CORTICOSTEROID TREATMENT FOR DRESS. REVIEW OF LITERATURE AND ANALYSIS OF LEVEL OF EVIDENCE.							
TREATMENT	**DOSES**	**TREATMENT DURATION**	**REFERENCE**	**STUDY DESIGN**	**OUTCOMES**	**LEVEL OF EVIDENCE**	**GRADE OF RECOMMENDATION**
Topical steroids vs Systemic steroids *For the initial 5 - 7 days, all patients treated conservatively with topical cs. Prednisolone was administered if there was evidence of internal organ involvement and persistent or aggravating clinical findings.	*Systemic corticosteroids (n=16) Prednisolone 1 mg/kg vs *Topical corticosteroids and antihistamines (n=22).	Tapered over 6 - 8 weeks (mean days of treatment 75.4) (range 25-208 days)	**Um SJ,et al.** JIACI 2010 [1]	Retrospective study 38 patients *16 Systemic cs *22 topical cs	36 patients complete recovery 2 pts with systemic corticosteroids had a poor outcome: one died due to an opportunistic infection secondary to long-term systemic corticosteroid treatment	2+	C
High or superhigh potency topical corticosteroids		2-3 times/day	Mockenhaupt Uptodate 2019 [6]	Review	Recommendation: If cases without severe organ involvement, only modest elevation of transaminases (<3ULN)	4	D
Systemic steroids *Intravenous dexametasone *Oral prednisolone	*15-20 mg/d and taper *0,5-0,7 mg/kg/d and taper	3-520 days	**Wongkitisophon P, et al.** Acta Derm Venereol 2012 [8]	Retrospective study **27 patients** *23 treated with systemic corticosteroid *4 supportive therapy.	Most patients were treated with systemic corticosteroids, for a mean duration of 49 days. *The mortality rate in this study was 3.7%. * 18% flare of DRESS when tapering dose * 77.8% no complications	3	D
Oral corticosteroids vs Non corticosteroid therapy (Supportive care and some topical CS)	Oral corticosteroid 0.6 – 1mg/kg/d IVIG therapy: 5 g /d for 3 to 5 days) if detection of herpesvirus reactivation.	Most patients required more than 8 weeks of oral steroids to achieve complete resolution	**Ushigome Y, et al.** J Am Acad Dermatol 2013 [14]	Retrospective study 34 patients *14 patients with oral corticosteroid treatment *20 with non-steroid treatment.	**Group with CS:** various infections were noted in the early phase, including herpesvirus diseases, P jiroveci pneumonia., CMV reactivation. **Group without CS**: 1 LES and 1 tiroiditis.	3	D

Oral prednisone ± Intravenous methylprednisolone	1-1,5 mg/kd/d	Slowly tapered and suspended after a mean of 122 days (range 50–345) Over a 6–8 week period after achieving clinical and laboratory control of the disease,	**Avancini J, et al.** Clinical and Experimental Dermatology 2015	Retrospective study **27 patients**	All patients were treated with prednisone at 1 mg/kg/d, beginning at admission. If no Improvement, the dose was increased to 1.5 mg/kg/day (three cases; 11.1%) or switched to iv methylprednisolone (one case; 3.7%). Mortality rate of 4%.	**3**	**D**
Pulsed intravenous methylprednisolone + oral prednisolone + topical steroids treatment + antihistamines	Pulsed intravenous methylprednisolone < 90kg: 500mg 3d >90kg: 1000mg 3d followed by 30-day tapering course of oral prednisolone, starting at 30 mg once daily and reducing by 10 mg every 10th day.	3 days Oral prednisone taper 10mg every 10 days	**Natkunarajah J, et al.** Eur J Dermatol 2011 [10]	Prospective study No control group 10 patients	They conclude: An aggressive corticosteroid regimen in the management of DRESS is associated with good clinical outcome and acceptable tolerance	**2-**	**C**
Methyl-lprednisolone iv pulse	*30 mg/kg 3 days (max 1 g/day) followed by oral prednisone	3 days 2 weeks symptoms completely resolved, laboratory tests were normal.	**Kocaoglu C, et al.** Case Reports in Pediatrics 2013 [11]	2 cases	Unresponsiveness to previous Intravenous IVIG. Resolved within two weeks.	3	D

