



## Corticosteroids

Updated: May 30, 2014.

### OVERVIEW

#### Introduction

The corticosteroids are a group of chemically related natural hormones and synthetic agents that resemble the human adrenal hormone cortisol and have potent antiinflammatory and immunosuppressive properties and are widely used in medicine. Corticosteroid therapy is associated with several forms of liver injury, some due to exacerbation of an underlying liver disease and some that appear to be caused directly by corticosteroid therapy. This discussion will cover eight agents: betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

#### Background

The corticosteroids are hormones that have glucocorticoid (cortisol-like) and/or mineralocorticoid (aldosterone-like) activities and which are synthesized predominantly by the adrenal cortex. In clinical practice, the term “corticosteroids” usually refers to the glucocorticoids and are represented by a large group of natural or synthetic steroid compounds that have varying potency, durations of action and relative glucocorticoid (measured by antiinflammatory activity) vs mineralocorticoid (measured by sodium retention) activities. Cortisol and the corticosteroids act by engagement of the intracellular glucocorticoid receptor, which then is translocated to the cell nucleus where the receptor-ligand complex binds to specific glucocorticoid-response elements on DNA, thus activating genes that mediate glucocorticoid responses. The number of genes modulated by corticosteroids are many and the effects are multiple and interactive with other intracellular pathways. Thus, the effects of corticosteroids on inflammation and the immune system cannot be attributed to a single gene or pathway. The potent antiinflammatory and immunosuppressive qualities of the corticosteroids have made them important agents in the therapy of many diseases. Corticosteroids are available in multiple forms, including oral tablets and capsules; powders and solutions for parenteral administration; topical creams and lotions for skin disease; eye, ear and nose liquid drops for local application; aerosol solutions for inhalation and liquids or foams for rectal application. Representative corticosteroids (and the year of their approval for use in the United States) include cortisone (1950), prednisone (1955), prednisolone (1955), methylprednisolone (1957), dexamethasone (1958), betamethasone (1961), and hydrocortisone (1983). All are available in generic forms. In this website, only the oral and intravenous formulations of corticosteroids are described and they are discussed together with common list of references and representative case reports.

The corticosteroids are used widely in medicine largely for their potent antiinflammatory and immunosuppressive activities. The clinical conditions for which corticosteroids are used include, but are not limited to: asthma, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, inflammatory bowel disease, nephritic syndrome, cancer, leukemia, organ transplantation, autoimmune hepatitis, hypersensitivity reactions,

cardiogenic and septic shock, and, of course, glucocorticoid deficiency diseases such as in Addison's disease and panhypopituitarism.

Corticosteroids are used in several liver diseases, most commonly in autoimmune hepatitis for which they have been shown to improve outcome and survival. Corticosteroids are also used after liver transplantation to prevent rejection. An important element in managing these liver diseases and conditions is to maintain the dose of corticosteroids at the lowest effective level. The adverse effects of long term corticosteroid therapy (which are rarely hepatic) are still major causes of morbidity and even mortality in these conditions.

Prednisone, prednisolone, methylprednisone and triamcinolone are the most commonly used oral agents as they are inexpensive, rapid in onset, intermediate in duration of action and have potent glucocorticoid with minimal mineralocorticoid activities, at least as compared to cortisone and hydrocortisone. Betamethasone and dexamethasone have greater glucocorticoid potency and less aldosterone-like activity than prednisone, but have a longer duration of action, and they are mostly used in topical or liquid forms for local application and in injectable forms for severe hypersensitivity reactions and inflammation. Methylprednisone and hydrocortisone are most commonly used for intravenous administration, typically given in emergency or critical situations in which rapid and profound immunosuppression or antiinflammatory activity is needed.

The table below provides the major forms of corticosteroids and their relative glucocorticoid and mineralocorticoid activity and equivalent daily doses.

RELATIVE POTENCIES OF CORTICOSTEROIDS			
AGENT	GLUCOCORTICOID ACTIVITY	MINERALOCORTICOID ACTIVITY	EQUIVALENT ORAL OR INTRAVENOUS DOSE
Cortisol	1	1	20
Cortisone	0.8	0.8	25
Prednisone	4	0.8	5
Prednisolone	4	0.8	5
Methylprednisolone	5	0.5	4
Triamcinolone	5	0	4
Betamethasone	25	0	0.75
Dexamethasone	25	0	0.75

**Cortisone** (kor' ti sone) is a short acting glucocorticoid that is used for therapy of adrenal insufficiency and for treatment of allergic and inflammatory conditions. Cortisone is available in generic forms in tablets of 25 mg, which is considered a daily physiologic dose in adults. Cortisone has both glucocorticoid and mineralocorticoid properties.

**Hydrocortisone** (hye" droe kor' ti sone) is a rapid and short acting glucocorticoid that is used for therapy of adrenal insufficiency and in treatment of allergic and inflammatory conditions. Hydrocortisone has the same chemical structure as cortisol and thus most closely resembles the human adrenal hormone. Hydrocortisone is available in generic forms in tablets of 5, 10 and 20 mg, with 20 mg being considered a daily physiologic dose in adults. Hydrocortisone is also available in multiple forms in solution for oral, rectal, topical or parenteral administration. A major use of intravenous hydrocortisone is in the acute therapy of severe hypersensitivity reactions and shock. Hydrocortisone has both glucocorticoid and mineralocorticoid properties.

**Prednisone** (pred' ni sone) is a synthetic, intermediate acting glucocorticoid that is widely used in the therapy of severe inflammation, autoimmune conditions, hypersensitivity reactions and organ rejection. Prednisone is converted to prednisolone, its active form, in the liver. Prednisone is available in multiple generic forms in

tablets of 1, 2.5, 5, 10, 20 and 50 mg and as oral solutions. Four times more potent than cortisol, prednisone is used in varying doses, with 5 mg daily being considered physiologic doses in adults.

**Prednisolone** (pred nis' oh lone) is a synthetic, intermediate acting glucocorticoid that is widely used in the therapy of severe inflammation, autoimmune conditions, hypersensitivity reactions and organ rejection. Prednisolone is available in multiple generic forms in tablets of 5, 10, 15 and 30 mg and in several forms for systemic administration. Four times more potent than cortisol, prednisolone is used in varying doses, with 5 mg daily being considered physiologic doses in adults.

