), 155–160.
Stroup, T.S., Gray, N., 2018. Management of common adverse effects of antipsychotic medications. World Psychiatry 17 (3), 341–356.
Stuhec, M., 2013. Clozapine-induced elevated C-reactive protein and fever mimic infection. Gen Hosp Psychiatr 35 (6), 680 (e685-686).
Taylor, D.M., Douglas-Hall, P., Olofinjana, B., Whiskey, E., Thomas, A., 2009. Reasons for discontinuing clozapine: matched, case-control comparison with risperidone long-acting injection. Br. J. Psychiatry 194 (2), 165–167.
Tham, J.C., Dickson, R.A., 2002. Clozapine-induced fevers and 1-year clozapine discontinuation rate. J Clin Psychiatry 63 (10), 880–884.
Thompson, H.J., 2005. Fever: a concept analysis. J. Adv. Nurs. 51 (5), 484–492.
Tremeau, F., Clark, S.C., Printz, D., Kegeles, L.S., Malaspina, D., 1997. Spiking fevers with clozapine treatment. Clin. Neuropharmacol. 20 (2), 168–170.
Trollor, J.N., Chen, X., Chitty, K., Sachdev, P.S., 2012. Comparison of neuroleptic malignant syndrome induced by first- and second-generation antipsychotics. Br. J. Psychiatry 201 (1), 52–56.
Verdoux, H., Pambrun, E., 2014. Clozapine use pattern in persons with and without treatment for Parkinson's disease in real-world conditions: a naturalistic study in a community-based sample. Acta Psychiatr. Scand. 130 (6), 487–497.
Verdoux, H., Pambrun, E., Cortaredona, S., Coldefy, M., Le Neindre, C., Tournier, M., Verger, P., 2016. Geographical disparities in prescription practices of lithium and clozapine: a community-based study. Acta Psychiatr. Scand. 133 (6), 470–480.
Verdoux, H., Quiles, C., Bachmann, C.J., Siskind, D., 2018. Prescriber and institutional barriers and facilitators of clozapine use: a systematic review. Schizophr. Res. 201, 10–19.
Wickert, W.A., Campbell, N.R., Martin, L., 1994. Acute severe adverse clozapine reaction resembling systemic lupus erythematosus. Postgrad. Med. J. 70 (830), 940–941.
Wolf, J., Sartorius, A., Alm, B., Henn, F.A., 2004. Clozapine-induced lupus erythematosus. J. Clin. Psychopharmacol. 24 (2), 236–238.
Wu, M.K., Chung, W., Wu, C.K., Tseng, P.T., 2015. The severe complication of Stevens-Johnson syndrome induced by long-term clozapine treatment in a male schizophrenia patient: a case report. Neuropsychiat Dis Treat 11, 1039–1041.
Yang, S.Y., Liao, Y.T., Liu, H.C., Chen, W.J., Chen, C.C., Kuo, C.J., 2013. Antipsychotic drugs, mood stabilizers, and risk of pneumonia in bipolar disorder: a nationwide case-control study. J Clin Psychiatry 74 (1), e79–e86.
Ziegenbein, M., Steinbrecher, A., Garlipp, P., 2003. Clozapine-induced aplastic anemia in a patient with Parkinson's disease. Can. J. Psychiatr. 48 (5), 352.