TREATMENT	DOSES	TREATMENT DURATION	REFERENCE	STUDY DESIGN	RECOMMENDATIONS	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Oral prednisolone	40-60 mg/d	Taper 6-8 weeks	**Shiohara T, et al.** Allergol Int 2006 [3]	Review article	Mild cases may recover by supportive care without the need of systemic CS. If symptoms deteriorate despite systemic corticosteroids, other options used include pulsed intravenous methylprednisolone (30 mg/kg for 3 days), intravenous immunoglobulin G (IVIG), and plasmapheresis, or a combination of these.	**3**	**D**
Prednisone	1-1.5 mg/kg/d	Taper	**Shiohara** in Pichler 2007 [17]	Review/ Expert opinion		3	D
Topical corticosteroids, emollients, H1-antihistamines *Topical steroids of high or superhigh potency)	Not specified		**Descamps V, et al.** Annales de dermatologie et de vénéréologie 2010 [4]	Consensus of experts Guidelines	Topical steroids in DRESS in absence of signs of severity		
Systemic Corticosteroid	Prednisone 1 mg / kg daily		**Descamps V, et al.** Annales de dermatologie et de vénéréologie 2010 [4]	Consensus of experts Guidelines	System corticosteroids: --if presence of signs of severity : corticosteroid therapy at 1 mg / kg daily prednisone - If Signs of vital threat: corticosteroid therapy + IVIG doses of 2 g / kg spread over five days. IVIG must not be proposed without associated general corticosteroids. -If Presence of signs of severity with confirmation of major viral reactivation:	3	D

					associate corticosteroid general and antiviral (ganciclovir) and / or IGIV and close monitoring.		
Oral prednisolone	40-50 mg/d	Taper 6-8 weeks	**Shiohara T, et al.** Chem Immunol Allergy 2012 [18]	Review article/ Expert opinion	Because patients with moderate disease can often recover from this syndrome by supportive care without the need of systemic corticosteroids within 3 weeks, the use of systemic corticosteroids is not necessarily recommended as a treatment option of DIHS. Anti- CMV medications with a gradual reducing dose of corticosteroids may help to avoid disease progression to full manifestations of IRS. Our trials of combining treatments, giving IVIG (0.1 g/kg per day for 3 days) together with systemic corticosteroids, have failed to show extra benefit compared with corticosteroids alone. Particularly, a small dose (prednisolone, 10– 20 mg/day) of systemic corticosteroids followed by small increments in dosage at short intervals should be avoided even for mild cases, because this may not be sufficient to ameliorate clinical symptoms and may result in unnecessarily	3	D

					protracted use of corticosteroids.		
Oral prednisone (or equivalent) ± Intravenous methylprednisolone	1 mg/kg/d prednisone or equivalent A course of pulsed methylprednisolone, 30 mg/kg intravenously for 3 days,	Gradual taper over 3 to 6 months after clinical and laboratory stabilization	**Husain Z, et al.** J Am Acad Dermatol 2013 [12]	Literature Review	If life-threatening cases with significant systemic involvement: Oral prednisone or intravenous methylprednisolone Initiate at 1.0 mg/kg and gradually taper.	4	D
Topical corticosteroids vs Systemic glucocorticoid therapy	Local high dose glucocorticoid therapy vs systemic glucocorticoid therapy (1 mg/kg/d)	Until complete disease control is achieved. The dose is then tapered slowly, often over several months	**Descamps V, Ranger-Rogez S.** Joint B Spine 2014 [5]	Review article	-In moderately severe forms, local high-dose glucocorticoid therapy ensures disease control. -Patients with severe DRESS syndrome should be given systemic glucocorticoid therapy (1 mg/kg/d) until complete disease control is achieved. The dose is then tapered slowly, often over several months. - Life-threatening forms require intravenous immunoglobulin therapy in addition to systemic glucocorticoid therapy. - Antiviral agents (ganciclovir, cidofovir) maybe given in addition to intravenous immunoglobulins and systemic glucocorticoids as soon as viral reactivation is detected.	4	D
Oral corticosteroids	1mg/kg/day	Taper 6-8 weeks	**Fernando SL.** Australas J Dermatol. 2014 [19]	Review article	Oral corticosteroids at 1 mg/kg daily is commenced and tapered	4	D

