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Implicações para o cuidado farmacêutico na síndrome DRESS

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REVISÃO DE LITERATURA

RESUMO

Objetivo: sintetizar as evidências sobre os principais medicamentos implicados na síndrome DRESS e reorganizá-las em um fluxo de cuidado voltado à atuação farmacêutica. Métodos: revisão narrativa com foco aplicado à prática clínica, priorizando revisões sistemáticas, coortes, estudos multicêntricos, investigações farmacogenéticas e consensos internacionais sobre DRESS induzida por medicamentos. **Resultados:** os estudos apontam que alopurinol, anticonvulsivantes aromáticos, lamotrigina, vancomicina, sulfonamidas, dapsona e esquemas antituberculose concentram parte relevante dos casos e dos desfechos graves. A janela de maior risco costuma situar-se entre duas e oito semanas após o início do fármaco, embora antibacterianos e contraste iodado possam desencadear quadros mais precoces. Para o farmacêutico, o reconhecimento imediato de exantema difuso, febre, edema facial, eosinofilia, icterícia, dispneia e deterioração hepática ou renal deve levar ao acionamento urgente da equipe assistencial, à revisão cronológica dos medicamentos e ao registro inequívoco da suspeita. **Conclusão:** o farmacêutico tem papel estratégico na estratificação do risco, educação do paciente, monitoramento inicial do tratamento, prevenção de reexposição e farmacovigilância, devendo incorporar um fluxo padronizado de avaliação e encaminhamento de usuários expostos a fármacos de maior risco.

Palavras-chave: síndrome DRESS; hipersensibilidade a medicamentos; farmacovigilância; cuidado farmacêutico.

Implications for pharmaceutical care in DRESS syndrome

ABSTRACT

Objective: to synthesize the evidence on the main drugs implicated in DRESS syndrome and reorganize it into a care flow focused on pharmaceutical practice. **Methods:** narrative review with an applied clinical perspective, prioritizing systematic reviews, cohorts, multicenter studies, pharmacogenetic investigations, and international consensus documents on drug-induced DRESS. **Results:** evidence indicates that allopurinol, aromatic anticonvulsants, lamotrigine, vancomycin, sulfonamides, dapsone, and antituberculosis regimens account for a relevant proportion of cases and severe outcomes. The highest-risk window usually occurs between two and eight weeks after treatment initiation, although antibacterials and iodinated contrast agents may trigger earlier presentations. For pharmacists, early recognition of diffuse rash, fever, facial edema, eosinophilia, jaundice, dyspnea, and hepatic or renal deterioration should prompt urgent communication with the care team, chronological medication review, and clear documentation of the suspected reaction. **Conclusion:** pharmacists play a strategic role in risk stratification, patient education, early treatment monitoring, prevention of re-exposure, and pharmacovigilance, and should incorporate a standardized assessment and referral flow for patients exposed to higher-risk drugs.

Keywords: DRESS syndrome; drug hypersensitivity; pharmacovigilance; pharmaceutical care.

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Introduction

Drug reaction with eosinophilia and systemic symptoms, known by the acronym DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), is a rare, severe, and potentially fatal adverse reaction characterized by cutaneous rash, fever, hematologic abnormalities, and systemic involvement, particularly hepatic and renal impairment. In addition to the skin, the syndrome may affect the lungs, heart, nervous system, and endocrine glands, including delayed manifestations after the acute phase, which reinforces its multisystem nature and the need for prolonged follow-up (CACOUB et al., 2011; BRÜGGEN et al., 2024; KROSHINSKY; CARDONES; BLUMENTHAL, 2024).

Although several drugs have been mentioned in case reports, the most robust studies show that the set of medications truly implicated is relatively limited. Historically, allopurinol and aromatic anticonvulsants have occupied a central position, whereas more recent reviews highlight lamotrigine, vancomycin, sulfonamides, dapsone, and antituberculosis regimens among the agents of greatest clinical and pharmacovigilance relevance (KARDAUN et al., 2013; JUNG et al., 2019; SIM et al., 2019; LIANG et al., 2024; ZIEBART et al., 2024).

