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DRESS SYNDROME: A RARE BUT POTENTIALLY LIFE-THREATENING ADVERSE DRUG REACTION – A COMPREHENSIVE REVIEW

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Abstract.

Background:

Although rare, DRESS syndrome has the potential to be fatal. Medication, allergies or unfavorable medication reactions are the causes of it. Antibiotics, furosemide, and antiepileptic drugs have been discovered to be mostly involved. Additionally, sulfonamides are mostly thought to be the cause of this illness.

Methods: Meta-analysis and literature review is done to makes it abundantly evident that the primary cause of Dress syndrome is ignorance of the illness and the medication that contributes to its occurrence. This calls for a continuous flow of ideas in the form of fresh knowledge and reminders to everyone who works with patients regarding the use of medication to treat a variety of ailments.

Conclusions: DRESS syndrome is a complex and serious condition that requires immediate attention from healthcare providers. Increased awareness, timely diagnosis, and appropriate treatment are vital to preventing severe complications and improving survival rates. Continued education and training for healthcare professionals on the recognition and management of DRESS syndrome will be essential in mitigating its potentially fatal consequences.

Key words: Dress syndrome, sulphonamides, awareness, adverse effects

Introduction

Some medications or combinations of medications can produce allergic reactions or adverse drug reactions, which are primarily inflammatory conditions such as pneumonitis, carditis, hepatitis etc. There are records that show it was also brought on by a single medication, such as ampicillin and furosemide. Healthcare professionals and practitioners alike need to be knowledgeable about the potential side effects of different medications. Dress syndrome is a side effect of a bad medication reaction that causes eosinophilia and is linked to systemic symptoms. Despite being a rare disorder, it can be fatal. The usage of various medications or medicine combinations, such as antibiotics, furosemide, and antiepileptic medications, is mostly to blame. The majority of the complaints that are present include fever, itching, and rashy skin eruptions. Thrombocytopenia may be related to eosinophilia. Hepatitis is the most prevalent internal organ involvement, and there may be swollen lymph nodes as well. Nephritis, encephalitis, pancreatitis, thyroiditis, pneumonitis, colitis, or myocarditis are possible conditions. [1,2]

This syndrome has been referred to by several names throughout the past 80 years. It was originally

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known as drug-induced pseudo lymphoma. Subsequently, it was dubbed anticonvulsant hypersensitivity syndrome. Subsequently, the medication produced hypersensitivity syndrome and delayed multi-organ hypersensitivity syndrome. [3-7]. The present term for DRESS syndrome was coined in 1996. It might show up as anything from a little rash to eosinophilia. When the problematic medicine is stopped, it reacts favorably. Immunosuppressive treatment may be required, and it may include several organs with a high death rate. The death rate has been reported to be as high as 10%, and the prevalence falls between 1 in 1,000 and 1 in 10,000 drug exposures [2]. Myocarditis and severe hepatitis leading to liver failure are the usual causes of mortality [2, 3]. No specific diagnostic test is present up till now. Clinical indicators such as diarrhea, fever, and skin rash can be used to diagnose this illness. Some people have allergic reactions and breathing difficulties when they first arrive. Hepatitis is the most typical one. It could manifest as thyroiditis in certain cases. Carditis affects a few persons. Thrombocytopenia and eosinophilia have been linked in certain instances. Some patients exhibit lymphadenopathy, and many of them involve internal organs. Effective management involves not only discontinuing the suspected drug but also providing supportive care tailored to the patient's specific symptoms and organ involvement. Corticosteroids are often employed as first-line treatment; however, their efficacy remains a topic of ongoing research. Other immunosuppressive therapies may also be considered in severe cases.

Aim & Objectives:

1. To have an overview about the existing literature on the epidemiology, pathophysiology, clinical manifestations, and treatment options for DRESS syndrome, providing a comprehensive resource for clinicians
2. To review and analyze the common drugs associated with DRESS syndrome, focusing on their mechanisms of action and potential risk factors for hypersensitivity reactions.

