UNIVERSITY OF UTAH
COLLEGE OF PHARMACY
L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID DUR REPORT
APRIL 2016

CORTICOTROPIN
(HP Acthar Injection)

Drug Regimen Review Center
Joanita Lake B.Pharm, MSc EBHC (Oxon), Clinical Pharmacist
Gary M. Oderda Pharm D, M.P.H, Professor
Justin Wesley Tran Pharm D Student

University of Utah College of Pharmacy
Copyright © 2016 by University of Utah College of Pharmacy
Salt Lake City, Utah. All rights reserved

Contents

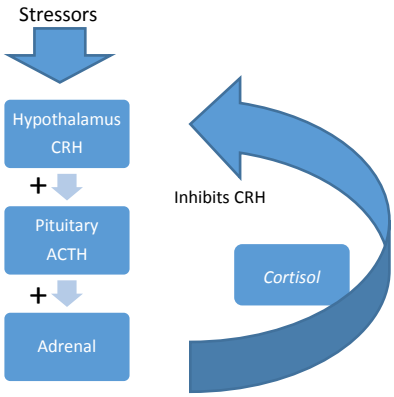
Introduction 3
Methodology 4
Natural Form versus Synthetic form 4
Indications, administration and dosage 5
Background for indications 6
Off-label use 10
Clinical Guidelines, Systematic Reviews and related evidence 11
A. Infantile Spasms/West Syndrome 11
B. Multiple Sclerosis 15
C. Rheumatic Disorders 18
D. Gout 19
E. Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis) 20
F. Dermatologic Diseases: Severe erythema multiforme, Stevens-Johnson syndrome 21
G. Allergic States: Serum sickness 22
H. Ophthalmic Diseases (Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis; iritis, iridocyclitis, diffuse posterioir uveitis and choroiditis, optic neuritis, chorioretinitis; anterior segment inflammation) 22
I. Respiratory Diseases: Symptomatic Sarcoidosis 23
J. Edematous State (to induce diuresis or remission of proteinuria in nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus) 23
Additional Evidence 26
The US Institute for Clinical and Economic Review (ICER) 26
Safety 26
Utah Medicaid Utilization Data 27
Appendix 1 – Drug information 30
Appendix 2 – Systematic review(s), Trial(s), and other reviews 31
Appendix 3 – Additional Guidelines 58
References 71

Introduction

Repository corticotropin (Acthar) is an adrenocorticotropic hormone (ACTH) analogue that is derived from bovine or porcine ACTH.[1,2]

Many different types of stress (stressors) stimulate the release of Corticotropin-releasing hormone (CRH) from the hypothalamus, causing the secretion of ACTH, also known as corticotropin. Repository and endogenous (secreted from the anterior pituitary) corticotropin stimulate the adrenal cortex to secrete glucocorticoids such as cortisol, corticosterone, aldosterone (little control over aldosterone secretion), and other weak androgenic substances. Glucocorticoids (i.e. elevated plasma cortisol levels) inhibit the release of CRH (negative biofeedback), thereby suppressing ACTH release.[1-3]

Figure 1. Adrenocorticotropic Hormone (ACTH, corticotropin) release and inhibition (adapted[3])



"Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are used primarily for their anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli."[4]

ACTH was originally approved by the FDA in 1952. The use of synthetic ACTH declined because it has to be injected and oral steroids preparations such as prednisolone are widely available.[5,6] In August 2007 H.P. Acthar gel repository injection became available. Acthar is distributed through a specialty pharmacy. Patients cannot get their Acthar prescription filled at a retail pharmacy, and hospitals wishing to acquire H.P. Acthar® Gel have to contact Specialty Distribution.[7] Currently, H.P Acthar Gel (repository corticotropin injection) is available as an 5 mL (80 units/mL) multi-dose vial requiring refrigeration between 2-8°C.[8] It is administered via intramuscular or subcutaneous route, and is formulated to provide extended release of ACTH following injection.[9,10]

ACTH has many FDA-approved indications and numerous uses are mentioned in the literature. The most common indications are Infantile spasms (West syndrome), multiple sclerosis (MS), and adreno-corticol testing.[6] In 2009, a review by Gettig et al. reported that the use of ACTH in the diagnosis of adrenal insufficiency and treatment of MS exacerbations is decreasing.[6] In 2014, it was reported that of the 19 FDA-approved indications, it is mostly used for: the treatment of proteinuria in idiopathic nephrotic syndrome (NS), the treatment of acute exacerbations of multiple sclerosis (MS) in adults, the treatment of infantile spasms (IS) in infants and children under two years of age, and the treatment of certain rheumatology related conditions, including the treatment of the rare and closely related neuromuscular disorders dermatomyositis and polymyositis.[14]

Methodology

The Agency for Healthcare Research and Quality (AHRQ; www.guideline.gov), Cochrane Library, the FDA website, PubMed, UpToDate, Micromedex, Lexicomp, the Institute for Clinical and Economic Review (ICER) website, the National Institute for Health and Clinical Excellence (NICE) website and clinicaltrials.gov, were searched for systematic reviews, clinical trials, guidelines, other reports, reviews, efficacy and safety information. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first, followed by phase 3 randomized controlled trials. Only guidelines for infantile spasms and gout were identified that mention corticotropin, ACTH, or Acthar. Use steroid or glucocorticoid as search terms resulted in 300 results on guidelines.gov. The search within function was then used to search for FDA-approved indications of corticotropin, and information was included in the relevant sections. The search in the Cochrane Library was also broadened to include FDA-approved indications regardless of whether corticotropin was included or mentioned (to capture steroid reviews as well).

Natural Form versus Synthetic form

H.P. Acthar Gel Repository Injection (Questcor Pharmaceuticals) is a 39-amino-acid peptide natural form of ACTH isolated from porcine pituitary extracts, however, there is also a synthetic form of ACTH available (that is created by isolating the first 24 amino acids from the 39-amino-acid ACTH peptide) known as cosyntropin (Cortrosyn, Amphastar), or tetracosactide in some countries outside the U.S.[5,6] "Cosyntropin combines with a specific receptor in the adrenal cell plasma membrane and, in patients with normal adrenocortical function, stimulates the initial reaction involved in the synthesis of adrenal steroids (including cortisol, cortisone, weak androgenic substances, and a limited quantity of aldosterone) from cholesterol by increasing the quantity of the substrate within the mitochondria. Cosyntropin does not significantly increase plasma cortisol concentration in patients with primary or secondary adrenocortical insufficiency. Cosyntropin has less immunogenic activity than ACTH because the amino acid sequence having most of the antigenic activity of ACTH, i.e., amino acids 25–39, is not present in cosyntropin."[16]

Table 1[1,5,6,15]

	Natural Form	**Synthetic form**
Product	H.P. Acthar Gel Repository Injection	Cosyntropin US brand name: Cortrosyn Canada brand names: Cortrosyn; Synacthen Depot) or known as tetracosactide in some countries outside the U.S (available in depot form). **Synonyms for cosyntropin include:** Corticotropin, Synthetic; Cortrosyn inj 0.25mg (CA); Synacthen; Synacthen depot (CA); Tetracosactide; Tetracosactrin; Tetracosapeptide; α^{1-24}-Corticotropin[17]
Formulation & Dose conversion		A dose of cosyntropin 0.25 mg, similar to a dose of 25 units of ACTH, stimulates the adrenal cortex. Depot formulation (Synacthen Depot) is not FDA-approved. A 2009 review states that it is available only through a compassionate-use program through the specialty pharmacy Caligor Rx in New York. "According to manufacturer data, patients receiving 40 units of natural corticotropin injection gel may be converted to 0.5 mg IM every **other** day of the synthetic

