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Drug reaction with eosinophilia and systemic symptoms (DRESS Syndrome) - A comprehensive review of clinical features, optimized diagnosis and management strategies

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms, also known as drug-induced hypersensitivity syndrome (DRESS/ DIHS), represents a rare, severe adverse drug reaction. The syndrome typically manifests with rash, fever, facial edema, and multiorgan involvement and requires a prompt withdrawal of the culprit drug. This review summarises existing knowledge on DRESS, including pathophysiology, clinical presentation, diagnostic approaches and treatment options.

Keywords: Drug hypersensitivity syndrome, Drug eruption, DRESS, Drug-related side effects and adverse reactions, Eosinophilia

1. INTRODUCTION

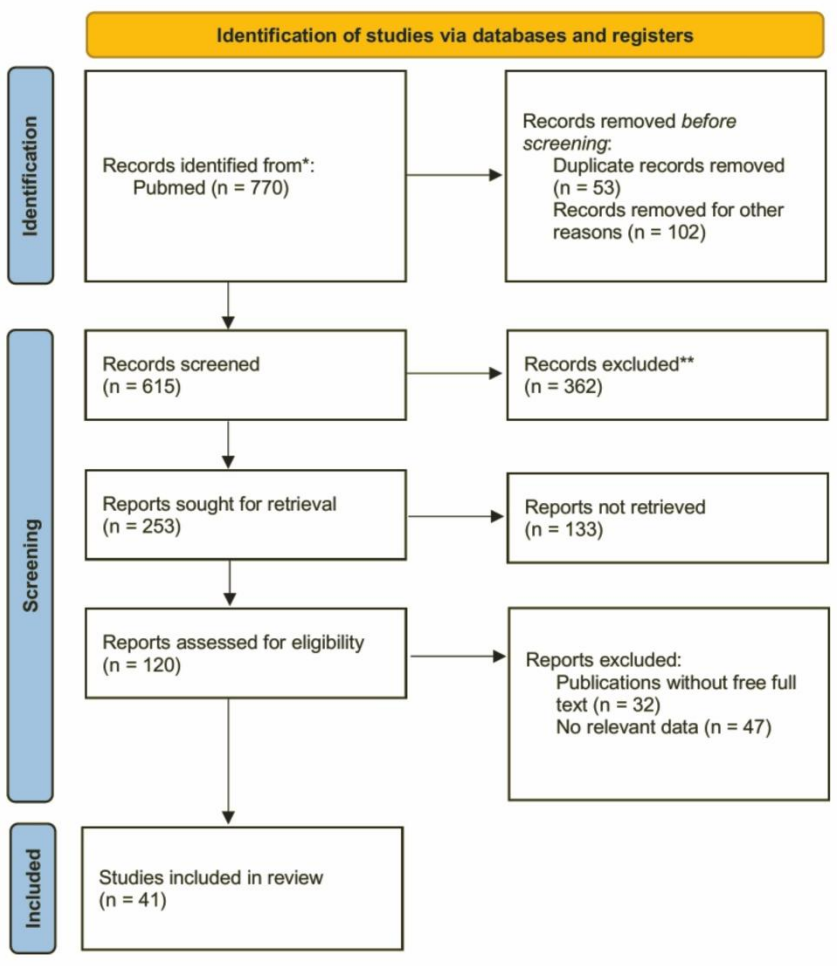
DRESS syndrome, first described in 1996 by Bocquet, is a rare, severe, and potentially life-threatening cutaneous adverse hypersensitivity reaction (Bocquet et al.,1996; Peter et al., 2017). The Japanese research group later proposed the term "Drug-induced hypersensitivity syndrome" (DiHS), which is often used interchangeably to describe the same syndrome. The disease usually begins 2-8 weeks after administration of the causative drug. It is most often associated with the use of anticonvulsants, antibiotics, allopurinol, and non-steroidal anti-inflammatory agents (NSAIDs), although many other drugs may also be involved in the pathogenesis.