Material & Methods:

Meta-analysis and literature review was done to go through the available information on dress syndrome. The analysis may help to enhance awareness of adverse drug reaction causing dress syndrome. To achieve this goal, an organized search was made in PubMed for literature related to this syndrome. Besides, specific keywords were used to discover case reports and relevant studies reported on this syndrome.

Literature review and Discussions:

The review of literature demonstrates a lack of knowledge on the etiology, manifestation, management, and prevention of this syndrome. The information that healthcare practitioners know about this syndrome will be improved by this review. By learning more about the medicines that are causing this illness, this will reduce its incidence.

The term "great mimicker" refers to this syndrome, which contributes to the diagnostic delay [8,9]. A rating system called RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) is used. By using this scoring system, many disorders such as toxic epidermal necrolysis, acute generalized exanthematous pustulosis, Steven-Johnson syndrome, and DRESS can be defined more precisely [2,10]. Cases of DRESS are divided into four categories based on the score: no case, likely case, probable case, and definite case [10].

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One more point that a Japanese committee came to an agreement regarding DRESS and included the reactivation of the human herpes virus (HHV)-6 as a criterion in addition to RegiSCAR. Cases are categorized by this group score as either atypical or typical DRESS [11]. The delay between exposure to medicine and the onset of symptoms is a well-defined hallmark of this illness. Typically, it lasts between two and six weeks, however records can show latency lengths of up to 105 days [12]. More than 40 medications have been linked to DRESS. The most often implicated medications are antibacterial sulfonamides, such as sulfasalazine, dapsone, and sulfamethoxazole, and aromatic anticonvulsants, such as carbamazepine and phenytoin. [2,3,5,12].

A case report states that DRESS syndrome is brought on by the loop diuretic furosemide [13]. This illness is probably caused by drug metabolite accumulation in metabolic pathways and drug-virus interactions that reactivate HHV-6 and HHV-7, EBV, and CMV [2,3,7,14,15,16]. Certain human leukocyte antigen allele (HLA) groupings and the development of drug-induced respiratory syndrome (DRESS) have been linked in certain ethnic populations [16, 17]. Minocycline-induced DRESS syndrome is more prevalent in Black Caribbean people [17].

Similarly, in some Chinese communities, allopurinol is linked to HLA-B* 5801 and abacavir-induced DRESS syndrome is linked to HLA-B* 5701 [18, 19].

Epidemology:

The incidence of DRESS syndrome varies significantly based on factors such as the specific medication involved and the immune status of the patient. Many cases go undiagnosed or untreated, contributing to this variability. In the general population, the estimated incidence is more than 1 case per 10,000 medication exposures. Other studies report an incidence of approximately 0.9 cases per 100,000 individuals and around 10 cases per million in the general population. Among hospitalized patients, incidence rates range from 2.18 to 40 cases per 100,000. Notably, a higher incidence of DRESS syndrome has been observed in Black populations and among women. Despite treatment efforts, the mortality rate associated with DRESS can range from 3.8% to 10%. In one prospective multinational study, the mortality rate was reported at 1.7%.

The diagnosis of DRESS syndrome is challenging. A high degree of suspicion is needed, and other etiologies must be ruled out. Due to the various systems involved and the febrile skin eruption, the differential diagnosis list is rather long. It includes infectious diseases (such as viral exanthema, shock syndromes caused by staphylococci and streptococci). The list also includes neoplastic disorders (such leukemia cutis, mycosis fungoides), autoimmune diseases (like Kawasaki disease, Stills' disease), and noninfectious drug eruptions (like Stevens-Johnson syndrome).

The differential diagnosis also includes lung infection caused by bacteria, viruses, or fungi; viral hepatitis; glomerulonephritis; pre- and post-renal causes of acute kidney injury; eosinophilic myocarditis; and parasite infection of the gastrointestinal tract, depending on the particular organs implicated. P is absent. Clinical diagnosis is performed by taking into account drug exposure and the interval between the start of symptoms and exposure to the drug. Re-challenging with the medication that caused the eruption has been the gold standard for diagnosing drug eruptions; however, because DRESS is a potentially fatal disease, this should not be done in suspected cases [7]. The response is most likely caused by furosemide. However, compared to sulfonamide antibiotics, furosemide has been

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substantially less commonly linked to DRESS. One explanation is that different reactive metabolites are formed by distinct metabolic pathways of different sulfa-containing substances [20]. Sadly, it lacks sensitivity, is challenging to perform, typically produces a negative result early in the course of the condition, and is not standardized for many medicines [21].

