

DRUG	DOSE	INTERVAL	REFERENCE	STUDY DESIGN	COMMENTS	LEVEL EVIDENCE	GRADE RECOM
<b>CYCLOSPORINE</b>							
Cyclosporine	*Cyclosporine 100 mg orally twice daily per 7 days *3-day course of oral cyclosporine at a dose of 5 mg/kg per day divided into twice-daily dosing or a dose of 175 mg twice daily	Short course (3-7 days) of Cyclosporine	<b>Kirchhof MG, et al.</b> JAMA Dermatol 2016 [48]	Case report *2 patients	Cyclosporine could be considered as first-line therapy, particularly in patients with concerns about using longer courses of systemic corticosteroids	3	D
Cyclosporine	* Intravenous cyclosporine administered at 4-5 mg /kg per day.  - Clinical worsening after initial systemic steroid cycle	Intravenous cyclosporine slowly tapered <b>Case 1:</b> Oral cyclosporine (0.7 mg/kg per day ) Follow-up: 48 months <b>Case 2:</b> Oral cyclosporine 1 mg/kg per day. Follow-up: 6 months	<b>González-Ramos J, et al</b> BJD 2016 [55]	Case report *2 cases  - <b>Case 1:</b> Overlap DRESS/ SJS  - <b>Case 2:</b> Overlap DRESS/TEN	Systemic steroids are the first line of treatment for DRESS syndrome, but if adverse effects arise or there is lack of efficacy, intravenous immunoglobulins or cyclosporine are effective second lines of treatment.	3	D
Cyclosporine + Dexamethasone + Oral prednisone	High dose of dexamethasone and cyclosporine, and then continued on prednisone	Not specified	<b>Daoulah A, et al.</b> Am J Emerg Med 2012 [52]	Case report *1 case	Despite treating her with high dose of steroid and cyclosporine, her symptoms persisted, and ultimately, she developed toxic myocarditis with a myocardial infarction. <b>Cyclosporine not effective</b>	3	D
Cyclosporine	Prednisolone 40mg/d Clobetasol propionate 0.05% 200g/weekly	Cyclosporine 6 months as a sparing agent	<b>Harman KE, et al</b> Clin Exp Dermatol 2003 [50]	Case report *1 case	First case reported treated with cyclosporine with success. Previous treatment with prednisolone and clobetasol didn't work	3	D

	Cyclosporine: 4mg/kg/d						
Cyclosporine	Non specified  4-day course of plasmapheresis and rituximab	1-month course of weekly rituximab + mycophenolate, 1500 mg twice daily + prednisone 15 mg/d	<b>Shaughnessy KK, et al</b> J Am Acad Dermatol 2010 [49]	Case report *1 case	* <b>Not effective cyclosporine</b> neither oral steroid, cyclophosphamide + OKT3.  Only after a 4-day course of plasmapheresis and rituximab did left ventricular function and symptoms improved.	3	D
Cyclosporine	100mg/12h	5 days	<b>Zuliani E, et al</b> Clin Nephrol 2005 [51]	Case report *1 case	A DRESS syndrome with acute interstitial nephritis and hepatitis.  Cyclosporine could represent a treatment option in cases of severe visceral involvement such as persistent renal insufficiency that do not improve after discontinuation of the offending agent and administration of high doses of steroid	3	D
Cyclosporine	100mg/12h	5 days	<b>Bomersmbach TJ, et al</b> Mayo Clin Proc. 2016 [13]	Systematic Review	Recommend: Cyclosporine used after corticosteroid failure and taper	3	C/D
Cyclosporine	Non specified		<b>Husain Z, et al</b> J Am Acad Dermatol 2013 [12]	Review study	Plasmapheresis and immunosuppressive drugs, such as cyclosporine, interferon, mycophenolate mofetil, and rituximab, may also be potential therapies.	3	C/D
Cyclosporine	Cyclosporine 100mg/24h + Methyl-prednisolone 60mg/d	1 month	<b>Lee JH, et al</b> J Korean Med Sci 2008 [53]	Case report *1 case	A recurrent DRESS syndrome with respiratory muscle weakness progressed resulting in the respiratory failure despite the cyclosporine infusion. IVIG with prednisone was administered after the onset of myositis, and the respiratory function resumed with the resolution of DRESS syndrome and polymyositis. <b>Cyclosporine not effective</b>	3	D
Cyclosporine	Not specified	Not specified	<b>Mockenhaupt M.</b>	Expert	Although evidence is limited,	4	D