**Methylprednisolone** (meth' il pred nis' oh lone) is a synthetic, intermediate acting glucocorticoid that is widely used in the therapy of severe inflammation, autoimmune conditions, hypersensitivity reactions and organ rejection. Methylprednisolone is available in multiple forms in tablets of 2, 4, 8, 16 and 32 mg generically and under the brand name of Medrol and in Medrol Dosepaks (21 tablets of 4 mg each). Injectable forms of methylprednisolone are also available generically and under brand names of Solu-Medrol and Depo-Medrol. Five times more potent than cortisol, methylprednisolone is used in varying doses, with 4 mg daily being considered physiologic doses in adults. Methylprednisolone has minimal mineralocorticoid activity.

**Triamcinolone** (trye" am sin' oh lone) is a synthetic, long acting glucocorticoid that is used in topical solutions and aerosols for therapy of allergic and hypersensitivity reactions and control of inflammation as well as in parenteral formulations for therapy of hypersensitivity reactions, shock and severe inflammation. Oral forms of triamcinolone include tablets of 4 and 8 mg and oral syrups. Parenteral forms for injection are available under various generic and trade names including Aristocort and Kenacort. Triamcinolone is five times more potent than cortisol in its glucocorticoid activity, but has minimal mineralocorticoid activity.

**Dexamethasone** (dex" a meth' a sone) is a synthetic, long acting glucocorticoid that is used parenterally as therapy of severe hypersensitivity reactions, shock and control of severe inflammation as well as in topical, otic, ophthalmologic solutions, aerosols and lotions or creams for local therapy of allergic reactions and inflammation. Dexamethasone is available in multiple forms for injection under various generic and trade names including Decadron. Dexamethasone is 25 times more potent than cortisol in its glucocorticoid activity, but has minimal mineralocorticoid activity.

**Betamethasone** (bay" ta meth' a sone) is a synthetic, long acting glucocorticoid that is used in parenteral forms for therapy of allergic and hypersensitivity reactions and control of severe inflammation. Betamethasone is available in solution for injection under the trade name of Celestone and in multiple generic forms as syrups and effervescent tablets for oral use, edemas and foams for rectal use, aerosols for nasal and respiratory use, and creams and lotions for topical use. Betamethasone is 25 times more potent than cortisol in glucocorticoid activity, but has minimal mineralocorticoid activity.

## Hepatotoxicity, Mechanism of Injury

Corticosteroids have multiple adverse side effects, due to their multiplicity of actions affecting virtually all organs. Long term use has very profound effects on growth and can lead to cataracts, glaucoma, opportunistic infections, thinning of the skin, weight gain and redistribution of fat, insulin resistance and diabetes, hypertension, headache, psychiatric problems, sodium retention and peripheral edema; all of the clinical features of Cushing syndrome.

Corticosteroids also have major effects on the liver, particularly when given long term and in higher than physiologic doses. Glucocorticoid use can result in hepatic enlargement and steatosis or glycogenosis. Corticosteroids can trigger or worsen nonalcoholic steatohepatitis. Long term use can also exacerbate chronic viral hepatitis. Importantly, treatment with corticosteroids followed by withdrawal or pulse therapy can cause reactivation of hepatitis B and worsening or de novo induction of autoimmune hepatitis, both of which can be fatal. Finally, high doses of intravenous corticosteroids, largely methylprednisolone, have been associated with

acute liver injury which can result in acute liver failure and death. Thus, the hepatic complications of corticosteroids usually represent the worsening or triggering of an underlying liver disease and rarely are the result of drug hepatotoxicity.

Corticosteroid therapy can cause hepatic steatosis and hepatic enlargement, but this is often not clinically apparent, particularly in adults. This effect can occur quite rapidly and is rapidly reversed with discontinuation. High doses and long term use has been associated with the development or exacerbation of nonalcoholic steatohepatitis with elevations in serum aminotransferase levels and liver histology resembling alcoholic hepatitis with steatosis, chronic inflammation, centrilobular ballooning degeneration and Mallory bodies (Case 1). However, symptomatic or progressive liver injury from corticosteroid induced steatohepatitis is uncommon. Furthermore, corticosteroids may act to worsen an underlying nonalcoholic fatty liver disease rather than causing the condition de novo. The worsening may be due to direct effects of glucocorticoids on insulin resistance or fatty acid metabolism or may be the result of weight gain which is common with long term corticosteroid therapy. While simple steatosis induced by corticosteroids is rapidly reversible, steatohepatitis can be slow to resolve upon withdrawal of corticosteroids.

Corticosteroids in high doses can also cause hepatic glycogenosis, in which liver cells exhibit a homogenous appearance and stain strongly for glycogen (using PAS staining with and without diastase). Glycogenosis can also be associated with hepatomegaly (in children) and elevations in serum aminotransferase levels with minimal or no change in alkaline phosphatase or bilirubin levels. Glycogenosis is usually asymptomatic and does not appear to progress to chronic liver injury, cirrhosis or acute liver failure. While glycogenosis has been described largely in patients with poorly controlled type 1 diabetes, it also can occur acutely in patients started on high dose corticosteroids.

An important complication of corticosteroid therapy is the worsening of an underlying chronic viral hepatitis. In chronic hepatitis B, corticosteroids can induce increases in viral replication and serum hepatitis B virus (HBV) DNA levels while decreasing serum aminotransferase levels. Eventually, however, the increase in viral replication can worsen the underlying liver disease. Exacerbation of hepatitis becomes particularly evident when corticosteroids are withdrawn or lowered to physiological levels. As the immune system recovers, hepatitis worsens and serum aminotransferase levels can rise to greater than 10- to 20-fold elevated usually accompanied by a prompt decrease in HBV DNA levels. This flare of disease following withdrawal of corticosteroids can be severe and result in acute liver failure or significant worsening of chronic hepatitis and development of cirrhosis (Case 2). Indeed, even patients with the "inactive carrier states" (as shown by the presence of HBsAg in serum without HBeAg or detectable HBV DNA or any elevation in serum aminotransferase levels) can suffer severe reactivation of disease and acute liver failure as a result of a short course of high dose corticosteroids as occurs with cancer chemotherapy or with treatment of severe autoimmune conditions or even asthma, hay fever or allergic dermatitis. Reactivation of hepatitis B can be prevented by prophylactic use of antiviral therapy during the period of immunosuppression, but even this may not prevent some degree of liver injury.