Due to the extremely low false positive results (less than 2%), a positive LAT is helpful in confirming the diagnosis; nevertheless, a negative test cannot rule out the illness [22]. All of these things hinder the test's widespread use. Cacoub et al.'s literature evaluation revealed that, in comparison to possible instances, probable/definite cases consistently showed more delayed onset of symptoms [2]. According to a research by Lee et al. [23] involving 25 individuals, hepatomegaly or an increase in liver enzymes indicates liver involvement. In a Taiwanese study conducted from 1998 to 2008, Chen et al. found that 80% of the 60 consecutive patients had liver involvement [24]. Between 11% and 28% of individuals have renal involvement [23, 25].

Etiolopathogenesis:

At least 44 different medications have been linked to DRESS syndrome, with the most commonly implicated being aromatic anticonvulsants such as phenytoin, carbamazepine, and phenobarbital; sulfonamides; sulfones like dapsone; nonsteroidal anti-inflammatory drugs (NSAIDs) including piroxicam, ibuprofen, and diclofenac; beta-lactam antibiotics; vancomycin; allopurinol; minocycline; and certain antiretrovirals. However, in 10–20% of cases, the specific drug responsible for triggering DRESS cannot be identified. While antibiotics like amoxicillin can contribute to DRESS, they typically act as aggravating factors in cases induced by other medications rather than being primary causes themselves.

Allopurinol is most frequently used in conjunction with renal involvement [3,26]. Even in patients who temporarily needed renal replacement therapy, some case reports showed good outcomes in renal recovery following treatment [27, 28].

Abacavir and minocycline are most frequently linked to lung involvement [26, 29]. Ten patients (67%) out of fifteen who were admitted to a critical care unit and had a 20% death rate from severe DRESS syndrome had lung involvement.

Allopurinol and minocycline were the most frequently offending agents in a study of critically sick patients with relation to lung involvement and increased mortality, respectively [30]. Although diarrhea has been identified as a component of DRESS, it is infrequently studied, which could lead to an underestimating of the frequency of GI involvement [31]. Colon involvement in DRESS has been reported in numerous case reports [32–34]. Colon involvement in DRESS can vary from moderate diarrhea that goes away on its own to severe diarrhea that causes an electrolyte imbalance.

Due to complications from extensive GI hemorrhage associated with hemophagocytic syndrome, one patient passed away 35]. Chung et al. report that one patient with severe diarrhea associated with DRESS syndrome was treated with intravenous hydrocortisone because oral prednisone did not improve his condition. The rationale offered was that inadequate steroid absorption was due to the digestive tract's hypermotility. IV steroids should be begun immediately in such patients [36]. It is imperative to rule out ischemic, inflammatory, and infectious parasite causes of diarrhea.

DRESS colitis may be included in the differential diagnosis for DRESS patients experiencing fever,

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diarrhea, and eosinophilia. DRESS typically involves cardiovascular problems. Despite being a rare illness, myocarditis has a high fatality rate of 55%. The unique characteristic of myocarditis in DRESS syndrome is its potential to manifest only after all other symptoms have subsided and test results have returned to normal.

It has been documented that even after a successful DRESS therapy, it may still happen four months later [37]. A common medication that causes DRESS is ampicillin. Chest discomfort and abnormalities in the ECG are among its indications. Reduced left ventricular ejection fraction, elevated heart rate, and ST segment elevation or depression are possible [3,37].

Certain writers hold the view that corticosteroids should not be administered in cases of verified viral infection because they may worsen the reactivation illness [25, 39].

Although some writers have utilized antiviral medications successfully, the effectiveness of these medications in cases of proven viral reactivation is unclear [40].