			Uptodate 2019 [6]	opinion Review	cyclosporine may be a second-line therapy for patients with DRESS and severe organ involvement who do not respond to systemic corticosteroids and for patients in whom corticosteroids are contraindicated.		
Cyclosporine	5 mg/kg/day for 7 days, followed by 100 mg twice daily for 14 days and then 150 mg daily for 20 days		Zhang ZX, et al. Indian J Dermatol Venereol Leprol. 2017 [54]	Case report *1 case	Initial corticosteroid therapy followed-by self-wean by patient Because relapse of DRESS and development of steroid induced diabetes mellitus, cyclosporine treatment was introduced. Full resolution; stable 6 months later	3	D
Cyclosporine	5 mg/kg/day	7 day course	Kuschel SL, et al. Pract Dermatol. 2018 [47]	Case report *1 case	Patient with poor clinical and analytical evolution despite prednisone treatment (1mg/kg/day), with elevation of liver enzymes; cyclosporine treatment is added as an alternative immunosuppressive therapy. Cyclosporine may provide an effective alternative or complement to systemic corticosteroid therapy.	3	D

DRUG	DOSE	INTERVAL	REFERENCE	STUDY DESIGN	COMENTS	EVIDENCE	RECOM
<b>CYCLOPHOSPHAMIDE</b>							
Cyclophosphamide	1 intravenous pulse of cyclophosphamide (750 mg/m <sup>2</sup> ), relayed by oral cyclophosphamide (100 mg/d) for 4 months	Intravenous pulsed + oral treatment cycle for 4 months	<b>Laban E, et al.</b> Am J Kidney Dis. 2010 [56]	Case report *1 case	Patient who developed corticosteroid-resistant DRESS syndrome with ocular and severe kidney involvement in the setting of Epstein -Barr virus reactivation Treatment with cyclophosphamide resulted in complete resolution of symptoms	3	D
Cyclophosphamide	-----	-----	<b>Esposito AJ, et al.</b> Clin Nephrol. 2017 [57]	Case report *1 case	Allopurinol-induced DRESS and acute kidney injury (AKI) requiring hemodialysis. After cyclophosphamide and glucocorticoids treatments, symptoms controlled and AKI resolved.	3	D
<b>ANTIVIRALS</b>							
Valganciclovir + N-Acetylcysteine+ CS	Orally, 900mg/12h for 4 days, reduced to 450mg/12h for general malaise	3 months	<b>Moling O, et al</b> Med Sci Monit 2013 [60]	Case report *1 case	They propose combination of N-acetylcysteine, prednisone and valganciclovir.	3	D
Ganciclovir	Not specified	Not specified	<b>Descamps V, et al.</b> Ann Dermatol Venereol. 2010 [4]	Expert opinion Review	Recommend treatment with antivirals if signs of severity with confirmation of viral reactivation	3/4	D
Ganciclovir	Intravenously 200mg/d	Not specified	<b>Asano Y, et al</b> Arch Dermatol. 2009 [20]	Case report *2 cases	For CMV infection Case 1: died Case 2: recovery	3	D
Ganciclovir, Foscarnet, or Cidofovir	Not specified	Not specified	<b>Mockenhaupt M.</b> Uptodate 2019 [6]	Expert opinion Review	Antivirals may be warranted for patients with DRESS in whom virus reactivation is demonstrated and suspected of contributing to severe complications (eg, encephalitis, hemophagocytosis, or severe erosive colitis)	3/4	D
<b>INTRAVENOUS IMMUNOGLOBULIN (IVIG)</b>							
IVIG	Total doses of 2g/kg 2	5 days	<b>Descamps V, et</b>	Expert opinion	Recommended associated to	4	D

+ CS	spread over five days		<b>al</b> Ann Dermatol Venereol. 2010 [4]	Review	corticosteroids if presence of signs of vital threat (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, respiratory failure).		
IVIG + CS	1g/kg/d	2 days	<b>Husain Z, et al</b> J Am Acad Dermatol 2013 [12]	Review	Recommended associated to corticosteroids when life-threatening signs and no response to corticosteroids.	4	D
IVIG + N acetylcysteine + CS	1g /kg/d	2 days	<b>Cumbo- Nacheli G, et al</b> Epilepsia. 2008 [39]	Case report *1 case	Success in a anticonvulsant induced DRESS with liver disfunction	3	D
IVIG + CS	*0.5 g/kg/d for 2 consecutive days every month as a corticosteroid-sparing agent *2 g/kg divided over 5 d in severe, life-threatening cases	*2 days per month  *total doses divided over 5 d	<b>Bommersbach TJ, et al.</b> Mayo Clin Proc. 2016 [13]	Systematic Review	Should be used in conjunction with corticosteroid drugs, not as monotherapy	3/4	D
IVIG as monotherapy	0.4 mg/kg/d	5 days	<b>Kito Y, et al.</b> Acta Dermat Vener 2012 [36]	Case report *1 case	Patient successfully treated with high-dose intravenous immunoglobulin (IVIG) containing a high titre of anti-HHV-6 antibodies. This course of treatment rapidly reduced disease activity without causing any worsening of the wound infection	3	D
IVIG + CS	0.5 g/kg/d	2 consecutive days every month, for 8 months	<b>Singer EM, et al</b> JAMA Dermatol. 2013 [43]	Case report 1 case	IVIG as a steroid-sparing agent.	3	D
IVIG	Not specified	Not specified	<b>Mockenhaupt M</b> Uptodate 2019 [6]	Expert opinion Review	While awaiting better evidence, we do not suggest the use of IVIG for the treatment of DRESS.	4	D