In the field of clinical pharmacy, DRESS is particularly relevant because pharmacists are often involved in prescription review, dispensing of higher-risk medications, monitoring of prolonged therapies, medication reconciliation, and reporting of adverse drug reactions. Thus, this study aimed to synthesize the main evidence on the medications implicated in DRESS syndrome and to propose a practical workflow for the pharmaceutical care of patients exposed to high-risk drugs.

Methodology

This is a narrative review of a descriptive nature, applied to pharmaceutical practice. International studies published in journals of recognized relevance in the fields of dermatology, allergy, clinical pharmacology, and pharmacovigilance were prioritized, with emphasis on systematic reviews, prospective and retrospective studies, multicenter cohorts, pharmacovigilance database analyses, pharmacogenetic investigations, and international consensus documents on drug-induced DRESS.

The selection prioritized publications with greater clinical utility for three analytical axes: identification of the medications and pharmacological classes most frequently associated with the syndrome; characterization of latency, severity, and visceral involvement; and practical implications for monitoring, health education, prevention of re-exposure, and reporting. The interpretation of the body of evidence was guided toward supporting the organization of a care workflow applicable to pharmaceutical care.

Results and discussion

Most commonly implicated drugs and implications for practice

The international literature consistently shows that DRESS is not evenly distributed across all medications. Reviews, cohorts, and multicenter studies demonstrate recurrence of a limited group of drugs, particularly allopurinol, aromatic anticonvulsants, lamotrigine, vancomycin, sulfonamides, dapsone, and antituberculosis drugs, as shown in Table 1 (CACOUB et al., 2011; KARDAUN et al., 2013; JUNG et al., 2019; SIM et al., 2019; LIANG et al., 2024).

Allopurinol remains one of the drugs most strongly associated with DRESS and with severe outcomes. Pharmacovigilance and pharmacogenetic studies demonstrate not only the frequency of this association, but also the importance of factors such as chronic kidney disease, advanced age, and the presence of the HLA-B*58:01 allele in specific populations, which supports stricter monitoring and, when available, discussion of genetic screening before therapy initiation (KO et al., 2015; SATO et al., 2021; LIANG et al., 2024).

Among anticonvulsants, carbamazepine, phenytoin, and phenobarbital occupy a classic position, whereas lamotrigine has gained prominence in more recent studies. In addition to the clinical risk, the literature suggests the potential utility of pharmacogenetics, especially for carbamazepine, due to its association with HLA-A*31:01 in certain populations. For pharmacists, this means that counseling should be reinforced from the time of dispensing, especially during the first weeks, with emphasis on recognizing widespread rash, fever, and facial edema as warning signs that should

not be underestimated (MUSHIRODA et al., 2018; SORIA et al., 2020; LIANG et al., 2024).

Antibacterials have assumed an increasingly prominent role in contemporary case series, particularly vancomycin, amoxicillin, cephalosporins, piperacillin/tazobactam, and trimethoprim-sulfamethoxazole. Vancomycin, in particular, has been the subject of specific investigation in a retrospective cohort, reinforcing its relevance in hospital settings and prolonged therapies. In these scenarios, the clinical pharmacist should integrate the review of serial laboratory tests, such as complete blood count, liver enzymes, and serum creatinine, into pharmacotherapeutic monitoring, especially when cutaneous rash is associated with fever or systemic clinical deterioration (SORIA et al., 2020; LIANG et al., 2024; ZIEBART et al., 2024).

Table 1 - Main pharmacological groups associated with DRESS syndrome and implications for pharmaceutical care