In cases of moderate to severe disease, the use of prednisolone in decreasing doses has dramatically improved symptoms, and the frequent relapses strongly support the use of systemic steroid therapy. The development of autoimmune diseases such as thyroiditis, type I diabetes, systemic lupus erythematosus (SLE), systemic sclerosis, or adrenal insufficiency is a long-term consequence of DRESS syndrome. These can happen months or years after the first incident. Vigorous monitoring and public education are essential for accurate diagnosis, prompt treatment, and good timing. [41, 42]

In one case autoimmune thyroiditis was seen [43]. In several studies, allopurinol has been identified as a significant trigger for this syndrome, with a notable incidence among patients receiving the drug for conditions such as hyperuricemia and gout [44]. While furosemide is not commonly associated with DRESS syndrome compared to other sulfonamide-containing drugs, its potential as an inciting agent should not be overlooked. Increased awareness among healthcare professionals regarding this association is crucial for timely diagnosis and management [45]. In some studies female sex has more chances of Dress Syndrome while in some studies there is male predominance [46] some studies indicate that adverse events are associated with genetic makeup & drug metabolites [47] In Kimura,s involving male, there is peripheral blood eosinophilia [48] In beta-lactam antibiotics induces Dress syndrome(D S), more monocytes are found as compared to eosinophils [49].

Clinical manifestations:

DRESS syndrome typically begins with prodromal symptoms, including general malaise, pruritus, and fever ranging from 38 to 40 °C. Fever often follows skin manifestations by several days and may persist for weeks. Up to 75% of patients experience lymphadenopathy, which is usually soft, measuring between 1 and 2 cm, and commonly located in the cervical, axillary, and inguinal regions. These lymph nodes may exhibit either a benign pattern or pseudolymphoma-like features upon histopathological examination.

In most cases, the reaction occurs 2 to 6 weeks after the initiation of the offending medication, which is a longer latency period compared to many other drug eruptions. However, in patients who are re-exposed to the triggering drug or those with existing hematological or liver function abnormalities, symptoms may appear more rapidly and with increased severity.

Skin involvement generally starts as a pruritic morbilliform rash that quickly becomes diffuse and

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infiltrative. Initially, it may affect the face, upper trunk, and upper extremities before spreading to the lower extremities. A rash is considered indicative of DRESS when it involves more than 50% of the total body surface area. Additional skin manifestations may include vesicles or bullae (likely due to dermal edema), atypical target lesions, purpuric spots, and small sterile follicular pustules. Approximately half of the patients may exhibit symmetrical facial edema, particularly in the midface and periorbital areas, which can be mistaken for angioedema. Mucous membrane involvement occurs in up to 50% of cases, typically affecting a single site such as cheilitis or an erythematous pharynx and occasionally progressing to erosions [50, 51]

Hematological manifestations associated with DRESS include leukocytosis (which may be preceded by leukopenia and lymphopenia), atypical reactive lymphocytes, thrombocytopenia, and anemia. Eosinophilia is present in 60–70% of cases and can take 1 to 2 weeks to develop; it may even arise after liver enzyme levels have normalized. Hemophagocytic syndrome—characterized by fever, jaundice, hepatosplenomegaly, low ferritin levels, elevated lactate dehydrogenase (LDH), and increased triglycerides—can occur but is rare. Up to 90% of patients experience involvement of at least one organ, with the liver being the most commonly affected (60–80% of cases). Liver involvement often presents as asymptomatic hepatitis but can also include hepatomegaly and jaundice. Liver function tests may reveal abnormalities such as alanine aminotransferase (ALT) levels exceed twice the normal range and alkaline phosphatase (ALP) levels greater than 1.5 times normal [52]

Renal complications can occur in up to 30% of cases and may manifest as moderate increases in creatinine and blood urea nitrogen (BUN), proteinuria, and urinary sediment changes including eosinophils. While most renal issues are mild and resolve after stopping the offending drug, severe interstitial nephritis can develop in some cases, potentially leading to kidney failure. Drugs frequently associated with renal injury include allopurinol, carbamazepine, and dapsone. Patients with pre-existing kidney conditions or those who are elderly are at greater risk for renal failure [53].