Corticosteroids also appear to worsen the course of chronic hepatitis C, although in a less dramatic fashion than in chronic hepatitis B. Corticosteroid therapy leads to a rise in hepatitis C virus (HCV) RNA levels which may eventually cause worsening of the underlying liver disease. Chronic hepatitis C appears to be more severe and is particularly difficult to manage in patients receiving chemotherapy or immunosuppression, and corticosteroids are believed to be a major factor in this effect. Thus, corticosteroids should be avoided if possible in patients with underlying chronic viral hepatitis.

Corticosteroids are used in the therapy of autoimmune hepatitis and, therefore, are likely to be beneficial rather than harmful in patients with this disease. The difficulty arises when corticosteroids are stopped, which can cause a rebound exacerbation of the autoimmune hepatitis that is often severe and can be fatal. Importantly, there have been multiple reported instances of de novo appearance of severe autoimmune hepatitis in patients who received a short course or pulse of corticosteroids for another, unrelated condition (such as asthma or

allergic reactions). In these situations, a mild and subclinical autoimmune hepatitis was likely present before corticosteroids were started, and the suppression of the disease followed by immune rebound caused the clinical presentation of the condition. These patients generally respond to restarting corticosteroids, but may require long term if not life long immunosuppressive treatment thereafter.

Finally, there have been several reports of an acute hepatitis-like liver injury arising after a short, high dose course of intravenous methylprednisolone that can be severe and even fatal, and in which viral hepatitis and autoimmune hepatitis cannot be clearly implicated (Case 3). The cause of this apparent hepatotoxicity is not known, but it may represent severe autoimmune hepatitis triggered by the sudden profound immunosuppression and subsequent immune reconstitution. Importantly, symptoms and jaundice develop 2 to 4 weeks after stopping methylprednisolone and the pattern of serum enzyme elevations is typically hepatocellular. These episodes are usually symptomatic and can be severe. Immunoallergic manifestations are uncommon and autoantibodies may not be present. Several instances have resulted in acute liver failure resulting in death or need for emergency liver transplantation. Restarting corticosteroids may be appropriate in this situation, but it has not been evaluated systematically and many instances have resolved spontaneously. Recurrence of injury, often in a more rapid and severe form, arises upon reexposure to high dose pulse methylprednisolone.

Drug Class: Corticosteroids

Selected Drugs in the Class: Betamethasone, [Budesonide](#), Cortisone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone

## CASE REPORTS

### Case 1. Nonalcoholic steatohepatitis after long term corticosteroid therapy.

[Modified from: Itoh S, Igarashi M, Tsukada Y, Ichinoe A. Nonalcoholic fatty liver with alcoholic hyaline after long-term glucocorticoid therapy. *Acta Hepato-Gastroenterologica* 1977; 24: 415-8. [PubMed Citation](#)]

A 34 year old woman with systemic lupus erythematosus was treated with betamethasone with good clinical response with improvements in rash, fatigue and laboratory tests. Over a 6 month period, the daily dosage was gradually decreased from 5 to 1.25 mg daily. Initially, her liver tests were normal, but with corticosteroid therapy, ALT and AST were mildly elevated (Table). However, after 16 months of therapy, serum aminotransferase levels were more than 5-fold elevated (ALT 256 U/L, AST 272 U/L) and she was readmitted for evaluation. Her weight had risen by 11 kilograms and she had firm hepatomegaly. Laboratory tests showed elevations in serum aminotransferase levels, but normal serum bilirubin, albumin, and prothrombin time. She had an abnormal glucose tolerance test (fasting 118 mg/dL, 2 hour postprandial glucose 248 mg/dL). Testing for HBsAg was negative. She was known to be positive for antinuclear antibody (1:128). She denied alcohol use, which was confirmed by family and friends. A liver biopsy showed marked steatosis with inflammation including neutrophils, occasional Mallory bodies and mild central sinusoidal and portal fibrosis. Weight loss led to slight decreases in serum ALT levels.

### Key Points

Medication:	Betamethasone (1.25 mg daily)
Pattern:	Hepatocellular or mixed (R= $\sim$ 4.6)
Severity:	Mild (serum enzyme elevations only)
Latency:	Several months

Table continued from previous page.

Medication:	Betamethasone (1.25 mg daily)
Recovery:	Not mentioned
Other medications:	None mentioned

## Laboratory Values

Time After Starting	Body Weight (kg)	ALT (U/L)	Alk P (U/L)	Albumin (g/dL)	Other
0	42.7	18	95	3.4	
6 months	52.2	58	62	3.9	
16 months	58.2	256	131	4.0	Protime 10.4 sec
17 months	55.5	134	76	4.2	
<b>Normal Values</b>		<b>&lt;40</b>	<b>&lt;85</b>	<b>&lt;3.5</b>	

## Comment

This is an early, but well documented report of nonalcoholic steatohepatitis arising during corticosteroid therapy. The patient was evidently asymptomatic of liver disease, but the height of the serum aminotransferase elevations led to a hospital admission and liver biopsy. An issue is whether the liver disease was due to corticosteroid therapy directly or was the result of weight gain and insulin resistance caused by the therapy. Betamethasone is a synthetic, high potency glucocorticoid; 1.25 mg of betamethasone is roughly equivalent to 15 mg of prednisone.

## Case 2. Reactivation of chronic hepatitis B by corticosteroids.

[Modified from: Hammond A, Ramersdorfer C, Palitzsch KD, Schölmerich J, Lock G. [Fatal liver failure after corticosteroid treatment of a hepatitis B virus carrier]. *Dtsch Med Wochenschr* 1999; 124: 687-90. German.