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					over at least 6–8 weeks to prevent the relapse of various cutaneous and visceral manifestations of the syndrome. If symptoms deteriorate despite corticosteroid therapy, then IVIG, plasma exchange, rituximab, valgangciclovir or a combination of these modalities can be considered. All these adjunctive therapies to corticosteroid therapy require further elucidation in larger studies.		
Oral Prednisone or equivalent ± Intravenous methylprednisolone	1-1.5 mg/kg/d 30 mg/kg intravenously for 3 d	Taper over 3-6 months	**Bommersbackh TJ, et al.** Mayo Clin Proc 2016 [13]	Systematic Review **Psycotropic Drug-induced DRESS** *96 articles were included (25 original articles, 12 review articles, 55 case reports, and 4 letters to the editor)	The author recommends: Intravenous metilprednisolone, 30 mg/kg intravenously for 3 d, if no improvement with oral corticosteroids or in severe cases	**3**	**D**
Oral prednisone (or equivalent)	40-60mg/d	Gradual dose reduction over 10 weeks	**Shiohara T, et al.** Expert Opin Drug Saf 2017 [16]	Literature review	Therapeutic choices should be guided not only by the severity in the acute stage but also by autoimmune responses and diseases as long-term consequences of DiHS/DRESS	3	D
Prednisone or equivalent	0.5-2 mg/kg/d	Taper 8-12 weeks Until	Mockenhaupt Uptodate 2019 [6]	Literature Review	When lung or kidney injury General consensus among experts on the use of	3	D

		normalization of laboratory parameters			systemic corticosteroids for the treatment of DRESS with severe organ involvement Cs in liver: unproven benefit for most forms of drug hepatotoxicity: Hepatologist consultation		

CORTICOSTEROIDS IN DRUG-INDUCED ACUTE INTERSTITIAL NEPHRITIS (DI-AIN)

TREATMENT	DOSES	TREATMENT DURATION	REFERENCE	STUDY DESIGN	OUTCOMES	LEVELS OF EVIDENCE	GRADES OF RECOMMENDATIONS
Corticosteroid treatment (IV Methylprednisolone + oral prednisolone) Vs Non corticosteroid treatment (only suspect causative drug withdrawal)	Intravenous pulses methylprednisolone (250–500 mg daily for 3–4 consecutive days) followed by oral prednisone (1 mg/kg/day)	3-4 d Tapering off over 8–12 weeks.	**González E** Kidney International 2008 [31]	Retrospective study 61 patients with biopsy-proven DI-AIN, *52 of whom were treated with steroids. *9 patients did not receive steroids	The final outcome of patients on steroid treatment was significantly better than that of group with no steroid treatment *Final serum creatinine was significantly lower in steroid treatment group *Significantly higher proportion of patients with no steroid treatment remained on	2+	C

					chronic dialysis after the DI-AIN episode (44.4 vs 3.8%). No side effects attributable to steroid treatment were observed. * Significant correlation between the delay in the onset of steroids and the final serum creatinine		
Steroid treatment vs conservative management	Oral prednisolone 40 - 60 mg/ day.	The median duration of treatment was 6 months (1 week–5 years) 32 patients (20.2%) were off steroids by 3 months	**Prendecki M., et al** Clin Kidney J. 2017 [30]	Retrospective study 187 eligible patients with AIN *158 were treated with steroids *29 were managed conservatively	Suggests a benefit of steroids in treatment of AIN with greater improvement in eGFR and fewer patients progressing to end-stage renal disease	3	D
Prednisone	0.8 mg/kg/d	2 weeks, followed by a tapering period of 5–6 weeks,	**Fernandez-Juarez G, et al.** Clin J Am Soc Nephrol 2018 [33]	Retrospective study 182 patients with biopsy-proven drug-induced acute interstitial	>75% recovery in patients treated within 15 days of diagnosis -No better if maintenance treatment >3wk - No better if treatment >8wks.	**3**	**D**

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				nephritis	-No better recovery with steroid pulses before the onset of oral prednisolone		
*Prednisone (97.5% patients) ± * Methylprednisolone in pulse (24%patientes) ± Immunosuppressive medications (29%)	30–40 mg/day **Prednisone** **77 patients (97.5)** **MP in pulse** **19 patients (24.1%)** Immunosuppressive medications 23 patients (29.1%) *mycophenolate (50–100mg/day for 6–12months), *azathioprine (50–100mg/day for 6–12months) or *cyclophosphamide (50mg/day, total 4–6 g)	**12 months**	**Su T, et al** Nephrology Dialysis and Transplantation 2018 [34]	Prospective non randomly controlled study 79 patients received scheduled follow-up for at least 24 months	Additional immunosuppressive medications, such as mycophenolate, azathioprine and cyclophosphamide, due either to unresponsiveness to prednisone treatment or relapse of the disease during follow-up. Methylprednisolone in pulses did not correlate with better recovery status.	**2+**	**C**
Oral prednisolone vs pulse methylprednisolone	Oral prednisolone 1 mg/kg for 3 weeks or a pulse methyl prednisolone 30 mg/kg for 3 days followed by oral prednisolone 1 mg/kg for 2 weeks	3 weeks 3 days + 2 weeks Tapered over 3 weeks	**Ramachandran R, et al.** Indian J Nephrol 2015 [35]	Randomized controlled trial 29 patients: *Oral prednisolone: 16 patients *MP in pulse: 13 patients.	Early steroid therapy, both oral and pulse steroid, is equally effective in achieving remission in drug-induced AIN.	2+	C