Pulmonary complications arise in up to 25% of DRESS cases and can present as dyspnea, non-productive cough, hypoxemia, along with signs of interstitial pneumonitis or pleural effusion visible on chest X-rays or CT scans. Minocycline is commonly linked to lung damage [54].

Cardiac involvement such as eosinophilic myocarditis or pericarditis can occur months after discontinuation of the offending drug and may be life-threatening. Symptoms typically include chest pain, tachycardia, dyspnea, and hypotension; cardiac enzymes may rise alongside findings of cardiomegaly on chest X-rays and ST-T wave changes on EKG.

Gastrointestinal involvement can also occur, leading to dehydration or gastrointestinal bleeding that necessitates evaluation via upper gastrointestinal endoscopy (EGD) or colonoscopy [55].

Endocrine abnormalities may emerge as long-term sequelae occurring 2 to 4 months post-drug cessation; thyroiditis is the most common finding. Symptoms of thyroiditis include palpitations, irritability, and sleep disturbances. Routine thyroid function tests are advised for at least two years following the event. Other endocrine issues like pancreatitis and type 1 diabetes mellitus can develop between three weeks to ten months after the onset of DRESS.

Neurological manifestations are less common but can include meningitis or encephalitis that may present 2 to 4 weeks after DRESS onset; these symptoms might be linked to reactivation of human

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herpesvirus 6 (HHV-6). Symptoms can include headache, seizures, cranial nerve palsy, and muscle weakness [56].

Identifying the responsible drug:

1. Patch Testing

Traditionally, patch testing is the preferred method for identifying the culprit drug in cases of DRESS when the lymphocyte transformation test (LTT) is unavailable. Its effectiveness largely depends on the specific drug being tested and has been demonstrated to be safe for immunocompetent patients.

The initial step in pinpointing the responsible drug is to conduct a comprehensive clinical history that includes all potential candidates, particularly those commonly associated with DRESS syndrome, based on context and existing literature. Antibiotics such as beta-lactams, vancomycin, and quinolones, along with other medications like carbamazepine and proton pump inhibitors, are more likely to yield a true positive result in patch testing. In contrast, drugs such as allopurinol and sulfasalazine may produce false negatives. Therefore, understanding the performance of the drugs being tested is crucial for accurate interpretation of results. All tests should be conducted 4 to 6 weeks after the adverse reaction, and patients should not be on immunosuppressive therapy or systemic corticosteroids for at least 4 weeks prior to testing to minimize the risk of false negatives [57].

The commonly recommended concentration for patch testing is 10% in petroleum jelly, although it can be increased to 30% depending on specific drug guidelines. Initial readings should be taken 48 hours after applying the patch, with a second reading at 96 hours. For certain medications, follow-up readings after 7 to 10 days may also be advised [58]**.**

2. Intradermal Testing

Intradermal tests can be beneficial for identifying the culprit in DRESS cases. This method is recommended if the patch test yields a negative result and the suspected drug is available for intravenous administration. Readings should occur at 6- and 24-hours post-test. For some medications, particularly beta-lactams, intradermal tests may provide better results than patch tests [59].

3. Lymphocyte Transformation Test

The lymphocyte transformation test measures lymphocyte proliferation in response to a suspected drug and can assist in identifying the culprit. It should be performed within 4 to 8 weeks following the reaction, ideally within the first 6 months. This test has a sensitivity of up to 73% and a specificity of 85%, and when combined with patch testing, it can enhance diagnostic accuracy.

One of the key benefits of this in vitro method is that it eliminates the risk of triggering a reaction through drug exposure, which, while rare, could be significant for immunosuppressed patients. Other testing methods, such as cytokine release assays using ELISA to detect IFN-γ in DRESS cases, exist, but there is insufficient evidence to support their routine use [60].Most commonly associated group of drugs is given in Table 1.