[PubMed Citation](#)]

A 69 year old man with ulcerative colitis and the HBsAg carrier state developed jaundice and hepatitis after 9 months of continuous prednisolone therapy and shortly after intravenous pulse treatment with methylprednisolone. He was known to be a carrier of HBsAg with normal serum aminotransferase levels and no detectable HBeAg or HBV DNA in serum for several years. Because of relapsing ulcerative colitis, he was started on prednisolone therapy in tapering doses (60 mg daily down to 5 mg daily). Approximately 8 months into therapy, he received a 7 day course of intravenous methylprednisolone. One week later, while still on low doses of oral prednisolone, he developed fatigue and nausea. Liver tests, which had been normal, were markedly elevated with ALT 517 U/L, Alk P 356 U/L and bilirubin 3.98 mg/dL (Table). He was admitted. On examination, he was jaundiced and had mild mental dullness and asterixis. At this point, he tested positive for both HBsAg and HBeAg, and HBV DNA levels (which had been undetectable in the past) were markedly elevated (>100 million copies/mL). In addition he had IgM anti-HBc. Despite initiation of lamivudine therapy for hepatitis B and intensive medical management, he developed progressive liver failure, coagulopathy, hepatic coma and died 25 days after admission. Autopsy was refused.

## Key Points

Medication:	Prednisolone, methylprednisolone
Pattern:	Hepatocellular (R=6.1)
Severity:	5+ (fatal)
Latency:	8 months of oral prednisone

Table continued from previous page.

Medication:	Prednisolone, methylprednisolone
Recovery:	None
Other medications:	5-Aminosalicylic acid, isosorbide dinitrate, theophylline, insulin

## Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Bilirubin (mg/dL)	Other
Pre		<30	<1.0	HBV DNA <100 copies/mL
7 months		60	<1.0	Methylprednisolone bolus
8 months		180	<1.0	Prednisone: 5 mg daily
9 months	0	517	<1.0	Alk P 356
	30 days	600	4.0	Admission; HBeAg positive
	32 days	700	14.0	
	34 days	830	20.0	
10 months	36 days	1140	24.0	
	6 weeks	980	34.0	
	7 weeks	220	36.0	
	8 weeks	50	41.0	Died
<b>Normal Values</b>		<b>&lt;4.5</b>	<b>&lt;1.2</b>	

\* Results and time sequence estimated from Figure 1.

## Comment

Reactivation of hepatitis B in an HBsAg carrier can be followed by a severe episode of hepatitis as immunosuppression is withdrawn. The clinical syndrome is similar to acute hepatitis B and IgM anti-HBc may become detectable. The diagnosis can be made based upon reappearance and/or marked rise in HBV DNA levels. Many cases present as "acute-on-chronic" liver failure rather than classical acute liver failure. The prognosis is poor and antiviral therapy appears to have little effect once hepatic failure is present. HBsAg carriers who undergo immunosuppressive therapy with prednisone should be monitored and prophylaxis during the immunosuppression with an oral nucleoside analogue such as tenofovir or entecavir is appropriate.

## Case 3. Severe acute hepatitis following bolus, high dose methylprednisone therapy.

[Modified from: Marinò M, Morabito E, Altea MA, Ambrogini E, Oliveri F, Brunetto MR, Pollina LE, et al. Autoimmune hepatitis during intravenous glucocorticoid pulse therapy for Graves' ophthalmopathy treated successfully with glucocorticoids themselves. *J Endocrinol Invest* 2005; 28: 280-4. [PubMed Citation](#)]

A 43 year old woman with Graves disease developed worsening ophthalmopathy despite adequate control of thyroid function. She received orbital radiotherapy and was started on cycles of intravenous methylprednisolone (15/mg/kg) given over two days every two weeks. After the sixth infusion (6 weeks after starting), she was found to have elevations in serum ALT (264 U/L) and AST (120 U/L) and the infusions were held. Over the next six weeks, serum aminotransferase levels rose further (Table), with no or minor elevations in serum alkaline phosphatase, gamma glutamyltranspeptidase and bilirubin. However, the prothrombin index worsened (61%) and platelet count fell to 89,000/ $\mu$ L. Tests of hepatitis A, B and C were negative. Immunoglobulin levels were

normal and tests for autoantibodies, including antinuclear antibody, smooth muscle antibody and liver-kidney microsomal antibody, were negative. A liver biopsy showed changes suggestive of chronic aggressive hepatitis with marked lymphocytic inflammation, interface hepatitis, and both focal and bridging necrosis. Because the histological and clinical features supported the diagnosis of severe autoimmune hepatitis, prednisone was initiated, with prompt improvements in serum aminotransferase levels. Prednisone doses were gradually reduced and ultimately withdrawn. Serum enzymes were normal within 2 months of starting prednisone and the dosage was gradually reduced and then withdrawn 3 months after initiation.

## Key Points

Medication:	Methylprednisolone
Pattern:	Hepatocellular
Severity:	1+ (serum enzyme elevations without jaundice)
Latency:	6 weeks
Recovery:	3 months
Other medications:	None mentioned

## Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	GGT (U/L)	Other
Pre		Normal	Normal	
3 cycles of two days of pulse methylprednisolone given 2 weeks apart				
8 weeks	2 weeks	264	40	
12 weeks	6 weeks	320	40	
13 weeks	7 weeks	610	80	Bilirubin and Alk P normal
14 weeks	8 weeks	1050	100	ANA negative, Protime 61%
15 weeks	9 weeks	1419	183	im Prednisolone started
4 months	10 weeks	600		Oral prednisone
	11 weeks	260	100	
5 months	15 weeks	65	50	
6 months	20 weeks	40	40	
<b>Normal Values</b>		<b>&lt;45</b>	<b>&lt;50</b>	

\* Values and time sequence estimated from Figure 1.