DRUG-INDUCED LIVER INJURY (DILI)							
TREATMENT	**DOSES**	**TREATMENT DURATION**	**REFERENCE**	**STUDY DESIGN**	**OUTCOMES**	**LEVELS OF EVIDENCE**	**GRADES OF RECOMMENDATIONS**
Prednisolone	*Prednisolone: 19 patients -Total PD equivalent 230 mg [70-475] *IVIG use: 1 patient	Duration, median 6.0 days [3.0-12.5 days]	**Lee T, et al.** J Am Acad Dermatol 2013 [25]	Retrospective study 29 patients with DRESS/DiHS and liver dysfunction *23 patients with **significant liver dysfunction** (80 IU/L < aspartate aminotransferase and alanine aminotransferase < 800 IU/L)	Use of systemic esteroids did not significantly affect either recovery from liver injury (nonusers 7d vs 4d users) or mortality (nonusers 0, users 4)	3	D
Systemic steroids in severe DILI patients (Bil T>5)	*Methylprednisolone, range 60-120 mg/day or prednisone, range 40-60 mg/day for 3-5 days and then prednisone 20 mg/day and 5-10 mg weekly reduction).	5-10 mg weekly reduction	**Hu PF, et al.** J Dig Dis 2016 [26] -	Retrospective study 203 DILI cases. *53 patients treated with corticosteroids	Corticosteroids are not detrimental to DILI, but instead improve liver injury and patient survival. Short-time use of corticosteroids is strongly recommended	+2	C

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	*Steroid pulse-therapy for 3-5 days: Methylprednisolone, range 60-120 mg/day.				to severe DILI patients with hyperbilirubinemia. Corticosteroids was only used in those patients with severe DILI (TB≥5 mg/dl). Response to treatment was defined as clinical symptoms improvement and the values of bilirubin, transaminases and INR fall (drop to 50% from peak value) and time to normalization.		
Systemic corticoids in severe acute liver injury or acute liver failure	*Corticosteroid bolus (500 mg /3 days), *oral prednisolone (1 mg/kg per day) which was subsequently tapered. Four of the patients also received supplementary topical corticosteroids.		**Ichai P, et al.** Transplantation 2017 [29]	Multicenter retrospective study 16 patients with severe acute liver injury or acute liver failure *9 patients received Intravenous/ oral corticosteroid	The spontaneous prognosis of patients with severe acute liver injury (SALI) or acute liver failure (ALF), due to DRESS is poor and was not improved by corticosteroid therapy. Systemic corticosteroids do not modify disease duration, mortality (including transplantation) or the recovery of liver function	3	D

				therapy - 5 patients improved - 4 patients died or were transplanted	Dynamic variables regarding factor V values are predictive of a poor outcome. All patients were managed at intensive care unit and treated with N-acetyl cysteine (NAC).		
Steroid step-down therapy	Not specified dose →Steroid step-down therapy with reduction of the daily dose over several weeks and the mean course of treatment was 79 ± 26 days.	Not specified	**Hou FQ, et al** Cell Biochem Biophys 2012 [27]	Retrospective study 300 DILI cases *267 patients with hepatocellular type of liver injury, -70 patients were TBIL > 109 ULN. →20 individuals were treated by steroid step-down therapy →The other 50 cases received non-steroid therapy.	In drug induced severe liver injury, steroid therapy might improve the curative effect and shorten the course of the disease and, hence, the step-down method used was safe. In steroid therapy group, 20 patients (100 %) resolved and no side effects were observed, while in non-steroid therapy group, 37 patients (74 %) resolved The course of the disease was shorter, no patient developed chronic liver disease or died, in the group of patients treated with steroids compared to the one who did not receive	2+	C

					steroid treatment In non-steroid therapy group, 6 (12 %) patients died and 7 (14 %) patients developed chronic liver disease Among 300 DILI patients, 8 patients had fulminant liver failure: 2 (25 %) patients who resolved had received steroid step-down therapy, while 6 (75 %) patients who died did not receive steroid therapy.		

Note: Complete references are included in the Supplementary file 2.