Pharmacological group	Examples	Key evidence points	Pharmaceutical implications
Xanthine oxidase inhibitor	Allopurinol	Strong association with DRESS and fatal outcomes; higher risk in patients with chronic kidney disease, advanced age, and in population groups carrying HLA-B*58:01.	Review indication and dose, consider renal function, counsel on early warning signs, and discuss genetic screening when available.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital, and lamotrigine	Classical group associated with the syndrome; lamotrigine has gained prominence in recent series; some cases show later latency.	Reinforce counseling from treatment initiation, document prior severe reactions, and avoid re-exposure to related drugs.
Antibacterials (Glycopeptide, beta-lactams, sulfonamides/antifolates)	Vancomycin, amoxicillin, cephalosporins, piperacillin/tazobactam, trimethoprim-sulfamethoxazole	Presentations may occur earlier; vancomycin and sulfonamides are prominent in pharmacovigilance and severe cases.	Monitor clinically and, in hospital settings, review complete blood count, transaminases, and creatinine; rash with fever should be treated as a potentially serious event.
Antibacterials (Sulfones)	Dapsone	Robust association with HLA-B*13:01 and risk of severe cutaneous adverse drug reactions, including DRESS.	Provide enhanced counseling, maintain high clinical suspicion, and consider pharmacogenetics in populations or services where this strategy is available.
Antibacterials (Antituberculosis drugs)	Ethambutol, rifampicin, pyrazinamide, isoniazid	Polypharmacy makes identification of the causal drug difficult; latency may be prolonged.	Perform detailed medication reconciliation, support safe sequential reintroduction, and alert the team early when rash, fever, or laboratory abnormalities occur.

Source: prepared by the author based on the reviewed literature.

Time window, warning signs, and severity

The classic presentation of DRESS usually develops between two and eight weeks after initiation of the suspected medication, especially with allopurinol, anticonvulsants, and dapsone. However, this timeline should not be applied rigidly, because some cases related to antibacterials and iodinated contrast media may occur within up to 15 days, which requires investigation of all drugs introduced in the previous weeks (SORIA et al., 2020; CALLE et al., 2023; KROSHINSKY; CARDONES; BLUMENTHAL, 2024).

From a clinical perspective, the pharmacist should value not only the rash itself, but also the combination of cutaneous manifestations and systemic signs. Persistent fever, facial edema, lymphadenopathy, marked malaise, jaundice, dark urine, dyspnea, new-onset cough, oliguria, and hepatic or renal laboratory deterioration are elements that increase suspicion of DRESS and require urgent medical evaluation. The severity of the syndrome depends less on the isolated extent of the rash and more on the associated visceral involvement, which is why laboratory tests and exposure chronology are central components of clinical reasoning (BRÜGGEN et al., 2024; KROSHINSKY; CARDONES; BLUMENTHAL, 2024).

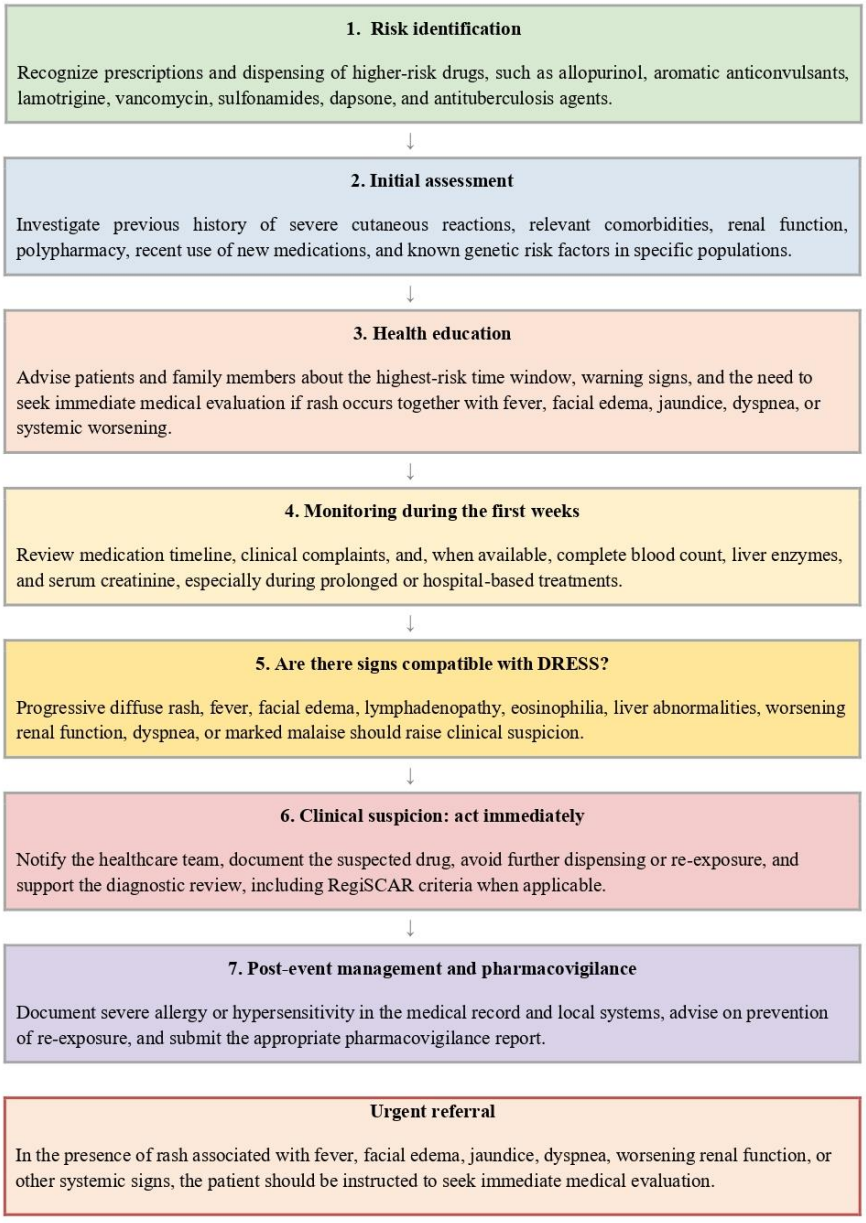
The RegiSCAR score may support diagnostic assessment by considering fever, lymphadenopathy, eosinophilia, atypical lymphocytes, extensive rash, internal organ involvement, time to resolution, and exclusion of alternative diagnoses. Although it does not replace specialized evaluation, this instrument contributes to the standardization of clinical suspicion and to the differentiation between DRESS and other drug-induced cutaneous conditions (KARDAUN et al., 2013; KROSHINSKY; CARDONES; BLUMENTHAL, 2024).