	Natural Form	Synthetic form
		long-acting cosyntropin depot"[18,19] (tetracosactide depot and Synacthen Depot)
FDA-labeled indications(s)	Several. Refer to "Indications, administration and dosage section"	Diagnostic testing of adrenal function: To differentiate primary adrenal insufficiency (Addison's disease) from secondary (pituitary) adrenocortical insufficiency (due to inappropriate or long-term appropriate use of corticosteroids)
Route of administration	Infantile spasms: IM Acute exacerbations of multiple sclerosis (MS): IM or SC route Other indications: IM or SC NEVER IV[9]	Cosyntropin **powder** for injection: IM or IV Cosyntropin **solution** for injection: IV only (manufacturer labeling does not recommend IM administration of solution for injection) Synacthen Depot (Canadian product): IM Tetracosactide Depot (Europe): IM
Efficacy comparison	"Data comparing the natural and synthetic forms are not available, but uncontrolled observations suggest that efficacy is similar."[18,20,21]	

Indications, administration and dosage

H.P. Acthar® Gel (repository corticotropin injection) is an adrenocorticotropic hormone (ACTH) analogue indicated for treatment of several conditions[2,22]:

1. **Infantile Spasms (West Syndrome)**

2. **Multiple Sclerosis:** According to the product label, "Controlled clinical trials have shown H.P Acthar Gel to be effective in speeding resolution of **acute exacerbations of multiple sclerosis**. However, there is no evidence that it affects the ultimate outcome or natural history of the disease."[9]

3. **Rheumatic Disorders:** Short-term use during an acute episode or exacerbation.

4. **Collagen Diseases -** Label: During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)

5. **Dermatologic Diseases:** Severe erythema multiforme, Stevens-Johnson syndrome

6. **Allergic States:** Serum sickness

7. **Ophthalmic Diseases:** Severe acute and chronic allergic and inflammatory processes involving the eye and is adnexa

8. **Respiratory Diseases:** Symptomatic sarcoidosis

9. **Edematous State:** To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus

The product label presents these in three categories in terms of dosage and administration:

A. **Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.** Administered twice daily by IM injection over a 2-week period, then tapered over a 2-week period to avoid adrenal insufficiency.[9] It is typically dosed based on body surface area (BSA) and the recommended dose is 150 U/m^2 daily (75 U/m^2 twice daily).[9]

B. **For the treatment of acute exacerbations of multiple sclerosis (MS) in adults.** Administered IM or SC at a recommended dose of 80-120 units daily for 2-3 weeks, and tapering may be necessary.[9]

C. **Other conditions (age >2 years):** According to the product label, dosing will need to be individualized, and it may be necessary to taper the dose.[9] Usual dose: 40-80 units IM or SubQ Q24-72H; Consider tapering down and increasing the injection interval to gradually discontinue after prolonged treatment.

Background for indications

Infantile spasms (West Syndrome)
This is a rare age-specific epileptic disorder of infancy and early childhood (incidence of 0.015–0.02% in children 10 years of age and younger) of which 90% of cases are diagnosed in the infant's first year.[6,18] It has three main characteristics: infantile spasms, mental retardation, and hypsarrhythmia (detected by electroencephalogram/EEG).[6,23] "Even though 90% of children are free of spasms by five years of age, 50% of them continue to experience a form of seizure disorder."[6,24] These patients have a poor prognosis for normal mental development, and psychomotor retardation is frequently found at follow-up.[6,23]

According to a recent Cochrane review, many different treatments are currently used worldwide in the treatment of this disorder and most treatments are associated with significant adverse effects.[23] Major options for treatment include corticotropin (ACTH) and vigabatrin.[18] The mechanism of action of corticotropin in the treatment of infantile spasms is unknown.[2,25] Pyridoxine is often used as first line treatment in Japan (without randomized controlled trial evidence).[18] Gettig in a 2009 review of H.P. Acthar Gel and Cosyntropin reports that the use of ACTH in infantile spasms is not easily dismissed because practice guidelines and reviews support its use.[6,24,26-29]

Multiple Sclerosis (MS)
MS is an autoimmune disease. Demyelinating diseases are neurological disorders defined by the destruction of central nervous system (CNS) tissue and are typically immune-mediated conditions.[30,31] MS is the most common demyelinating disorder and is characterized by inflammation, demyelination, scarring, and neuronal loss.[30,31] Patients with MS can exhibit benign illness to a debilitating disease resulting in significant changes to one's lifestyle.[30,31] Multiple sclerosis affects nearly 400,000 individuals in the United States and 2.5 million individuals worldwide.[32-34] The average estimated lifetime cost of illness for a patient with MS is estimated to be $1.2 million.[32-35] Prevalence is higher in women than men and the disease is usually diagnosed between the ages of 20 and 50 years.[32,33,35]

The cause of multiple sclerosis is not known.[30,31] Both genetic (race and gender) and environmental factors (geographical location, exposure to the sun, birth month) are linked to the disease.[36-38] Immunology also plays a role; MS is thought to be an auto-immune disease mediated by T-cells that compromise the blood brain barrier and allow inflammatory mediators to enter and attack the CNS. Diagnosis of MS is based on clinical symptoms in combination with evidence of lesions on magnetic resonance imaging (MRI). Symptoms vary depending on the location and severity of the CNS lesions and may include sensory loss, optic neuritis, weakness, parasthesias, ataxia, tremor, fatigue, cognitive changes, and bladder dysfunction.[30,31]

Multiple sclerosis (MS) is a chronic disease that can progress intermittently or continuously and is divided into four disease courses: relapsing-remitting multiple sclerosis (RRMS), primary-progressive multiple sclerosis (PPMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis (PRMS).[30,31] Relapsing-remitting multiple sclerosis is the most common form of MS (85%) and is characterized by exacerbations of neurological dysfunction followed by remissions.[6,39] RRMS may eventually

develop into secondary progressive multiple sclerosis which is characterized by a neurologic deterioration with or without relapses. Primary progressive multiple sclerosis occurs in 10-15% of patients with MS and is characterized by disease progression with some minor improvements and without any exacerbations.[38,40] Progressive relapsing multiple sclerosis affects less than 5% of patients and is characterized by disease progression with acute relapses. Most medications used in the treatment of MS are indicated in the treatment of RRMS or SPMS; there are currently no medications labeled for use in PPMS.[30,31]

Treatment of MS varies depending on the clinical subset of MS present and individual patient characteristics.[30,31,33,35] In general, treatment may include disease modifying agents in combination with symptomatic treatment.[30,31] Symptomatic treatments include glucocorticoid therapy, benzodiazepines, muscle relaxants, anticonvulsants, antidepressants, and medications used to treat urinary disorders.[30,31] Currently, no curative medication therapies are available in the treatment of MS.[33,35] Disease-modifying agents provide symptomatic relief and reduced disease progression.