## Comment

An example of an acute hepatitis-like syndrome arising after pulse methylprednisolone therapy. These episodes arise typically 2 to 4 weeks after a third or fourth cycle of pulse therapy, and range in severity from an asymptomatic and transient rise in serum aminotransferase levels to an acute hepatitis and even fulminant hepatic failure. In this instance, the marked and persistent rise in serum enzymes coupled with liver histology suggesting chronic hepatitis led to a diagnosis of new-onset autoimmune hepatitis, despite the absence of serum autoantibodies or hypergammaglobulinemia. Autoimmune hepatitis may initially present in this fashion, without the typical pattern of serum autoantibodies during the early, anicteric phase. The diagnosis was further supported by the prompt improvements in serum enzymes with prednisone therapy. The acute hepatitis-like syndrome that can occur after pulses of methylprednisolone is best explained as a triggering of an underlying chronic autoimmune hepatitis caused by the sudden and profound immunosuppression followed by rapid



withdrawal. This syndrome can be severe, and fatal instances have been reported. Whether reinitiation of corticosteroid therapy with gradual tapering and withdrawal is effective in ameliorating the course of illness is unclear, but anecdotal reports such as this one suggest that they are beneficial and should be initiated promptly on appearance of this syndrome. Long term follow up of such cases is also necessary to document that the autoimmune hepatitis does not relapse once corticosteroids are withdrawn again.

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Betamethasone – Generic, Celestone®

Cortisone – Generic

Dexamethasone – Generic, Decadron®

Hydrocortisone – Generic, Cortef®

Methylprednisolone – Generic, Medrol®

Prednisolone – Generic

Prednisone – Generic

Triamcinolone – Generic, Aristocort®, Kenacort®, Kenalog®

### DRUG CLASS

Glucocorticoids, Synthetic

### COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULAS AND STRUCTURES

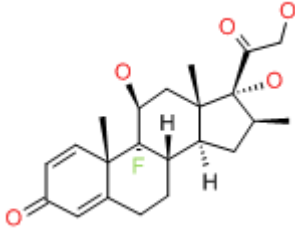
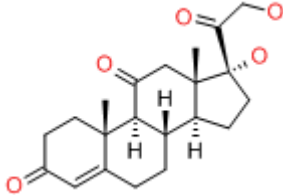
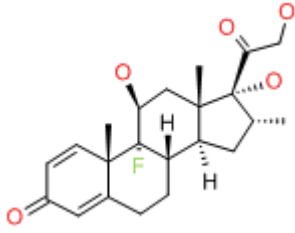
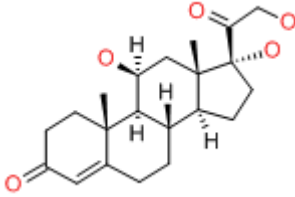
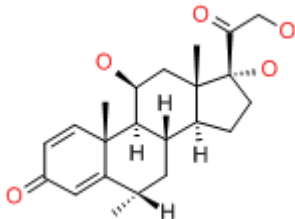
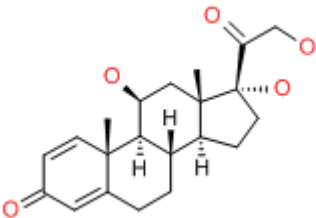
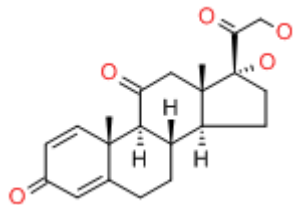
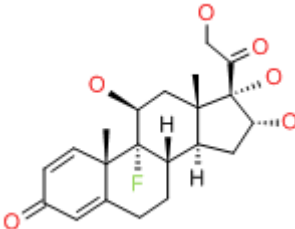
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Betamethasone	378-44-9	C <sub>22</sub> -H <sub>29</sub> -F-O <sub>5</sub>	 The chemical structure of Betamethasone is a corticosteroid with a four-ring steroid nucleus. It features a ketone group at C3, a double bond between C4 and C5, a fluorine atom at C6, and a 17β-acetoxy side chain. Stereochemistry is indicated with wedges and dashes at C13 and C14.
Cortisone	53-06-5	C <sub>21</sub> -H <sub>28</sub> -O <sub>5</sub>	 The chemical structure of Cortisone is a corticosteroid with a four-ring steroid nucleus. It features a ketone group at C3, a double bond between C4 and C5, and a 17β-acetoxy side chain. Stereochemistry is indicated with wedges and dashes at C13 and C14.

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DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Dexamethasone	50-02-2	C <sub>22</sub> -H <sub>29</sub> -F-O <sub>5</sub>	
Hydrocortisone	50-23-7	C <sub>21</sub> -H <sub>30</sub> -O <sub>5</sub>	
Methylprednisolone	83-43-2	C <sub>22</sub> -H <sub>30</sub> -O <sub>5</sub>	
Prednisolone	50-24-8	C <sub>21</sub> -H <sub>28</sub> -O <sub>5</sub>	
Prednisone	53-03-2	C <sub>21</sub> -H <sub>26</sub> -O <sub>5</sub>	
Triamcinolone	124-94-7	C <sub>21</sub> -H <sub>27</sub> -F-O <sub>6</sub>	

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Chitturi S, Farrell GC. Corticosteroids. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 613-4.

*(Review of liver injury from corticosteroids mentions hepatic steatosis and acute liver injury following high dose methylprednisolone).*

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*(Textbook of pharmacology and therapeutics).*

Steinberg H, Webb WM, Rafsky HA. Hepatomegaly with fatty infiltration secondary to cortisone therapy: case report. Gastroenterology 1952; 21: 304-9. PubMed PMID: 14937220.

*(14 year old boy treated for rheumatic fever with cortisone developed marked hepatomegaly beginning on day 6, and by day 43 liver biopsy showed fat and inflammation, which resolved rapidly upon stopping therapy; liver biopsy 20 days later showed normal liver without steatosis).*

Hill RB Jr, Droke WA. Production of fatty liver in the rat by cortisone. Proc Soc Exp Biol Med 1963; 114: 766-9. PubMed PMID: 14120343.

*(Rats treated with cortisone developed fatty liver and increases in hepatic triglyceride levels).*

Itoh S, Igarashi M, Tsukada Y, Ichinoe A. Nonalcoholic fatty liver with alcoholic hyaline after long-term glucocorticoid therapy. Acta Hepato-Gastroenterologica 1977; 24: 415-8. PubMed PMID: 74931.