The clinical presentation of the disease is progressive. DRESS is characterized by generalized skin rash with facial swelling, fever, lymphadenopathy, hematologic abnormalities, particularly eosinophilia and lymphocytosis, and more or less severe involvement of visceral organs, such as hepatitis, nephritis, pneumonia, and myocarditis. The pathophysiology of this heterogeneous syndrome is complex, multifactorial, and not fully understood (Kroshinsky et al., 2024). Viral reactivation of HHV-6,7, EBV, and CMV is a significant aspect of disease presentation. This viral

reactivation may cause a prolonged antiviral response that can lead to the development of systemic effects (Hama et al., 2022; Miyagawa et al., 2021). In the treatment of DRESS syndrome, it is important to discontinue the drug causing the hypersensitivity reaction. In addition to prompt withdrawal of all suspected causative drugs, treatment includes administration of glucocorticosteroids or other immunosuppressive agents, as indicated.

2. REVIEW METHODS

To write this review, we used the scientific database PubMed. We focused on recent, relevant publications written in English. The search focused on studies addressing the clinical features, pathogenesis, diagnosis, and management strategies of DRESS syndrome. We selected studies in an advanced search strategy using keywords related to the subject, such as „Drug hypersensitivity syndrome", „DRESS", „Eosinophilia", „Drug eruption", or „Drug-related side effects and adverse reactions". To prepare articles for this study, we conducted research from December 2025 to February 2026. The selection procedures are shown in Figure 1.



*n- number of articles

Figure 1. Flow chart

3. RESULTS AND DISCUSSION

Epidemiology

The true incidence of DRESS varies depending on the drug involved and the patient'simmune status and is likely underestimated due to underdiagnosis and underreporting. It's reported incidence lies between 2 and 5 cases per million per year with estimated prevalence being approximately 2 cases per 100,000 population (Kroshinsky et al., 2024).

DRESS syndrome can occur at any age but is seen more often in adults, with age distribution varying by population and causative drug (Del Pozzo-Magaña et al., 2022; Rahnama-Moghadam et al., 2025; Toniato et al., 2021). A higher incidence of DRESS has been observed among Black individuals and women (Hiransuthikul et al., 2016; Wang and Mei, 2017; Kardaun et al., 2013). Despite appropriate treatment, the mortality rate remains between 3.8% and 10%. (Hiransuthikul et al., 2016).

Etiology

At least 60 medications have been associated with DRESS. Those most frequently implicated are aromatic anticonvulsants (phenytoin, carbamazepine, and phenobarbital), sulfonamides, sulfones (dapsone), nonsteroidal anti-inflammatory drugs (piroxicam, ibuprofen, and diclofenac), beta-lactam antibiotics, vancomycin, allopurinol, minocycline, and antiretrovirals. Criado et al., (2025) and Liang et al., (2024) reported that the FAERS database for over 20 years up to 2023 recorded 15,751 cases of DRESS, of which 1,043 were fatal. Study showed that the most common drugs causing DRESS were two antibiotics, while allopurinol was the agent most responsible for death cases. Table 1 describes the main medications listed as potential triggers for DRESS (Stirton et al., 2022; Criado et al., 2025; Calle et al., 2023).

Table 1. Summary of the most commonly associated drugs.

Drug Category	Drug Name
Anticonvulsants - Aromatic	Carbamazepine, phenytoine, lamotrigine, phenobarbital, oxcarbazepine
Anticonvulsants - Non-aromatic	Ethosuximide, sodium valproate or valproic acid, zonisamide, gabapentin, levetiracetam
Antibiotics	Sulfonamides, sulfamethoxazole-trimethoprim, sulfasalazine, dapsone, vancomycin, minocycline, ampicillin, ampicillin/sulbactam, azithromycin, ceftriaxone, cefepime, clindamycin, spiramycine, metronidazole, amoxicillin, amoxicillin/clavulanate, linezolid, clindamycin, levofloxacin, hydroxychloroquine, teicoplanin, voriconazole
Antituberculosis agents	rifampin, ethambutol, pyrazinamide, isoniazid, streptomycin
Analgesics	Diclofenac, celecoxib, ibuprofen, acetylsalicylic acid, piroxicam, metamizole, dexketoprofen
Antidepressant and antipsychotic	Bupropion, fluoxetine, olanzapine, quetiapine, desipramine, amitryptyline, clomipramine,
Antihypertensive	Amlodypine, captopril, enalapril, diltiazem, spironolactone
Antivirals	Telaprevir, boceprevir, abacavir, raltegravir, nevirapine, zalcitabine
Others	Allopurinol, omeprazole, esomeprazole, propylthiouracil, nivolumab, ipilimumab, Traditional Chinese Medicine, quinine, mexiletine, hydroxychloroquine, ranitidine, thiamine, vitamin B12, rivaroxaban