The mechanism of corticosteroids in MS is thought to be related to the reduction of inflammation in the brain and the spinal cord; "reduce edema in the demyelinated area of nerve fibers, induce apoptosis of mature lymphocytes, and restore the blood brain barrier."[6,41] Gettig in the review of H.P. Acthar Gel and Cosyntropin mentioned earlier reports that high-potency corticosteroids have become the standard of therapy for MS exacerbations.[6] ACTH's role in the treatment of MS is to stimulate corticosteroid production, and Gettig reports that this role has been diminishing because it "has been replaced by high-potency corticosteroids because of their comparable, if not greater, effectiveness."[6] Corticosteroids should only be used in exacerbations of MS and not long-term because of the well-known potentially serious adverse effects i.e. hypothalamic-pituitary-adrenal axis (HPA) suppression, osteoporosis, cataracts, and psychosis.[6]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease (unknown cause).[42] When an immune system mistakenly attacks its own body's tissues, it results in inflammation such as in RA. It typically affects the small joints in your hands and feet, but it could also affect other organs such as the skin, eyes, lungs, and blood vessels.[43] In RA, joint cartilage is affected, which results in painful swelling, usually affecting bilaterally.[42,43] Over time, this results in bone erosion and joint deformity. Early diagnosis and prompt treatment is important to reduce the damage caused by the disease.[43,44] Symptoms of RA include joint pain, stiffness, and fatigue and progression to nodules under the skin (usually a sign of more severe disease), numbness, tingling or burning in the hands and feet. Other symptoms of RA include pleurisy, Sjogren syndrome, ocular burning itching and discharge, and insomnia.[42]

The onset of RA is typically after the age of 40 (generally between the ages of 30 and 50 years), but it could develop at any age.[43-45] RA is more common in women and older adults and affects about 1.3-1.5 million people in the United States.[46-48]

There is no cure for RA and it usually requires lifelong treatment, with the goal of remission or slowed disease progression.[42,45] Treatment focuses on controlling symptoms by reducing inflammation by blocking the production or activity of immune cells and their products, to slow disease progression and prevent joint damage.[43,44,49] Treatment includes medications, physical therapy, exercise, education, and in some cases, surgery.[42] Pharmacological treatment options include non-steroidal anti-inflammatory medications (NSAIDs) such as aspirin, ibuprofen, naproxen, or celecoxib (COX-2 inhibitors); corticosteroids; conventional disease modifying antirheumatic drugs (DMARDs); biologic DMARDs, and a new oral non-biologic DMARD, tofacitinib.[49] Conventional DMARDs include methotrexate (the most widely used DMARD), azathioprine, leflunomide, hydroxychloroquine, minocycline (not FDA approved for RA) or sulfasalazine.[49] "NSAIDs and corticosteroids are widely prescribed, but these drugs alone do not prevent disease progression."[49] Conventional and biologic DMARDs may be used alone or in combination with anti-inflammatory drugs.[49]

Nephrotic syndrome

Nephrotic syndrome is the result of damage to the glomeruli due to diseases such as those affecting the kidneys focal segmental glomerulosclerosis (FSGS), membranous nephropathy (primary causes of nephrotic syndrome) or systemic diseases such as diabetes or lupus (secondary causes of nephrotic syndrome).[50] The damaged glomeruli allows protein and albumin to leak into the urine (proteinuria: ≥3 grams/24-hour period which is 20 times the amount that healthy glomeruli allow); hypoalbumina: low blood levels).[50] This results in edema (albumin draws extra fluid from the body into the bloodstream so low levels in the blood inhibit this), and hyperlipidemia (due to increased synthesis of low and very low-density lipoproteins in the liver).[50,51] Fluid accumulates in interstitial tissues causing puffiness around the eyes, leg edema, pleural effusion/ pulmonary edema, ascites, or anasarca (generalized edema).[51] The loss of different proteins can lead to a variety of complications such as thrombophilia and thrombosis (antithrombin III loss), increased risk of infection (immunoglobulin loss), hypothyroidism, anemia (transferrin loss), coronary artery disease, hypertension, and acute kidney injury.[50,51] Other potential symptoms include weight gain, fatigue, foamy urine (due to lowering of the surface tension by the severe proteinuria), loss of appetite, dyspnea (due to pleural effusion or ascites/diaphragmatic compression).[50,51]

Treatment aims at addressing the underlying cause as well as treating the symptoms and the effects or complications of the syndrome e.g. hypertension, edema, and cholesterol management. Corticosteroids are used in the management of nephrotic syndrome in children (reduced mortality rate around 3%) and adults.[52,53] It is reported that children can often die of infections if left untreated, and that most children with nephrotic syndrome respond to corticosteroid drugs (prednisone, prednisolone), but they usually have repeat episodes.[52] It is important to consider that patients with nephrotic syndrome are at increased risk of infections as mentioned earlier, and medications to treat nephrotic syndrome can also increase the risk of these infections. Other well recognized potentially serious adverse effects of corticosteroids include obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and behavioral disturbances.[52]

Systemic lupus erythematosus (SLE)

"SLE is a chronic systemic autoimmune disease characterized by a relapsing-remitting course. When a mild/moderate flare occurs, treatment with corticosteroids is often instituted."[54]

Erythema multiforme & Stevens-Johnson Syndrome

Erythema multiforme is a hypersensitivity reaction that could occur as an allergic reaction to medications (e.g. penicillins, sulfonamides, barbiturates, or phenytoin), or with infections (e.g. herpes simplex or mycoplasma), or illness.[55] Erythema multiforme minor is not very serious, but erythema multiforme major is more severe and a characteristic of Stevens-Johnson syndrome (usually an allergic drug reaction).[55] Severe forms are difficult to treat and complications include cellulitis, sepsis, shock (due to loss of body fluids), myocarditis, pneumonitis, nephritis, hepatitis, skin damaging and scarring.[55] Treatments are aimed at the cause of the condition, treating symptoms and preventing infection.[55] Treatment may include corticosteroids to control inflammation if symptoms are severe.[55]

Serum sickness

This is a "prototypic example of the Gell and Coombs "type III" or immune complex-mediated hypersensitivity disease".[56] Serum sickness occurs when immunized with serum proteins (nonhuman) and immune complexes are formed (refer to table 2 below).[56] However, it has been used to describe other related syndromes (serum-sickness-like reactions) such as rash, arthritis, and fever that occurred as a result of a drug allergy (most commonly caused by antibiotics) or infection.[56] Antibodies are directed at antigen(s) so antigen-antibody or immune complexes form which are usually cleared by the mononuclear phagocyte system, but excess immune complexes may form in the circulation and deposit in tissues or form directly in the involved tissues if the system is not functioning well or is overloaded.[56] Joints are affected possibly because the synovial

endothelium is fenestrated (with more permeable pores or slits) and thus is more accessible to proteins and protein complexes.[56] The deposited immune complexes in these tissues trigger an inflammatory response.[56] The most common symptoms of serum sickness are rash, fever, malaise, and polyarthralgias or polyarthritis.[56] Usually it resolves within a few weeks of discontinuing the drug.[56] However, subsequent exposure to the antigen may cause a more rapid reaction (instead of taking 7-14 days it can occur within 12-36 hours) and typically it is more acute and severe.[56] Acute anaphylaxis is also possible (if IgG or IgE antibodies are still present from a previous exposure). Diagnosis is based on history (exposure) and characteristic pattern of physical and laboratory findings.[56] Discontinuation of the responsible agent will usually resolve the reaction (if symptoms are mild), but symptomatic treatments may be used such as antihistamines (for pruritis), nonsteroidal anti-inflammatory agents and analgesics (for low-grade fever and arthralgias).[56] Glucocorticoids are used (short-term) if symptoms are more severe such as higher fever (eg, temperature >38.5ºC), more severe arthritis and arthralgias, or extensive rashes. It is important to avoid the responsible drug in the future.[56]

Table 2 - Heterologous proteins causing serum sickness (adapted from UpToDate)[57]

Microbial anti-toxins	**Immunizations**
Equine anti-diphtheria	Rabies antigens (human diploid cell rabies vaccine)
Equine or ovine anti-rabies	Pneumococcal vaccine (?)
Equine anti-botulinum toxin	Hemophilus B vaccine (?)
Immune and cell metabolism modulators	**Tissue culture protein**
Equine or rabbit anti-thymocyte globulin	Bovine serum albumin (tissue culture media) (?)
Murine anti-CD3 (OKT3)	**Therapeutic fibrinolytic proteins**
Rituximab (murine/human chimeric anti-CD20)	Streptokinase
Infliximab (murine/human chimeric anti-TNF-alpha)	**Insect protein**
Adalimumab (recombinant human anti-TNF-alpha) (?)	Mosquito salivary proteins (?)
Alemtuzumab (humanized anti-CD52) (?)	Insect stings
Omalizumab (humanized anti-IgE) (?)	**Venom anti-toxins**
Natalizumab (humanized anti-alpha-4 integrin) (?)	Equine anti-spider venom (*Lactrodectus*) anti-venin
Dalotuzumab (anti-insulin growth factor 1) (?)	Equine, rabbit, ovine anti-snake venom (*Crotalidae* [pit vipers, rattlesnakes] anti-venin, *Micrurus* [coral snake] anti-venin)

(?): case reports; causality is unclear.
TNF: tumor necrosis factor.