IVIG + CS	1 g/kg/day for 2 days	2 days  4 cycles of treatment	<b>Lee JH, et al</b> J Korean Med Sci. 2008 [53]	Case report *1 case	IVIG with prednisone was administered after the onset of myositis, and the respiratory function resumed with the resolution of DRESS syndrome and polymyositis.	3	D
IVIG + CS	1g/kg/d	2d	<b>Scheuerman O, et al.</b> Pediatrics. 2004 [40]	Case report *1 case	6-year-old boy Start of treatment with IVIG due to clinical and analytical worsening after 5 days of treatment with oral steroids. Within 24 hours of the first IVIG dose, the patient showed dramatic improvement.	3	D
IVIG without associated corticosteroids	200mg/kg/d	5d	<b>Joly P, et al</b> Arch Dermatol. 2012 [44]	Prospective 6 severe DRESS	This study does not support a beneficial effect of IVIG treatment in patients with DRESS, since 5 of 6 patients experienced severe adverse events, and 4 patients had to be treated with oral corticosteroids because of IVIG adverse effects (n=2) or uncontrolled DRESS (n=2).	3	D
IVIG (previous treatment with Cs)	1g/kg	2d	<b>Fields KS, et al</b> J Drugs Dermatol 2005 [42]	Case report *HIV patient with liver injury	IVIG was effective	3	D
IVIG + CS	1-2 g/kg/d,	2 doses  Interval between doses 1-7 weeks	<b>Marcus N, et al</b> J Allergy Clin Immunol Pract 2018 [46]	Retrospective study	7 severe DRESS patients successfully treated with IVIG. Cases resistant to regular drug withdrawal and systemic corticosteroid. There was no mortality	3	D
<b>OTHER TREATMENT OPTIONS</b>							

<b>MEPOLIZUMAB + CS + IVIG</b>	100 mg / monthly subcutaneously	3 months	<b>Ange N, et al.</b> J Allergy Clin Immunol Pract 2018 [64]	Case report *1 case	It was effective as an steroid sparing agent. Mepolizumab, an anti-IL-5 mAb, may be a useful adjunct to steroids in the treatment of DRESS syndrome.	3	D
<b>N-ACETYLICISTEINE (N-AC) + IVIG + CS</b>	Loading dose for IV N-AC was 150 mg/kg IV in 200 mL 5% dextrose over 60 min. After the initial dose, the infusion was maintained at 50 mg/kg IV in 500 mL 5% dextrose over 4 h, followed by 100 mg/kg IV in 1000 mL 5% dextrose over 16 h	1 day	<b>Cumbo-Nacheli G, et al</b> Epilepsia 2018 [39]	Case report *1 case	In the presence of liver dysfunction, the use of N-acetylcysteine (N-AC) and intravenous immunoglobulin (IVIG) may have altered the course of the disease. That alternative regimens should be given special consideration especially in those critical clinical situations where supportive measures appear to be unsuccessful.	3	D
<b>PLASMAPHERESIS + Rituximab + Mycophenolate + CS</b>		4 days	<b>Shaughnessy KK, et al</b> J Am Acad Dermatol 2010 [49]	Case report *1 case	Successful plasmapheresis and rituximab treatment for minocycline-induced myocarditis associated with DRESS syndrome.	3	D
<b>LIVER TRANSPLANTATION</b>							
Liver transplantation	Living-donor liver transplantation on hospital day 9.		<b>Song SM, et al.</b> Korean J Pediatr 2013 [24]	Case report *1 case Pediatric case	A 14-year-old girl Acute liver failure, in the presence of aggravated hepatic encephalopathy, azotemia. The patient was refractory to medical treatments, included intravenous high dose of methylprednisolone initiated upon an initial suspicion of DRESS syndrome	3	D
Liver transplantation	Liver transplantation on hospital day 10		<b>Mennicke M, et al.</b>	Case report *1 case	Patient with polyarthritis treated with sulfasalazine	3	D

			Am J Transplant 2009 [23]		who developed DRESS and fulminant liver failure after additional vancomycin treatment. After a liver transplantation and initial recovery, the patient developed a recurrence of DRESS that affected the transplanted liver and caused his death		
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Note: Complete references are included in the Supplementary file 2.

Accepted Article