Table 1: Most commonly associated drugs with DRESS Syndrome [61].

S.No	Group	Drugs
1.	Antiepileptics	Aromatic antiepileptic drugs (Carbamazepine, lamotrigine

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		phenobarbital, phenytoine, oxcarbazepine)
2.	Antibiotics	Amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, sulfamethoxazole- trimethoprim, vancomycin
3.	Antituberculosis agents	Ethambutol, isoniazid, pyrazinamide, rifampin
4.	NSAIDS	Aspirin, celecoxib, diclofenac, ibuprofen, piroxicam
5.	Others	Allopurinol, amitriptyline, dapsone, hydroxychloroquine, imatinib, nevirapine, omeprazole, sulfasalazine

Treatment:

The French team led by Descamps et al. has proposed a treatment algorithm for DRESS syndrome, which is organized into four distinct scenarios. First Scenario: In cases where there are no signs of severity, the recommended management includes the use of topical corticosteroids, discontinuation of the suspected medication, application of emollients, and administration of antihistamines. Second Scenario: If any signs of severity are present—such as transaminase levels exceeding five times the normal range, kidney failure, lung disease, hemophagocytosis, or cardiac abnormalities—treatment should involve systemic corticosteroids like prednisolone at a dosage of 1 mg/kg per day. Third Scenario: In instances where life-threatening symptoms occur—such as hemophagocytosis, spinal cord failure, encephalitis, liver failure, or respiratory failure—management should include both corticosteroids and intravenous immunoglobulin (IVIG) at a dose of 2 g/kg for five days. Fourth Scenario: When signs of severity are accompanied by confirmed viral reactivation, treatment should consist of corticosteroids, IVIG, and antiviral medications such as ganciclovir. This structured approach aims to provide clear guidelines for clinicians in managing DRESS syndrome based on the severity and specific clinical features presented by the patient [62]. Figure 1 depicts the recommended treatment algorithm for DRESS syndrome,

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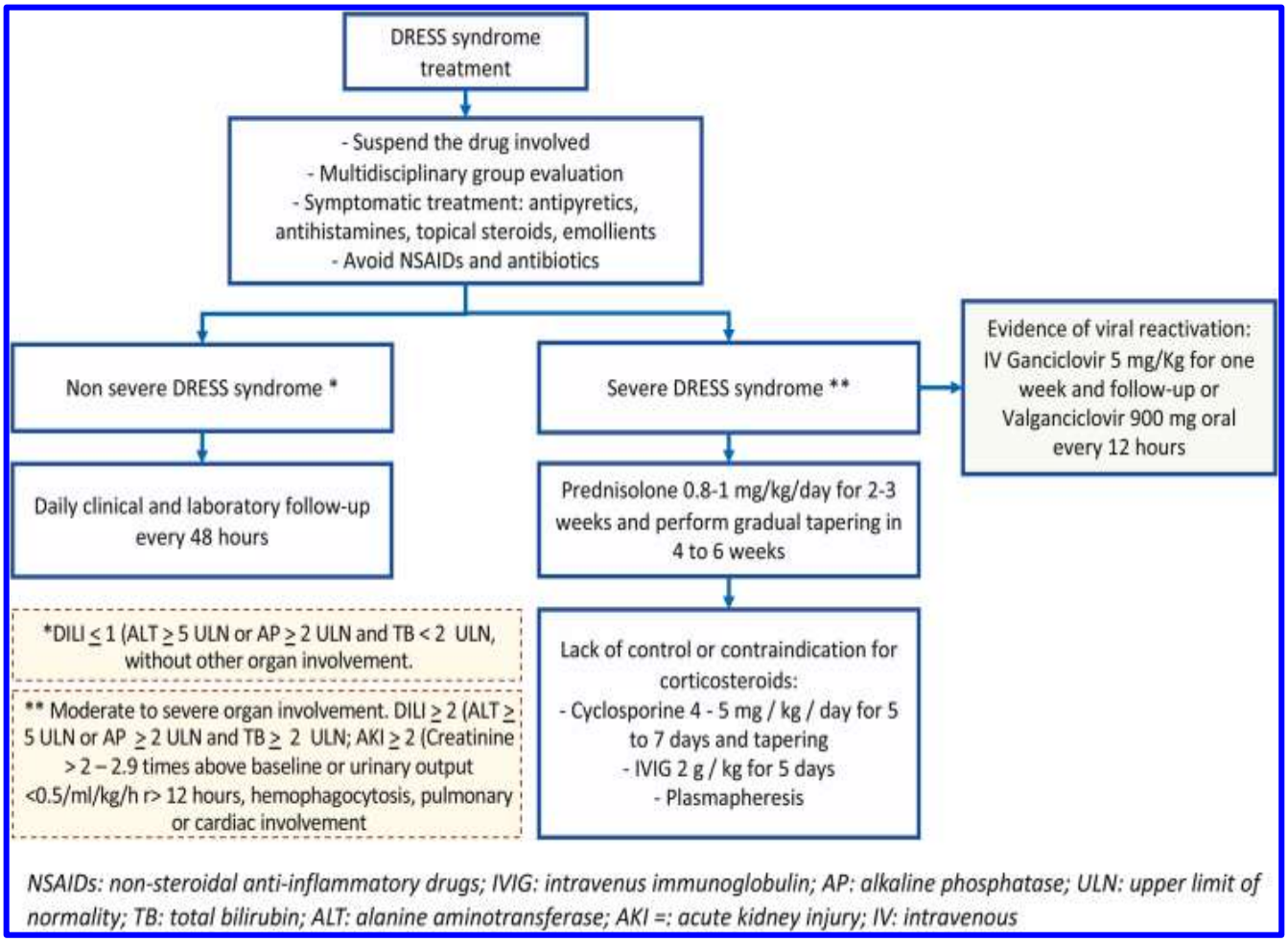