*(56 year old woman with systemic lupus treated with betamethasone for 16 months gained 24 pounds and developed insulin resistance, moderate increases in ALT [from 18 to 272 U/L] and Alk P [95 to 121 U/L] levels without jaundice; biopsy showed steatohepatitis and Mallory bodies: Case 1).*

Iancu TC, Shiloh H, Dembo L. Hepatomegaly following short-term high-dose steroid therapy. J Pediatr Gastroenterol Nutr 1986; 5: 41-6. PubMed PMID: 3944744.

*(Among 140 children treated with prednisone [2-4 mg/kg/day], 19 developed hepatomegaly within 3-6 days, regressing with stopping treatment; liver biopsies showed glycogenosis and some degree of steatosis; no mention of ALT levels).*

Hoofnagle JH, Davis GL, Pappas SC, Hanson RG, Peters M, Avigan MI, Waggoner JG, et al. A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1986; 104: 12-7. PubMed PMID: 3940480.

*(Clinical trial of 4 week course of prednisolone [60 mg/day for 2 weeks, 30 mg/day for 2 weeks] in 15 patients with chronic hepatitis B found flares of hepatitis occurring in most patients 1-2 months after withdrawal that could be prolonged and lead to worsening of liver histology).*

- Wald JA, Farr RS. Abnormal liver-function tests associated with long-term systemic corticosteroid use in subjects with asthma. *J Allergy Clin Immunol* 1991; 88: 277-8. PubMed PMID: 1880328.
- (Retrospective analysis of 80 patients with asthma found mean ALT and Alk P levels were higher among 25 patients on "high dose" corticosteroids compared to those on no or low doses; 80% on high doses had at least one liver test abnormality compared to 23% on low doses and 5% on no corticosteroid therapy).*
- Koga Y, Kumashiro R, Yasumoto K, Shakado S, Ono N, Noguchi H, Nagata K, et al. Two fatal cases of hepatitis B virus carriers after corticosteroid therapy for bronchial asthma. *Intern Med* 1992; 31: 208-13. PubMed PMID: 1600269.
- (53 year old woman with asthma and HBsAg developed acute hepatitis 2-3 weeks after 1 month course of intravenous hydrocortisone [200-300 mg/day], with jaundice, hepatic failure and death 6 weeks later; 68 year old man with asthma and HBsAg developed symptoms and jaundice 1 month after 8 day course of intravenous hydrocortisone, with progression to acute liver failure and death).*
- Fong TL, Valinluck B, Govindarajan S, Charboneau F, Adkins RH, Redeker AG. Short-term prednisone therapy affects aminotransferase activity and hepatitis C virus RNA levels in chronic hepatitis C. *Gastroenterology* 1994; 107: 196-9. PubMed PMID: 8020662.
- (Among 10 patients with chronic hepatitis C treated with 7 week course of prednisone, most had rise in HCV RNA levels during therapy with fall in ALT and rebound afterwards, but without clinically apparent flares).*
- Gerolami R, Mambrini P, Barthet M, Jean-Pastor MJ, Salducci J, Grimaud JC. [Acute hepatitis caused by Solupred in a patient with Crohn disease]. *Gastroenterol Clin Biol* 1997; 21: 236-7. French. PubMed PMID: 9161506.
- (27 year old woman with Crohn disease received methylprednisolone [50 mg/day] followed by intravenous prednisone [60 mg/day] and developed abnormal liver tests 6 days later, ALT levels rising from normal to 11 times ULN, Alk P to 3.2 times ULN, ANA negative, resolving within 1 week of starting oral corticosteroids; elevations possibly due to acute glycogenesis).*
- Hammond A, Ramersdorfer C, Palitzsch KD, Schölmerich J, Lock G. [Fatal liver failure after corticosteroid treatment of a hepatitis B virus carrier]. *Dtsch Med Wochenschr* 1999; 124: 687-90. German. PubMed PMID: 10394348.
- (69 year old man with HBsAg carrier state and ulcerative colitis developed jaundice and progressive hepatic failure starting at the end of a 9 month course of prednisone [60 mg down to 5 mg/day], with appearance of HBV DNA, ALT 1140 U/L, and death 30 days later: Case 2).*
- Nanki T, Koike R, Miyasaka N. Subacute severe steatohepatitis during prednisolone therapy for systemic lupus erythematosus. *Am J Gastroenterol* 1999; 94: 3379. PubMed PMID: 10566758.
- (53 year old woman with systemic lupus had rise of ALT [144 rising to 658 U/L] starting after 38 days of oral prednisolone therapy [20 mg/day], liver biopsy showing steatohepatitis; patient reported to have died of liver failure subsequently, but no clinical details given).*
- Shiota G, Harada K, Oyama K, Udagawa A, Nomi T, Tanaka K, Tsutsumi A, et al. Severe exacerbation of hepatitis after short-term corticosteroid therapy in a patients with "latent" chronic hepatitis B. *Liver* 2000; 20: 415-20. PubMed PMID: 11092261.
- (46 year old woman with polyneuropathy developed hepatitis after each of 3 pulses of methylprednisolone [1 g/day for 3 days], twice with jaundice [bilirubin normal, rising to 20 mg/dL, ALT 500-1500 U/L, no detectable HBsAg, but "occult" HBV DNA identified in liver).*
- Weissel M, Hauff W. Fatal liver failure after high-dose glucocorticoid pulse therapy in a patient with severe thyroid eye disease. *Thyroid* 2000; 10: 521. PubMed PMID: 10907999.