Pathophysiology

Pathophysiology of DRESS primarily involves a complex interaction between immunological mechanisms and genetic predisposition. The disease is mediated by T-cell activation and cytokine release (Criado et al., 2025). Moreover, certain human leukocyte antigens have been linked to different drug hypersensitivity reactions, which also include DRESS syndrome. Also, the relation between reactivation of latent viruses, such as HHV-6, plays a vital role in the development of the syndrome (Stirton et al., 2022; Criado et al., 2025; Calle et al., 2023). Additional predisposing factors likely exist but remain still unknown. It highlights the need to change this model as our understanding of DRESS pathogenesis evolves (Hung et al., 2005; Calle et al.,2023).

Clinical manifestations

DRESS syndrome typically develops within 2 weeks to 2 months after the initiation of the offending drug and is characterized by progressive multi-organ involvement, affecting the skin, hematologic system, and various internal organs (Stirton et al., 2022). DRESS syndrome typically begins with prodromal flu-like symptoms, including malaise, pruritus, pharyngitis, lymphadenopathy, and high fever (38–40 °C), which occurs in 75–100% of patients and often precedes the rash by several days. The clinical course of DRESS syndrome is usually gradual, with progressive involvement of multiple symptoms (Cacoub et al., 2011; Criado et al., 2025; Kardaun et al., 2013).

Cutaneous manifestations of DRESS are diverse and typically involve over 50% of the body surface area. The most characteristic early signs, present in up to 75% of patients, are periorbital and facial edema, often accompanied by micropustules. Facial edema may be a distinguishing feature from more mild forms of DRESS or maculopapular eruption (MPE). (Shiohara and Mizukawa, 2019) The rash in DRESS is often polymorphic (in around 85% of cases), including maculopapular, lichenoid, exfoliative, urticarial, purpuric, eczematous, and pustular lesions, with widespread erythema (Lehloenya et al., 2020; Kardaun et al., 2013)

Most patients develop a maculopapular exanthema that progresses in a craniocaudal, symmetrical manner, sparing the palms and soles (Shiohara and Mizukawa, 2019).

Mucosal involvement occurs in up to 56% of DRESS patients, usually affecting a single site such as the lips, pharynx, or tonsils, and may occasionally progress to erosions. It is typically mild and non-hemorrhagic, which helps to distinguish it from SJS/TEN (Eshki et al., 2009). In 20-30% of cases, erythema progresses to erythroderma. (Criado et al.,2025) Cutaneous manifestations may continue for several weeks to months even after the causative drug has been withdrawn (Cacoub et al., 2011).

Hematological abnormalities are common in DRESS, with atypical lymphocytosis often being one of the most frequent findings, though it can be easily overlooked. Eosinophilia, appearing later in 60–90% of patients across multiple studies (although the majority show greater than 80%), may take 1–2 weeks to develop and can persist even after liver enzymes have normalized (Stirton et al., 2022; Calle et al., 2023; Kardaun et al., 2013). Less commonly, DRESS may present with lymphopenia, leukopenia, thrombocytopenia, thrombocytosis, or pancytopenia, which are generally linked to a more severe prognosis (Stirton et al., 2022).

Systemic involvement of internal organs in DRESS is observed in up to 91% of patients. The most common manifestations of visceral organ involvement are hepatitis, nephritis, and pneumonia. Lymphadenopathy is seen in 50-75% of cases. Hepatic injury is common in patients with DRESS syndrome, occurring in up to 97% of cases. Typically it is characterised by an elevation of liver enzymes, which is usually mild, anicteric and may take months to normalize. The primary cause of mortality in DRESS is a rarely seen severe liver failure, occurring with extensive necrosis, coagulopathy and encephalopathy (Criado et al., 2025).