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown etiology that is characterized by inflammation and granulomas (immune cell clusters) and it typically affects young adults. It usually starts in the lungs (pulmonary reticular opacities), skin (and/or joint or eye lesions), and/or lymph nodes (bilateral hilar adenopathy).[58,59] Signs or symptoms range from none or mild to serious complications depending on the organs affected.[59] "Sarcoidosis most frequently involves the lung, but up to 30 percent of patients present with extrathoracic manifestations of sarcoidosis."[58] Lofgren's syndrome is typically seen in some patients and this classic set of signs and symptoms could include fever, enlarged lymph nodes, arthritis (usually in the ankles), and/or erythema nodosum (red or reddish-purple bumps on your ankles and shins).[58] "Sarcoidosis is more likely among some ethnic groups (including African-Americans and African-Caribbeans), for whom the disease has worse outcomes."[60] According to UpToDate, "most patients with pulmonary sarcoidosis do not require treatment, as a high proportion have asymptomatic, nonprogressive disease or experience a spontaneous remission."[61] "For those with more severe lung involvement, therapy of sarcoidosis is aimed at reducing the burden of granulomatous inflammation and preventing the development of irreversible end-organ damage (eg, honeycombing and fibrotic lung disease), while avoiding excess toxicity from medications. Unfortunately, no specific treatment for sarcoidosis exists, as the cause of sarcoidosis is unknown."[61] Oral glucocorticoids have been the most commonly used agents for the relief of symptoms and control of

potentially disabling respiratory impairment from pulmonary sarcoidosis, but the exact mechanism of action of glucocorticoids in the treatment of sarcoidosis is unknown.[61]

Other uses

Corticotropin can be used to treat medical conditions where systemic corticosteroid therapy is indicated, because it stimulates corticosteroid release. In 2009, Gettig et al. reported that the product label stated that H.P. Acthar Gel has limited therapeutic values in those conditions responsive to corticosteroid therapy; "in such cases, corticosteroid therapy is considered to be the treatment of choice."[6,62] A stepwise approach was therefore suggested where corticosteroids are used first, and ACTH could be tried if patients do not respond to corticosteroids.[6] In fact, MS exacerbations was used as an example for this stepwise approach.[6] The MS Society website contains the following information for H.P. Acthar® (Repository Corticotropin) (U.S.): "ACTH was approved in 1978 by the U.S. Food and Drug Administration (FDA) as a short-term treatment for acute exacerbations of MS. According to its FDA labeling, corticosteroids (such as methylprednisolone or dexamethasone) are considered the treatment of choice for acute exacerbations. ACTH is available for those individuals who cannot tolerate the side effects of high dose corticosteroids; have been treated unsuccessfully with corticosteroids in the past; prefer the convenience of self-injection; or have difficulty receiving intravenous medication because of poor venous access. ACTH is included in the updated list of medications covered under the Medicare Replacement Drug Demonstration Project."[10] However, the product label statement mentioned above does not appear to be in the current product label.[9]

Off-label use

Several off-label uses are listed in Micromedex[2]:

- **Acquired epileptic aphasia**, which is based on a single case of Landau-Kleffner syndrome that was successfully treated with corticotropin. "Landau-Kleffner syndrome is a rare syndrome of childhood characterized by an acquired aphasia associated with abnormal electroencephalogram, with about two-thirds of cases also exhibiting seizure activity."[2,63] It is reported that "corticotropin 80 units/day was given for 3 months; after 3 weeks of treatment electroencephalographic results improved and after 6 months speech returned. When after 2 years the aphasia recurred corticotropin was immediately reinstituted; within a few weeks speech and electroencephalogram returned to normal."[2,63]
- **Diagnosis of adrenal insufficiency.** However, cosyntropin is preferred for diagnosis.[2] Gettig et al. report that the cosyntropin test takes 30-60 minutes compared to an overnight wait that is required for the ACTH test.[6] Also, an allergic response is possibly less likely with cosyntropin.[6] "Cosyntropin has less immunogenic activity than ACTH because the amino acid sequence having most of the antigenic activity of ACTH, i.e., amino acids 25–39, is not present in cosyntropin."[16]
- **Alveolar hypoventilation** based on a small, placebo-controlled, single-blind study (n=12). It was found that IV administration of human corticotropin-releasing hormone, as well as of thyrotropin-releasing hormone, increases respiration and reduces the carbon dioxide threshold.[2,64]
- **Lipid metabolism disorder** based on limited evidence in hemodialysis patients where it was found that ACTH lowered lipoprotein(a) and low-density-lipoprotein levels.
- **Gout** based on a 2001 review that evaluated the literature available (MEDLINE 1966-August 2000) regarding the safety and efficacy of corticotropin for acute gout.[2,65]
  - ⇨ "3 studies using corticotropin showed it to be effective in relieving pain".[2]
  - ⇨ "In 2 of the studies, single intramuscular injections of corticotropin 40 mg brought pain relief in a significantly shorter time than did oral indomethacin 50 mg 3 or 4 times daily (8 vs 48 hours, p=0.003, in one study; 3 vs 24 hours, p less than 0.0001, in the other)."[2]
  - ⇨ "All studies had major weaknesses, such as lack of blinding, small sample size, or concomitant administration of other medications."[2]

The authors concluded that "Corticotropin alone or in combination with colchicine was more rapidly effective and associated with fewer adverse effects than indomethacin. This regimen may be considered an alternative, especially for patients with medical problems in which other regimens are contraindicated."[65]

- **Nicotine dependence** based on limited evidence. **"**Use based upon decreases in serum cortisol associated with nicotine withdrawal."[2] Limited evidence (clinical studies): refer to table 7 in appendix 2. McElhaney reports on the results from a family practice clinic of 15 patients where repository corticotropin injection (ACTH) was used as an adjunct to smoking cessation during the initial nicotine withdrawal period (the first 1 to 2 weeks of abstinence).[2,66]

Clinical Guidelines, Systematic Reviews and related evidence

H.P Acthar Gel compared to synthetic ACTH analogue: tetrocosactide (Depot available in Europe)
No head-to-head trials/evidence available.[5]

A. Infantile Spasms/West Syndrome

- Current guidelines support the use of ACTH as a first-line treatment option for infantile spasms.[67,68]
- Guidelines do not appear to support the use of any other agents over ACTH for infantile spasms, but suggest that corticosteroids or vigabatrin could be considered.
- According to systematic review evidence "The optimum treatment for infantile spasms has yet to be proven with confidence" (few well-designed RCTs and not many patients)."[23]
- Insufficient data for use of steroids (including ACTH) in treating childhood epilepsies: "clinicians using steroids in childhood epilepsies, other than for epileptic spasms, should take this into account before using these agents." [69]

Evidence below include information from a 2009 review followed by current guideline and systematic review information.