- (71 year old woman with Graves disease developed hepatitis after fifth monthly cycle of high dose methylprednisolone [1 g/day for 3 days], with acute liver failure, death and massive necrosis on autopsy; patient also on methimazole and few clinical details given).*
- Marcocci C, Bartalena L, Tanda ML, Manetti L, Dell'Unto E, Rocchi R, Barbesino G, et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. *J Clin Endocrinol Metab* 2001; 86: 3562-7. PubMed PMID: 11502779.
- (Controlled trial of intravenous methylprednisolone [15 mg/kg in 4 cycles] vs oral prednisone [starting at 100 mg/day] in 82 patients with Graves' ophthalmopathy; one methylprednisolone treated patient had marked, asymptomatic increase in ALT at end of treatment, with recovery in 2 months; authors also mention an unpublished fatal case that they had seen before).*
- Dourakis SP, Sevastianos VA, Kaliopi P. Acute severe steatohepatitis related to prednisolone therapy. *Am J Gastroenterol* 2002; 97: 1074-5. PubMed PMID: 12003403.
- (67 year old woman with dermatomyositis developed jaundice after 8 days of intravenous prednisolone [75 mg/day] [bilirubin 10.8 mg/dL, ALT 545 U/L, Alk P 467 U/L, negative ANA], resolving on decreasing dose, but patient died of pneumonia shortly thereafter, liver histology showing severe fat without fibrosis).*
- Stravitz RT, Sanyal AJ. Drug-induced steatohepatitis. *Clin Liver Dis* 2003; 7: 435-51. PubMed PMID: 12879993.
- (Review of drugs that can cause steatohepatitis including glucocorticoids; mechanism unknown).*
- Candelli M, Nista EC, Pignataro G, Zannoni G, de Pascalis B, Gasbarrini G, Gasbarrini A. Steatohepatitis during methylprednisolone therapy for ulcerative colitis exacerbation. *J Intern Med* 2003; 253: 391-2. PubMed PMID: 12603510.
- (25 year old man with ulcerative colitis developed elevated ALT [106 U/L], fatty liver by ultrasound, and steatohepatitis on liver biopsy 40 days after starting oral methylprednisolone, ALT elevations and ultrasound changes resolving within 6 months of stopping).*
- Marinó M, Morabito E, Brunetto MR, Bartalena L, Pinchera A, Marocci C. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid* 2004; 14: 403-6. PubMed PMID: 15186621.
- (Among 800 patients with Graves ophthalmopathy treated with intravenous methylprednisolone, 7 [~1%] developed acute hepatitis-like illness following 3-6 courses, ages 30-63 years, arising 3-17 weeks after starting, 3 were jaundiced and died, 4 were asymptomatic [ALT 179-2490 U/L, Alk P 100-498 U/L], autoantibodies uncommon, resolving spontaneously in 9-22 weeks).*
- Salvi M, Vannucchi G, Sbrozzi F, Del Castello AB, Carnevali A, Fargion S, Beck-Peccoz P. Onset of autoimmune hepatitis during intravenous steroid therapy for thyroid-associated ophthalmopathy in a patient with Hashimoto's thyroiditis: case report. *Thyroid* 2004; 14: 631-4. PubMed PMID: 15320978.
- (43 year old woman with ophthalmopathy developed hepatitis after fourth course of methylprednisolone [ALT rising to 1152 U/L, ANA positive], responding to oral prednisone in tapering doses, but still on low doses of prednisone [2.5 mg/day] 6 years later).*
- Marinó M, Morabito E, Altea MA, Ambrogini E, Oliveri F, Brunetto MR, Pollina LE, et al. Autoimmune hepatitis during intravenous glucocorticoid pulse therapy for Graves' ophthalmopathy treated successfully with glucocorticoids themselves. *J Endocrinol Invest* 2005; 28: 280-4. PubMed PMID: 15952415.
- (43 year old woman with ophthalmopathy who developed marked ALT elevations [1419 U/L] with normal bilirubin and Alk P levels after 3 pulse cycles of methylprednisolone, ANA negative, but biopsy showed chronic aggressive hepatitis which responded to oral prednisone therapy).*

- Hofstee HM, Nanayakkara PW, Stehouwer CD. Acute hepatitis related to prednisolone. *Eur J Intern Med* 2005; 16: 209-10. PubMed PMID: 15967341.
- (46 year old woman with multiple sclerosis developed marked ALT elevations [peak levels 1095, ~1550 and ~2300 U/L with Alk P 140 U/L, LDH 473 U/L, ANA negative] 4-6 weeks after methylprednisolone pulse therapy on multiple occasions, always without jaundice and resolving rapidly each time).*
- Das D, Graham I, Rose J. Recurrent acute hepatitis in patient receiving pulsed methylprednisolone for multiple sclerosis. *Indian J Gastroenterol* 2006; 25: 314-6. PubMed PMID: 17264438.
- (48 year old woman developed nausea and jaundice 6 weeks after a third course of high dose pulse methylprednisolone for multiple sclerosis [bilirubin ~12 rising to ~35 mg/dL, ALT 1625 U/L, Alk P 210 U/L, ANA negative], resolving in 1-2 months and recurring 1 year later after a fourth course).*
- Topal F, Ozaslan E, Akbulut S, Küçükazman M, Yüksel O, Altiparmak E. Methylprednisolone-induced toxic hepatitis. *Ann Pharmacother* 2006; 40: 1868-71. PubMed PMID: 16926305.
- (47 year old woman developed jaundice one week after finishing 7 day course of methylprednisolone [32 mg/day] [bilirubin rising to 15 mg/dL, ALT 2478 U/L, Alk P 138 U/L, ANA negative], resolution in 8 weeks, also on topiramate which was also stopped, but restarted briefly).*
- Reuss R, Retzlaff K, Vogel S, Franke FE, Oschmann P. Autoimmune hepatitis after high-dose intravenous methylprednisolone pulse in RR-MS. *CEJ Med* 2007; 2: 356-9. (Not in PubMed)
- (42 year old woman with multiple sclerosis developed elevations in ALT [1082 U/L] without jaundice 3 weeks after second pulse of intravenous methylprednisolone; liver biopsy showed necrosis, collapse and fibrosis, levels slowly improved; no mention of ANA or bilirubin levels).*
- Le Moli R, Baldeschi L, Saeed P, Regensburg N, Mourits MP, Wiersinga WM. Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in Graves' ophthalmopathy. *Thyroid* 2007; 17: 357-62. PubMed PMID: 17465867.
- (Among 27 patients with Graves ophthalmopathy receiving 1-4 pulses of methylprednisolone, 7 had transient ALT elevations [peak level 120 U/L] shortly after infusion, all resolved and none were jaundiced).*
- Takahashi A, Kanno Y, Takahashi Y, Sakamoto N, Monoe K, Saito H, Abe K, et al. Development of autoimmune hepatitis type 1 after pulsed methylprednisolone therapy for multiple sclerosis: a case report. *World J Gastroenterol* 2008; 14: 5474-7. PubMed PMID: 18803363.
- (43 year old woman with multiple sclerosis developed acute hepatitis 1 month after third course of pulse methylprednisolone [1 g/day for 3 days] [bilirubin 3.4 mg/dL, ALT 1067 U/L, Alk P 377 U/L, IgG 1370 mg/dL, ANA negative] with bilirubin rising to 19.1 mg/dL, attributed to beta interferon; but developed hepatitis again 2 weeks after a subsequent pulse of methylprednisolone [bilirubin 1.7 mg/dL, ALT 875 U/L, Alk P 214 U/L, IgG 1785 mg/dL and ANA 1:80], resolving with oral prednisolone therapy).*
- Rivero Fernández M, Riesco JM, Moreira VF, Moreno A, López San Román A, Arranz G, Ruiz Del Arbol L. [Recurrent acute liver toxicity from intravenous methylprednisolone]. *Rev Esp Enferm Dig* 2008; 100: 720-3. Spanish. PubMed PMID: 19159178.
- (57 year old woman with multiple sclerosis developed ALT elevations after each of 3 pulse cycles of methylprednisolone [peak ALT 1223, 833 and 2685 U/L, Alk P 113 and 115 U/L, ANA negative] without jaundice and with rapid resolution, biopsy showing acute hepatitis with "lytic" necrosis).*
- Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. [PubMed Citation](#)