The second most commonly affected organ in DRESS is the kidney. Renal manifestations occur in up to 30% of DRESS cases. Most of the time, the injury is mild and resolves after discontinuation of the causative medication. It may present as moderate increases in creatinine, proteinuria, and eosinophils in the urinary sediment. However, sometimes renal impairment may be severe and manifest as interstitial nephritis, potentially progressing to end-stage renal disease. Patients at highest risk of kidney failure include the elderly, those with pre-existing renal disease, and cases of DRESS associated with allopurinol (Taweesedt et al., 2019).

The third most commonly affected organ in DRESS is the lung. Studies have shown that interstitial pneumonitis is the main pulmonary manifestation. Minocycline is the drug most frequently linked to pulmonary damage (Criado et al., 2025). Cardiac involvement in DRESS, typically manifests as eosinophilic myocarditis orpericarditis, which can have potentially fatal outcomes. Most commonly, it appears around 70 days after symptom onset and can occur even months after drug discontinuation. Heart failurein DRESS is characterized by chest pain, tachycardia, hypotension and dyspnea. It has typically been reported after administration of minocycline (Calle et al., 2023).

In addition to the more common organ involvement, patients with DRESS may occasionally develop pancreatitis, colitis, cholangitis, encephalitis or meningoencephalitis, hemophagocytic syndrome, and thyroiditis (Criado et al., 2025; Cacoub et al., 2011; Kardaun et al., 2013).

How to identify the causative DRESS drug?

Knowledge about the drug responsible for causing DRESS syndrome is crucial to stop disease progression and prevent re-exposure. It has been reported that intradermal testing can detect both immediate and delayed drug adverse reactions. Previously, specialists were divided on the use of those tests in severe reactions; however, with certain precautions, they are now widely considered a safe and useful tool for identifying the causative DRESS drug. The lymphocyte transformation test is another valuable, widely used diagnostic

tool for identifying delayed-type allergic reactions. It may help detect the causative drug by measuring drug-specific lymphocyte proliferation. When performed 4-8 weeks after the reaction, ideally within 6 months, it has a sensitivity of up to 73% and specificity of 85%. Moreover, it can be enhanced when combined with patch testing (Cabañas et al., 2018). It is important to note that the lymphocyte transformation test does not carry the risk of provoking a reaction through drug re-exposure. However, there is still a lack of complete standardization of this method (Kardaun et al., 2013).

When the lymphocyte transformation test is unavailable, patch testing is performed. Studies have shown its safety in immunocompetent patients (Cabañas et al., 2018). Patch testing should be used 4–6 weeks after the reaction. The positive predictive value of this method reaches up to 80% for carbamazepine but only around 20% for phenobarbital (Calle et al., 2023; de Groot, 2022; Woodruff and Botto, 2022). Further studies are needed to establish a gold standard method to identify the culprit drug of DRESS syndrome.

Diagnosis of DRESS syndrome

DRESS syndrome is considered to be a challenging diagnosis, mainly due to its heterogeneous clinical features (Calle et al., 2023). The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) and the Japanese Consensus Group (J-SCAR) are three different diagnostic scoring systems that use distinct sets of criteria. Bocquet et al., (1996) were the first to propose diagnostic criteria for DRESS. These included drug-induced rash, eosinophilia >1500 × 10^9/L, presence of atypical lymphocytes, and systemic involvement such as lymphadenopathy, hepatic, renal, lung, or cardiac manifestations. The RegiSCAR group later suggested another set of diagnostic criteria, in which cases were categorized as „no", „possible", „probable" or „definite" DRESS (Kardaun et al., 2007). However, this standardized scoring system did not include HHV6 reactivation. Studies have reported that although the RegiSCAR criteria are well-suited for clinical trials, Bocquet's criteria seem more useful in daily practice. Kim and Koh, (2014) proposed that these two scoring systems may be used in a complementary manner. Shiohara et al., (2006) and the Japanese Consensus Group (J-SCAR) established another set of diagnostic criteria. Instead of DRESS, they prefer to use the acronym DIHS. This DIHS scoring system consists of seven criteria: maculopapular rash occurring more than three weeks after starting therapy, persistence of clinical symptoms two weeks after causative drug withdrawal, fever (>38°C), liver alterations (ALT >100/L), at least one of leukocyte alterations (leukocytosis (>11 × 109/L), atypical lymphocytosis (> 5%), eosinophilia (>1.5 × 109/L)), lymphadenopathy and HHV-6 reactivation. It is important that J-SCAR only includes some drugs as potential triggers for DIHS: carbamazepine, phenytoin, phenobarbital, mexiletine, sulfasalazine, allopurinol and minocycline (Criado et al., 2025). Moreover, compared with the previously mentioned scoring systems, it considers reactivation of viruses in the Herpesviridae family. To establish typical DIHS, all 7 criteria must be met; however, a diagnosis of a modified, atypical version of DIHS can be confirmed by the presence of only the first 5 criteria (Shiohara et al., 2006; López-Rocha et al., 2014). Recent studies compared RegiSCAR and Japanese consensus scoring systems.