2009 Review by Gettig et al. stated the sources included in their paper generally agreed that:
ACTH appears to be as effective as, if not more effective than, other therapies for the short-term cessation of infantile spasms.[26-28] Note: Mackay is 2nd author in updated 2012 American Academy of Neurology and the Practice Committee of the Child Neurology Society Guidelines; Updated Cochrane (Hancock) available *Hancock et al.(meta-analysis)* ○ 12 studies were small (≤60 patients) ○ 2 trials ≥100 patients ○ Authors of meta-analysis of 14 trials (667 patients) indicated that methodology of trials were poor and were at high risk for biased results.[6] ○ "the authors concluded that hormonal treatment, which does not distinguish between corticosteroids and ACTH or cosyntropin, resolved infantile spasms faster and more often than vigabatrin and that differences in long-term outcomes between treatments could not be derived from the published evidence."[6] *Gettig's summary table of prospective comparative trials included the studies included in the meta-analysis mentioned above as well as 2 studies by Lux et al.[6,70,71]* ○ UK Multicentre-RCT (n=107) Comparing vigabatrin with prednisolong or tetracosatide at 14 days. "Conclusion: At 14 days, hormonal treatment might be more effective than vigabatrin for stopping infantile spasms and hypsarrhythmia; however, given the small number of patients, it is difficult to draw conclusions about the comparative efficacy of prednisolone and tetracosactide."[6,70] ○ UK Multicentre-RCT (n=107) comparing hormone treatment with vigabatrin. "Conclusion: Treatment of infantile spasms with hormone or vigabatrin appears to produce similar developmental outcomes and cessation of spasms at 14 months. Hormonal treatment may result in better developmental outcomes than vigabatrin in patients with an unknown cause of infantile spasms, but further research is warranted."[6,71]
ACTH appears to be as effective as, if not more effective than, other therapies for the short-term termination of hypsarrhythmia.[26-28]
The effect of ACTH on long-term developmental outcomes in patients with infantile spasms warrants further research.[24,26-28]
The preferred dose and duration of treatment of infantile spasms with ACTH cannot be determined from the available evidence.[26,27]
Additional data. Several points are worth noting:

Some of the less-well-designed and more poorly reported studies do not explicitly distinguish between ACTH and cosyntropin; it cannot be determined whether the study patients received natural or synthetic ACTH.[6]
Because some countries (e.g., Japan) do not have ready access to ACTH, cosyntropin is used interchangeably with ACTH.[72]
Some countries (e.g., the United Kingdom) advocate the use of vigabatrin (CPP-109, Catalyst) as a first-line therapy for infantile syndrome.[73] [18] Although vigabatrin is not commercially available in the U.S., it is in phase II trials and is being studied in cocaine and methamphetamine addiction.[74,75]"

Guidelines

Evidence-based guideline update: medical treatment of infantile spasms: report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. 2004 May 25 (revised 2012 Jun 12).[67]

"Are Other Forms of Corticosteroids as Effective as Adrenocorticotropic Hormone (ACTH) for Treatment of Infantile Spasms?
Data are insufficient regarding the equivalence of other corticosteroids to ACTH (Class III and IV evidence).
Recommendation: The evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms (Level U).

Are Low-Dose ACTH Regimens Effective for Short-term Treatment of Infantile Spasms?
A Class I study showed similar efficacy between low-dose (20–30 IU) and high-dose (150 IU/m2) natural ACTH, and a Class II study using the same low-dose natural ACTH showed clinical and electroencephalographic (EEG) response rates of >40%. The evidence suggests that low-dose ACTH is probably as effective as high-dose ACTH for short-term treatment of infantile spasms (Class I and II evidence).
Recommendation: Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).

Is ACTH More Effective Than Vigabatrin (VGB) for Short-term Treatment of Infantile Spasms?
Two Class III studies (1 from the 2004 parameter and a later study) demonstrated that ACTH is more effective than VGB for short-term treatment of children with infantile spasms (excluding those with tuberous sclerosis complex [TSC]). A small Class III study and a Class IV study found no difference in short-term outcome between ACTH and VGB.
Recommendation: ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).

What Other Agents Are as Effective as ACTH for Treatment of Infantile Spasms?
Data from previously reviewed and updated evidence are insufficient to determine whether valproic acid (VPA), vitamin B6, nitrazepam (NZP), levetiracetam (LEV), zonisamide (ZNS), topiramate (TPM), the ketogenic diet, sulthiame, or other novel therapies (e.g., intravenous immunoglobulin [IVIg], thyrotropin-releasing hormone [TRH]) are effective in the treatment of infantile spasms (Class III and IV evidence). A single Class III study showed better outcome for combination therapy with ACTH and magnesium sulfate (MgSO4).
Recommendation: The evidence is insufficient to recommend other therapies (VPA, vitamin B6, NZP, LEV, ZNS, TPM, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms (Level U).

Does Successful Early Treatment of Infantile Spasms Lead to Long-term Improvement of Neurodevelopmental Outcomes or Decreased Incidence of Epilepsy?
A Class II study showed that hormonal therapy (ACTH or prednisolone) relative to VGB therapy leads to better neurodevelopmental outcome in children with cryptogenic spasms. One previous Class III study and 1 newer Class II study showed that shorter lag time to treatment improves long-term cognitive outcomes.
Recommendations:
1. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome (Level C).
2. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be considered to improve long-term cognitive outcomes (Level C)."[67]

2010 United States consensus report (2010)[68]

"There was consensus in the ISWG that use of ACTH is effective as first-line therapy for IS. There was insufficient evidence to precisely define the optimum ACTH dose and duration of treatment for IS, although short duration was preferable (i.e., approximately 2 weeks followed by taper)."[68]

"The ISWG began with a discussion of the AAP/AAN/CNS consensus statement and reviewed literature (Mackay et al., 2004), with further discussion of the additional literature published since the practice parameter. Vigorous discussion and debate of the available evidence followed. Although the ISWG did not reach consensus on initial treatment dosage levels, there was strong consensus on the following conclusions:

1 The need for a broad clinical evaluation, including detailed clinical neurophysiology, is strongly recommended.
2 At this time, ACTH and VGB are the only drugs with proven efficacy to suppress clinical spasms and abolish the hypsarrhythmic EEG in a randomized clinical trial setting (Mackay et al., 2004) and thus remain first-line treatments.
3 Regardless of the chosen medication, timely assessment of treatment efficacy (i.e., 2 weeks for ACTH followed by taper; 2 weeks or less following dose titration for VGB) and, if indicated, prompt treatment modification, is strongly recommended as longer treatment trials (i.e., greater than 2 weeks for ACTH; greater than 3 months for VGB) are not likely to be effective and may come at the expense of serious adverse events.
4 Effective treatment for IS should produce both cessation of spasms and resolution of hypsarrhythmia on EEG and is an "all-or-none" response."[68]

⇨ There is a need for further research[68]

Epilepsies: diagnosis and management NICE guidelines [CG137] Published date: January 2012 [76]

"1.9.8 Pharmacological treatment of infantile spasms

First-line treatment in infants with infantile spasms

1.9.8.1 Discuss with, or refer to, a tertiary paediatric epilepsy specialist when an infant presents with infantile spasms. [new 2012]

1.9.8.2 Offer a steroid (prednisolone or tetracosactide* or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. Carefully consider the risk–benefit ratio when using vigabatrin or steroids. [new 2012]

1.9.8.3 Offer vigabatrin as first-line treatment to infants with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid (prednisolone or tetracosactide*). Carefully consider the risk–benefit ratio when using vigabatrin or steroids. [new 2012]

* At the time of publication (January 2012), this drug did not have UK marketing authorisation for this indication and/or population (see Appendix E in the original guideline document for details). Informed consent should be obtained and documented."