*(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, none were attributed to corticosteroid therapy or methylprednisolone).*

Hoofnagle JH. Reactivation of hepatitis B. *Hepatology* 2009; 49 (5 Suppl): S156-65. PubMed PMID: 29399803.

*(Review of reactivation of hepatitis B as caused by chemotherapy or immunosuppression).*

Loraschi A, Banfi P, Mauri M, Sessa F, Bono G, Cosentino M. Hepatotoxicity after high-dose methylprednisolone for demyelinating disease. *Clin Neuropharm* 2010; 33: 52-4. PubMed PMID: 19935411.

*(One man and one woman, ages 33 and 27 years with demyelinating disease developed abnormal ALT levels [1042 U/L and 122 U/L] 5 and 1 week after starting high dose methylprednisolone therapy [4 and 6 days of 2.5 and 4.5 g], resolving rapidly; no mention of symptoms or jaundice).*

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.

*(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to methylprednisolone or other corticosteroids).*

Gutkowski K, Chwist A, Hartleb M. Liver injury induced by high-dose methylprednisolone therapy: a case report and brief review of the literature. *Hepat Mon* 2011; 11: 656-61. PubMed PMID: 22140391.

*(24 year old woman with multiple sclerosis developed jaundice 4 weeks after a pulse of methylprednisolone and 1 week after 2 doses of interferon beta [bilirubin 17.9 mg/dL, ALT 740 U/L, Alk P 186 U/L, prothrombin index 35%, SMA >1:320], resolving spontaneously, but recurring after another pulse of methylprednisolone with interferon beta [bilirubin 7.3 mg/dL, ALT 1129 U/L, Alk P 164 U/L], again resolving spontaneously).*

Furutama D, Kimura F, Shinoda K, Maeda T, Tanaka T, Ohsawa N. Recurrent high-dose intravenous methylprednisolone succinate pulse therapy-induced hepatopathy in a patient with multiple sclerosis. *Med Princ Pract* 2011; 20: 291-3. *(11 year old girl with multiple sclerosis had 3 episodes of marked serum ALT elevations [peak levels ~700-1400 U/L] 1-2 months after bolus therapy with methylprednisolone, PubMed PMID: 21455003.*

*with minimal symptoms and no jaundice or bilirubin elevations).*

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; 144: 1419-25. PubMed PMID: 23419359.

*(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, of which none were attributed to corticosteroids or methylprednisolone).*

Carrier P, Godet B, Crepin S, Magy L, Debette-Gratien M, Pillegand B, Jacques J, et al. Acute liver toxicity due to methylprednisolone: consider this diagnosis in the context of autoimmunity. *Clin Res Hepatol Gastroenterol* 2013; 37: 100-4. PubMed PMID: 23318289.

*(30 year old woman with multiple sclerosis developed jaundice 3 weeks after a second bolus dose of methylprednisone [bilirubin 25.8 mg/dL, ALT 547 U/L, Alk P 141 U/L, ANA negative], with rapid resolution on stopping and recurrence 2 and 5 years later with subsequent single bolus doses of methylprednisone [peak bilirubin 6.6 and 9.6 mg/dL, ALT 415 and 2826 U/L and Alk P 60 and 148 U/L, latency 10-20 days]).*

D'Agnolo HM, Drenth JP. High-dose methylprednisolone-induced hepatitis in a patient with multiple sclerosis: a case report and brief review of literature. *Neth J Med* 2013; 71: 199-202. PubMed PMID: 23723114.

*(48 year old woman developed abdominal pain and nausea 19 days after high dose methylprednisolone for multiple sclerosis [bilirubin 1.7 mg/dL, ALT 3028 U/L, GGT 182 U/L], resolving within the following few weeks; by history, she had a similar event 14 years earlier, but did not develop clinically apparent liver injury after 3 subsequent courses of oral dexamethasone [200 mg/day]).*

Melamud B, Lurie Y, Goldin E, Levi I, Esayag Y. Methylprednisolone-induced liver injury: a diagnostic challenge. *Isr Med Assoc J* 2014; 16: 180-1. PubMed PMID: 24761710.

*(52 year old man with Graves disease developed liver injury within a few weeks of intravenous methylprednisolone, which recurred when he received a second course [bilirubin 3.4 mg/dL, ALT 465 U/L, Alk P 80 U/L], resolving on no therapy within 7 months).*