Sasidharanpillai et al., (2022) suggested that RegiSCAR criteria should be used for diagnosis of DRESS/DIHS, while reactivation of HHV-6, HHV-7, CMV and EBV should rather be treated as prognostic factors. The standardized literature on DRESS syndrome management is scarce. Brüggen et al., (2024) conducted an international expert consensus and reported key aspects of DRESS diagnosis, management, as well as proposed disease severity scale. They established generalized diagnostic workup which should be applicable to all patients suspected with DRESS. It includes complete differential blood count, kidney and liver function tests, urine sediment analysis and electrocardiography. Additionally in patients with suspected specific organ manifestations, more targeted tests should be performed. It can be coagulation studies, lesional skin or liver biopsy, cardiac biomarkers (troponin T, BNP or NT-proBNP), transthoracic echocardiography, pancreatic enzymes, chest or brain imaging, bronchoscopy and lumbar puncture. Brüggen et al., (2024) also recommend assessment for HHV-6, EBV, CMV reactivation. HHV-7, hepatitis B virus and hepatitis C virus may be checked in selected groups of patients. There is a paucity of literature on the classification of DRESS syndrome severity. Brüggen et al., (2024) suggested the first DRESS severity scale. Cases are categorized into mild, moderate, or severe based on liver, renal, and hematologic markers. Patients with any other organ involvement are classified as severe cases.

How to differentiate DRESS syndrome?

Diagnosis and differentiation of DRESS is challenging due to its high degree of heterogeneity in its clinical presentation. However, patients presenting with classic, typical disease progression, maculopapular rash, fever, and lymphadenopathy that occur weeks after administration of a culprit drug generally do not pose a significant diagnostic challenge (Criado et al., 2025). Conducting the recommended diagnostic workup and taking the patient's history can help with differential diagnosis (Brüggen et al., 2024). Stevens-

Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), extensive erythema multiforme, acute generalized exanthematous pustulosis (AGEP), and staphylococcal scalded skin syndrome are the most common diseases that may present with a clinical picture similar to DRESS. Clinicians should also be aware of viral conditions such as EBV infection, CMV, hepatitis A and B, acute HIV infection, COVID-19, and parvovirus B19 (Calle et al., 2023). Dondi et al., (2021) observed cases of DRESS-like viral rash with midfacial edema and systemic symptoms in children treated with amoxicillin during viral illnesses (EBV-infectious mononucleosis (IM) and parainfluenza virus). Moreover, to diagnose DRESS syndrome, specialists must rule out other differentials such as autoimmune and rheumatologic conditions and hematologic malignancies. Clinicians must also distinguish DRESS from other skin-involving diseases, such as vasculitis.

Treatment

The most important step in DRESS management is early discontinuation of potentially causal drugs (Manieri et al., 2023; Choudhary et al., 2013). Clinicians should be aware that DRESS treatment should start as soon as possible, as it can improve the prognosis (de Groot, 2022). Treatment is essentially supportive and systemic. In patients with moderate to severe DRESS, systemic corticosteroids seem to have shown the best outcome in recovery and are considered to be a first-line medication in the acute phase of the disease. However, it should be noted that there are no randomized controlled trials guiding the use of steroids in DRESS, and this therapeutic approach is largely based on clinical opinions.