Pharmaceutical care workflow for patients using high-risk medications

The analysis of the evidence made it possible to propose an applicable operational workflow for pharmaceutical care, shown in Figure 1, for outpatient, hospital, and dispensing settings. The aim of this workflow is to standardize the approach to patients who are about to start or are already using medications with a higher risk of DRESS, thereby reducing diagnostic delays and inappropriate re-exposure. In all settings, the central logic should combine prior risk stratification, patient

education, monitoring during the first weeks, and a rapid response in the presence of warning signs (BRÜGGEN et al., 2024; KROSHINSKY; CARDONES; BLUMENTHAL, 2024).

Figure 1 - Pharmaceutical care workflow for patients using medications associated with DRESS syndrome



Source: prepared by the author based on the reviewed literature.

In practice, this workflow is based on four key questions in any encounter involving a patient with rash or systemic complaints while using a high-risk medication: Which drugs were started within the last eight weeks? Was there fever, facial edema, or lymphadenopathy? Are there recent abnormalities in complete blood count, liver enzymes, or serum creatinine? Is there a previous history of a similar reaction to the same medication or to related drugs? These questions help to organize clinical suspicion and improve communication with the healthcare team.

In the hospital setting, the clinical pharmacist can increase the sensitivity of this workflow through alerts directed at higher-risk therapies and by serial review of laboratory tests. In outpatient and dispensing settings, the main benefit lies in health education, recognition of the temporal risk window, and explicit guidance not to underestimate cutaneous rash accompanied by fever or facial edema. In both scenarios, event reporting and clear documentation of the suspected reaction are essential measures to prevent re-exposure and strengthen institutional and national pharmacovigilance.

Conclusion

The evidence gathered demonstrates that DRESS syndrome is recurrently associated with a limited set of medications and that early identification of the event depends on the integration of exposure chronology, recognition of systemic signs, and consideration of predisposing factors. Allopurinol, aromatic anticonvulsants, lamotrigine, vancomycin, sulfonamides, dapsone, and antituberculosis drugs deserve special vigilance, particularly during the first weeks of treatment.

In this context, the pharmacist plays a strategic role by combining risk stratification, qualified counseling, initial clinical monitoring, prevention of re-exposure, and reporting of adverse events. The incorporation of a standardized care workflow may make this role more objective, reduce delays in recognizing the syndrome, and improve patient safety in the face of one of the most severe adverse drug reactions in clinical practice.

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