Infantile spasms are defined as: "A specific seizure type presenting in the first year of life, most commonly between 3 and 9 months. Spasms are brief axial movements lasting 0.2–2 seconds, most commonly flexor in nature, involving flexion of the trunk with extension of the upper and lower limbs. They are occasionally referred to as 'salaam seizures'."[76]

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. (2015)[77]

Epileptic spasms
Diagnosis and investigation

"Clinical suspicion remains the cornerstone of diagnosis of epileptic spasms

An EEG of sufficient length to capture wakefulness, sleep, and awakening is sufficient as the minimum standard level of care and is mandatory for the diagnosis and management of epileptic spasms.[78] However, there are insufficient data to support the exact type and duration of the EEG study. Twenty-four hour video-EEG recording has the best chance for detecting hypsarrhythmia and recording the spasms. As such prolonged video-EEG recording may be recommended as the optimal level of care in centers where the facility is available. In practice centers with capacity for prolonged studies often monitor suspected patients for 3–12 hours until enough data is collected to confirm the diagnosis. Common practice (level C evidence)

MRI of the brain should be performed in all children (level A evidence-based on data for all infantile epilepsies)

Genetic and metabolic studies should be performed in children with a high index of clinical suspicion for a genetic or metabolic disorder. However, there is insufficient evidence to recommend any specific tests in all infants with spasms (level U evidence)"[77]

Treatment and management

"ACTH is preferable in the short-term control of spasms[71] (level B evidence)

Oral steroids are probably effective in the short-term control of spasms[67] (level C evidence)

Data are insufficient to comment on the optimal preparation, dosage, and duration of treatment of steroids (level U evidence)

Low-dose ACTH may be considered as an alternative to high-dose ACTH for treatment of epileptic spasms (level B evidence)

Vigabatrin is possibly effective in the short-term control of spasms (level C evidence), especially in the case of tuberous sclerosis complex (level C evidence)

Treatment with ACTH/oral steroids may result in a better long-term neurodevelopmental outcome than treatment with vigabatrin in children with epileptic spasms due to unknown etiologies (level C evidence)

A shorter interval from the onset of spasms to treatment initiation may improve the long-term neurodevelopmental outcome, especially in cases where there is no identified etiology (level C evidence)"[77]

Systematic Review(s)

- ⇨ "The optimum treatment for infantile spasms has yet to be proven with confidence, in part because of the different aims of existing studies. However, some useful conclusions can be drawn from current evidence."[23] "More information and further research are needed to compare currently available therapies."[23]

The authors of a 2013 Cochrane review concluded "To date, few well-designed RCTs have considered the treatment of infantile spasms, and the numbers of patients enrolled have been small. In the majority, methodology has been poor, hence it is not clear which treatment is optimal in the treatment of this epilepsy syndrome. Hormonal treatment resolves spasms in more infants than vigabatrin, but this may or may not translate into better long-term outcomes.* If prednisolone or vigabatrin is used, high dosage is recommended. Vigabatrin may be the treatment of choice in tuberous sclerosis. Resolution of the EEG features may be important, but this has not been proven. Further research using large studies with robust methodology is required."[23]
* "one study suggested that hormonal treatment (prednisolone or tetracosactide) might improve long-term neurodevelopmental outcomes in infants and young children for whom no underlying cause for their infantile spasms has been identified."

Up to Date include limitations of the studies: "Lack of adherence to standardized case definitions and outcome measures is one problem with many studies. Another is that inclusion of a control group is critical, as the natural history of the disease is that clinical spasms subside and electroencephalogram patterns evolve without therapy, yet many clinicians would be reluctant not to treat as there is some observational data that delayed therapy may worsen prognosis. As a result, many questions still remain regarding the mechanism, optimal drug, dose, duration of therapy, and the importance of prompt initiation of treatment after the appearance of spasms."[18]

Epilepsy in children (other than epileptic spasms)

- ⇨ Insufficient data (There is a need for larger, well-designed studies)

In a recently published Cochrane systematic review (2015) Mehta et al. assessed the efficacy of steroids (including ACTH) compared to placebo or other antiepileptic drugs in children with epilepsy, excluding epileptic spasms, and concluded that no new evidence has been found for the efficacy of corticosteroids in treating childhood epilepsies. The original review included only one small study which included data from three out of five participants, and therefore no conclusions could be drawn regarding the role of corticosteroids in children with epilepsy. The authors state that "clinicians using steroids in childhood epilepsies, other than for epileptic spasms, should take this into account before using these agents." [69]

Clinical Studies (Product label)

The H,P. Acthar Gel product label only includes clinical evidence for infantile spasms (and not for the other indications) under Clinical Studies (included below).

"The effectiveness of H.P. Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2 week course of treatment with H.P. Acthar Gel (75 U/m2 intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to H.P. Acthar Gel as compared to 4 of 14 patients (28.6%) given prednisone (p<0.002). The 2-week treatment was followed by a 2-week period of taper. Nonresponders to the prednisone treatment were eligible to receive H.P. Acthar Gel treatment. Seven of 8 patients (87.5%) responded to H.P. Acthar Gel after not responding to prednisone. Similarly, the 2 nonresponder patients from the H.P. Acthar Gel treatment were eligible to receive treatment with prednisone. One of the 2 patients (50%) responded to the prednisone treatment after not responding to H.P. Acthar Gel.

A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m2 once daily for 3 weeks, n=30) of H.P. Acthar Gel with low-dose, short-duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Nonresponders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for cessation of spasms but not for the resolution of hypsarrhythmia."[9]

B. Multiple Sclerosis

- No guidelines were identified specifically mentioning corticotropin. Guidelines include steroids/glucocorticoids. The MS Society Bulletin includes ACTH as another option.
- Best to refer people with MS to an appropriate specialist or consult healthcare professional with expertise in MS ("not all relapses need treating with steroids"[79])
- Corticosteroids appear to be appropriate first-line treatment.
- Some evidence (systematic review) that corticosteroids or ACTH "are effective in the treatment of acute exacerbation, increasing the probability of ameliorating the episode and speeding up patient recovery."[41] "Indirect comparisons suggest a significantly greater effect of MP versus ACTH."[41]
- Insufficient evidence for corticosteroids on prevention of new exacerbations and long-term disability.[41]
- According to the product label, "Controlled clinical trials have shown H.P Acthar Gel to be effective in speeding resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease."[22] However, the product label only includes study information regarding infantile spasms under "Clinical studies".

Guidelines

Guideline on disease modifying therapies (February 2002; Current guideline. Reaffirmed October 17, 2003 and July 19, 2008.)[80]

"Glucocorticoids:

1. On the basis of several and generally consistent Class I and Class II studies, glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in patients with acute attacks of MS. It is appropriate, therefore, to consider for treatment with glucocorticoids any patient with an acute attack of MS (Type A recommendation).

2. There does not appear, however, to be any long-term functional benefit after the brief use of glucocorticoids in this clinical setting (Type B recommendation).

3. Currently, there is not compelling evidence to indicate that these clinical benefits are influenced by the route of glucocorticoid administration, the particular glucocorticoid prescribed, or the dosage of glucocorticoid, at least at the doses that have been studied to date (Type C recommendation).

4. On the basis of a single Class II study, it is considered possible that regular pulse glucocorticoids may be useful in the long-term management of patients with RRMS (Type C recommendation)"

National Multiple Sclerosis Society released a Clinical Bulletin in 2012[81]

"Treatment of Acute Exacerbations
Exacerbations (flares, flare-ups, relapses, attacks) of MS are caused by inflammation in the CNS that causes damage to the myelin and slows or blocks transmission of nerve impulses. A true exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. However, most exacerbations last from a few days to several weeks or even months. Exacerbations can be mild or severe enough to interfere with a person's ability to function at home and at work. Severe exacerbations are most commonly treated with intravenous, high-dose corticosteroids to reduce the inflammation, although comparable doses or oral steroids may be used (Frohman et al., 2007). Steroids decrease acute inflammation in the CNS, but have no long-term benefits.
Intravenous immune globulin (IVIG) and plasmapheresis are sometimes used to treat exacerbations when patients can't tolerate or don't respond to steroids.
Another option for the treatment of acute exacerbations is ACTH (H.P. Acthar Gel [repository corticotropin injection])."