Figure 1: Depicts the recommended treatment algorithm for DRESS syndrome.[63]

Mepolizumab has been successfully used in hyper eosinophilic syndrome and asthma for the treatment of dress syndrome. Mepolizumab, an anti-IL-5 monoclonal antibody, has emerged as a promising treatment option for patients suffering from Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, particularly those who are refractory to conventional therapies. [64]. Cyclosporine is an alternative drug if resistant to steroids [65]

Follow up:

The skin rash and organ damage associated with DRESS syndrome typically improve gradually after discontinuing the offending medication. On average, the recovery period lasts between 6 to 9 weeks; however, in over 20% of cases, symptoms may persist for several months, with potential relapses. Factors contributing to a prolonged course of the disease include severe liver involvement and the presence of atypical lymphocytes.

The estimated mortality rate for DRESS syndrome is around 3.8%, primarily due to complications such as fulminant hepatitis and liver necrosis. Indicators of poor prognosis include eosinophil counts exceeding 6000 × 10^3/μL, thrombocytopenia, pancytopenia, leukocytosis, coagulopathy, pre-existing comorbidities like chronic kidney disease, and the use of medications such as minocycline and allopurinol.Patients who experience DRESS syndrome are at risk for long-term complications;

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therefore, ongoing monitoring focused on detecting autoimmune diseases is recommended for these individuals.

Conclusions:

Dress syndrome is a very uncommon and undertreated ailment. This illness is curable and preventive. For an accurate diagnosis and prompt, patient-safe treatment, all physicians and other healthcare professionals need to be aware of the warning signs and symptoms. There is a knowledge, attitude, and experience gap that needs to be filled. Most countries lack proper records because of a lack of knowledge. In order to develop effective awareness campaigns for patients and healthcare professionals, it is advised that records be kept and updated at the level of practices, hospitals, regions, and nations. To identify it, all pertinent healthcare professionals need to be on the lookout.

Increasing the knowledge of healthcare professionals is vital, and specifically planned educational sessions ought to be conducted on a regular basis. When it comes to specific medications and drug combinations that have the potential to cause it, pharmacologists and pharmacists play a crucial role. The awareness will be aided by the use of contemporary pharmacy software that notifies doctors of possible drug interactions.

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