Nevertheless, they are still widely considered the most optimal treatment method (Calle et al., 2023). In general, it is recommended to start with prednisolone (or equivalent) 0.5–1 mg/kg/day with gradual tapering over 2- 3 months to prevent severe or fatal relapses (Shiohara and Kano, 2017). Clinicians should be aware that, besides a slow steroid-tapering regimen, patients with DRESS, in some cases, may need to have them administered for a year or longer due to the increased risk of autoimmune DRESS complications (Ushigome et al., 2013). The results of the study by Santiago et al., (2010) revealed that all 30 patients with DRESS syndrome treated with systemic corticosteroids showed dramatic improvements in symptoms and laboratory results. Moreover, they didn't develop any secondary skin or soft-tissue infections. In mild cases of DRESS, topical steroids and antihistamines are recommended (Hama et al., 2022).

Patients who are steroid-resistant or who cannot tolerate steroids can be treated with different options such as cyclosporine, mycophenolate mofetil, or cyclophosphamide (Wang et al., 2024; Giri et al., 2011). Cyclosporine has been reported as a potential replacement for steroids in immunosuppressive therapy in DRESS patients. However, only a limited number of cases have reported this line of treatment in the literature. Studies have shown that cyclosporine may be successfully used either in patients previously treated with steroids or as a steroid-sparing agent. Typically, doses range from 3 to 5 mg/kg/d. Zita et al., (2023) reported that cyclosporine was also an effective treatment for patients who couldn't tolerate prolonged corticosteroid therapy.

Another drug that may be used in DRESS treatment is Mycophenolate mofetil, an immunosuppressive medication that selectively targets lymphocytes. However, specialists should be aware of its potential side effects, which include gastrointestinal, hematologic, and genitourinary systems (Finelli et al., 2006). Although there is scarce information in the literature about the efficacy of cyclophosphamide in severe DRESS, it is still considered a potential steroid alternative, especially for patients with kidney failure and myocarditis (Wang et al., 2024).

For steroid-resistant and steroid-dependent DRESS patients, intravenous immunoglobulin (IVIG) (Hung et al., 2024; Ushigome et al., 2013), anti-IL-5/anti-IL-5R biologics, and tumor necrosis factor TNF-α are other DRESS treatment options (Wang et al., 2024). Brüggen et al., (2024), following Japanese, Spanish, and French guidelines, agreed that ganciclovir or valganciclovir should be considered in patients with a high CMV viral load or life-threatening CMV-related manifestations.

Follow-up care

Long-term autoimmune sequelae of DRESS syndrome have been reported in the literature. They may be a continuation of the clinical manifestations of the acute phase or may occur after disease remission. Studies have reported that the interval between the acute phase of DRESS and the onset of sequelae can be as long as 4 years. Complications developing within the first weeks after DRESS clinical manifestations include autoimmune thyroiditis, fulminant type 1 diabetes mellitus, fulminant hepatic failure, autoimmune hemolytic anemia, renal failure, and disseminated intravascular coagulation. Arthralgia (including rheumatoid arthritis), vitiligo, alopecia areata, and systemic lupus erythematosus may persist for months to years. Hama et al., (2022) and Brüggen et al., (2024), in an international consensus, suggested that patients should attend follow-up consultations within the first month and be closely monitored during the

first 6 months after DRESS initiation. Close monitoring of patients should include screening for autoantibodies and thyroid dysfunction, screening for steroid adverse effects, as well as active offering of psychological support.

4. CONCLUSION

DRESS syndrome is a rare but severe condition, characterized by rash, fever, systemic and hematological symptoms, and lymphadenopathy. Clinicians should be aware that prompt recognition and discontinuation of the potential medication causing DRESS plays a key role in the patient's treatment. As significant chronic sequelae may occur, long-term monitoring is required. Given the limited literature on optimal management strategies for DRESS, there remains a need for established, standardized guidelines for clinicians.

Abbreviations used:

CMV - Cytomegalovirus
DIHS/DRESS - Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms
HHV - Human herpesvirus
J-SCAR - Japanese SCAR
RegiSCAR - Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples
FAERS- FDA's Adverse Event Reporting System
FDA- Food and Drug Administration
HLA- Human Leukocyte Antigen
SCAR - Severe cutaneous adverse drug reaction
SJS/TEN - Stevens-Johnson syndrome and toxic epidermal necrolysis
CYP- Cytochrome P450

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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