Canadian Drug Expert Committee (CDEC) Recommendation for drug therapies for relapsing-remitting multiple sclerosis (2013).[82]
Not mentioned (steroids also not mentioned)

National Clinical Guideline Centre. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. 36 p. (Clinical guideline; no. 186).[79]

"Coordination of Care
Care for people with MS using a coordinated multidisciplinary approach. Involve professionals who can best meet the needs of the person with MS and who have expertise in managing MS including:

- Consultant neurologists
- MS nurses
- Physiotherapists and occupational therapists
- Speech and language therapists, psychologists, dietitians, social care and continence specialists
- General practitioners"

"Optic Neuritis and Neuromyelitis Optica
If a person has an episode of isolated optic neuritis, confirmed by an ophthalmologist, refer them to a consultant neurologist for further assessment.
Diagnosis of neuromyelitis optica should be made by an appropriate specialist based on established up-to-date criteria."

"Relapse and Exacerbation
Treating Acute Relapse of MS with Steroids
Develop local guidance and pathways for timely treatment of relapses of MS. Ensure follow-up is included in the guidance and pathway.
Non-specialists should discuss a person's diagnosis of relapse and whether to offer steroids with a healthcare professional with expertise in MS because not all relapses need treating with steroids."
Recognising a Relapse
Diagnose a relapse of MS if the person:

- Develops new symptoms or
- Has worsening of existing symptoms

And these last for more than 24 hours in the absence of infection or any other cause after a stable period of at least 1 month.
Before diagnosing a relapse of MS:

- Rule out infection – particularly urinary tract and respiratory infections and
- Discriminate between the relapse and fluctuations in disease or progression

Assess and offer treatment for relapses of MS, that affect the person's ability to perform their usual tasks, as early as possible and within 14 days of onset of symptoms.

Do not routinely diagnose a relapse of MS if symptoms are present for more than 3 months.

Treating a Relapse

Offer treatment for relapse of MS with oral methylprednisolone 0.5 g daily for 5 days.

Consider intravenous methylprednisolone 1 g daily for 3 to 5 days as an alternative for people with MS:

- In whom oral steroids have failed or not been tolerated or
- Who need admitting to hospital for a severe relapse or monitoring of medical or psychological conditions such as diabetes or depression

Do not prescribe steroids at lower doses than methylprednisolone 0.5 g daily for 5 days to treat an acute relapse of MS.

Do not give people with MS a supply of steroids to self-administer at home for future relapses.

Information About Treating a Relapse with Steroids

Discuss the benefits and risks of steroids with the person with MS, taking into account the effect of the relapse on the person's ability to perform their usual tasks and their wellbeing.

Explain the potential complications of high-dose steroids, for example temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes.

Give the person with MS and their family members or carers (as appropriate) information that they can take away about side effects of high-dose steroids in a format that is appropriate for them.

Ensure that the MS multidisciplinary team is told that the person is having a relapse, because relapse frequency may influence which disease-modifying therapies are chosen and whether they need to be changed.

Medical, Therapy and Social Care Needs at Time of Relapse or Exacerbation

Identify whether the person having a relapse of MS or their family members or carers have social care needs and if so refer them to social services for assessment.

Offer inpatient treatment to the person having a relapse of MS if their relapse is severe or if it is difficult to meet their medical and social care needs at home.

Explain that a relapse of MS may have short-term effects on cognitive function.

Identify whether the person with MS having a relapse or exacerbation needs additional symptom management or rehabilitation."

Implementation of the Guideline

Description of Implementation Strategy

"Treating Acute Relapse of MS with Steroids

Offer treatment for relapse of MS with oral methylprednisolone 0.5 g daily for 5 days."

"Potential Harms

- Even short courses of steroids are associated with adverse effects and these need to be balanced against the potential benefits. Oral steroids may present a significant risk of gastrointestinal symptoms. Other potential complications of high-dose steroids include temporary effects on mental health (such as depression, confusion and agitation) and worsening of blood glucose control in people with diabetes."

Systematic Review(s)

Citterio et al. reviewed the efficacy of corticosteroids or adrenocorticotrophic hormone (ACTH) versus no treatment (placebo) in decreasing disability in MS patients affected by acute relapse, and its effect on prevention of long-term morbidity.[41] Secondary objectives of their review included safety and efficacy of different types of drugs and different schedules of treatment.[41] This review included six studies (totaling 377 participants).[41] "The main results of this review show that corticosteroids (methylprednisolone (MP)) or ACTH favored recovery from acute exacerbation, increasing by more than 60% the probability of ameliorating the episode within the first five weeks of treatment. Clinical recovery was found to be accelerated and reduction of disability was assessed as a 1.5-point change in EDSS score during the first week of therapy. The quality of evidence was moderate. The drugs were well tolerated. No clear data on long-term effects were found. Evidence on the efficacy of different types or schedules of therapies was limited. Indirect comparisons suggest a significantly greater effect of MP versus ACTH. A short-term course (5 days) of MP seems to be more effective than long-term treatment (15 days). The interval between exacerbation onset and the start of treatment does not seem to influence the outcome. Overall, this review provides evidence to support the use of corticosteroids in treating relapses in people with MS. These agents are effective over the short term in improving symptoms, thus favoring recovery."[41]

C. Rheumatic Disorders

- No guidelines were identified specifically mentioning corticotropin.
- Sufficient evidence (systematic review) for short-term corticosteroid use in RA.[83]
- Disease progression (RA): Sufficient evidence (systematic review) that glucocorticoids have a 'disease modifying' effect in RA.[84]

Guidelines

2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications.[85,86]

- ⇨ Steroids were not considered.

NICE CG 153: Psoriasis: the assessment and management of psoriasis.[87]

"As soon as psoriatic arthritis is suspected, refer the person to a rheumatologist for assessment and advice about planning their care."

- ⇨ Systemic corticosteroid not considered

Management/Treatment considered include topical treatments (corticosteroid, Vitamin D analogues, Coal tar, and Dithranol), phototherapy (broad or narrow band ultraviolet B [UVB]), photochemotherapy (psoralen and local ultraviolet [PUVA]), and systemic therapy (Ciclosporin, Methotrexate, and Biological therapy

2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis.[88]

- ⇨ Steroids were not considered.

Systematic Review(s)

- ⇨ Sufficient evidence for short-term corticosteroid use[83]

Gøtzsche et al. concluded that "prednisolone in low doses (not exceeding 15 mg daily) may be used intermittently in patients with rheumatoid arthritis, particularly if the disease cannot be controlled by other means. The risk of harms needs to be considered, however, especially the risk of fractures and infections. Since prednisolone is highly effective, short-term placebo controlled trials studying the clinical effect of low-dose prednisolone or other oral corticosteroids are no longer necessary."[83]

- ⇨ Disease progression: Sufficient evidence that glucocorticoids have a 'disease modifying' effect in RA[84]

Kirwan et al. reviewed glucocorticoid efficacy (low dose ≤10 mg prednisone daily) in inhibiting the progression of radiological damage in rheumatoid arthritis, and found high quality evidence that glucocorticoids given in addition to standard therapy can substantially reduce the rate of erosion progression in rheumatoid arthritis, but remains concern about potential long-term adverse reactions to glucocorticoid therapy, such as increased cardiovascular risk or osteoporosis and requires further research.[84]

Ankylosing spondylitis

- ⇨ No relevant systematic reviews or trials identified in the Cochrane Library regarding corticotropin or corticosteroids/glucocorticoids.

D. Gout

- Based on current guidelines, corticotropin is recommended as an alternative to intraarticular corticosteroid injection or IV/IM methylprednisolone for acute gout in patients unable to take oral medications (to relieve the signs and symptoms of acute gout).[8,89]

Guidelines

2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis.[89,90]

Summary
Treatment of an acute gout attack if patient is not taking anything by mouth (NPO):
- ACTH subQ is recommended as an alternative to intraarticular corticosteroid injection or IV/IM methylprednisolone

More information
"Systemic and Intraarticular Corticosteroids and Adrenocorticotropic Hormone (ACTH)
When selecting corticosteroids as the initial therapy, the TFP recommended to first consider the number of joints with active arthritis. For involvement of 1 or 2 joints, the TFP recommended the use of oral corticosteroids (evidence B); the TFP additionally recommended the option of intraarticular corticosteroids for acute gout of 1 or 2 large joints (evidence B) (see Figure 3C in the original guideline document). For intraarticular corticosteroid therapy in acute gouty arthritis, it was recommended that dosing be based on the size of the involved joint(s), and that this modality could be used in combination (see Table 1 in the original guideline document) with oral corticosteroids, NSAIDs, or colchicine (evidence B). Specific doses for intraarticular corticosteroid therapy in specific joints were not considered during TFP voting.
Where intraarticular joint injection is impractical (e.g., polyarticular joint involvement, patient preference, or injection of the involved joint site is not in the scope of the provider's usual practice), the TFP recommended oral corticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation (evidence A), or alternately, 2–5 days at the full dose, followed by tapering for 7–10 days, and then discontinuation (evidence C). Acknowledging current prevalence of usage, the TFP recommended, as an appropriate option according to provider and patient preference, the use of an oral methylprednisolone dose pack for initial treatment of an acute attack of gout (evidence C).
The TFP also recommended, as appropriate in each case scenario, an alternative regimen of intramuscular single-dose (60 mg) triamcinolone acetonide, followed by oral prednisone or prednisolone (evidence C). However, there was no consensus by the TFP on the use of intramuscular triamcinolone acetonide as monotherapy. Last, the TFP vote also did not reach a consensus on use of ACTH (evidence A) for acute gout in patients able to take medications orally, but did consider ACTH in separate voting, as described below, for patients unable to take oral anti-inflammatory medications."

"Case Scenarios for the Nothing by Mouth (NPO) Patient
Acute gout attacks are common in the in-hospital setting, where patients may be NPO due to different surgical and medical conditions. In such a scenario, the TFP recommended intraarticular injection of corticosteroids for involvement of 1 or 2 joints (with the dose depending on the size of the joint; evidence B) (see Figure 4 in the original guideline document). The TFP also recommended, as appropriate options, intravenous or intramuscular methylprednisolone at an initial dose at 0.5–2.0 mg/kg (evidence B).
The TFP also recommended, as an appropriate alternative for the NPO patient, subcutaneous synthetic ACTH at an initial dose of 25–40 IU (evidence A), with repeat doses as clinically indicated (for either ACTH or intravenous steroid regimens). There was no voting by the TFP on specific follow-up ACTH or an intravenous steroid dosing regimen, given a lack of evidence. In the scenario of the NPO patient with acute gout, there was no consensus on the use of intramuscular ketorolac or intramuscular triamcinolone acetonide monotherapy. Biologic IL-1 inhibition therapy remains an FDA-unapproved modality for NPO patients, without specific past evaluation in this population."

Spanish Society of Rheumatology: Clinical practice guidelines for management of gout. (2013)[91]

"Gout and Kidney Failure
Treatment of Acute Attacks
Colchicine
Recommendation 16: In patients with chronic kidney disease (CKD), the use of oral colchicine can be assessed to reduce the severity of an acute attack, following Summary of Product Characteristics (SmPC) specifications (LE 1b; GR A).
Recommendation 17: In patients with CKD, consider discontinuing statins while using colchicine (LE 3a; GR B).

Corticosteroids
Recommendation 18: In cases of CKD and diabetes, a therapeutic option for the treatment of acute gout may be colchicine rather than non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (LE 3a; GR B).
Corticotropin (Adrenocorticotropic Hormone [ACTH])
Recommendation 19: In case of CKD, note that corticotropin has similar indications and efficacy to corticosteroids in the treatment of acute gout attacks (LE 1b; GR A).
"Corticotropin (Adrenocorticotropic Hormone [ACTH])"

Kidney Transplant
"Treatment of Acute Inflammation Episodes
Recommendation 33: If it is necessary to use colchicine in patients with kidney transplant and cyclosporine A, it is recommended to reduce the dose of colchicine to one-third in acute episodes and to one-fourth in prophylaxis (LE 2b; GR B).
Recommendation 34: In kidney transplant patients corticosteroids may be a therapeutic option in the treatment of acute attacks (LE 3b; GR B).
Recommendation 35: In patients with kidney transplant, corticotropin is a potential therapeutic alternative for the treatment of acute attacks (LE 4; GR C)."

Systematic Review(s)

Acute gout

- ⇨ Inconclusive evidence

Janssens HJ et al. (2008)[92] focused on corticosteroids: "the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, NSAIDs, colchicine, other active drugs, other therapies, or no therapy."

Intra-articular injections

- ⇨ Insufficient evidence / Intra-articular glucocorticoids possibly in people when NSAIDs or colchicine are contraindicated

According to Wechalekar MD et al. evidence suggests **intra-articular glucocorticoids** may be a safe and effective treatment in **osteoarthritis and rheumatoid arthritis.**[93] "Although intra-articular glucocorticoids are a commonly used intervention in the treatment of acute gout, there is little evidence to support their safety and efficacy in this setting."[93] The authors of this review did not identify any RCTs that evaluated the efficacy and safety of intra-articular glucocorticoids for **acute gout**.[93] However, they state that evidence in osteoarthritis and rheumatoid arthritis may be generalizable to people with acute gout, especially in people when non-steroidal anti-inflammatory drugs or colchicine are contraindicated.[93] Note that the authors excluded two studies identified; an open single arm trial[94], and a case series[95]. The authors discussed the evidence for osteoarthritis and it is important to note that the Cochrane review that they referred to has recently been updated.[96,97] Based on current evidence, the authors concluded "Whether there are clinically important benefits of intra-articular corticosteroids after one to six weeks remains unclear in view of the overall quality of the evidence, considerable heterogeneity between trials, and evidence of small-study effects. A single trial included in this review described adequate measures to minimise biases and did not find any benefit of intra-articular corticosteroids."[97]

E. Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)

- ➢ Limited evidence

Guidelines

No relevant guidelines were identified apart from the guidelines covered under Edematous State regarding nephritis.

Systematic Review(s)

Collagen Diseases – Systemic lupus Erythematosus
No systematic reviews identified in the Cochrane Library regarding corticotropin or corticosteroids/glucocorticoids.

Clinical Trial(s)

Danowski et al. report that when a mild/moderate flare occurs, a triamcinolone injection or a short-term boost of oral prednisone or methylprednisolone can be given, and they investigated in a randomized trial (50 patients) whether triamcinolone (100 mg IM) is superior to oral corticosteroids o(ral methylprednisolone with rapid tapering; medrol dose-pack) for mild/moderate flare in patients with lupus. The authors concluded that "The triamcinolone and oral methylprednisolone groups did equally well. Triamcinolone may lead to a more rapid response than the oral methylprednisolone (69.5% vs 41.6% with some improvement at day one)."[54]

In a recently published conference abstract, Furie et al. report the results of an 8 week double-blind randomized placebo-controlled pilot study (38 subjects) that assessed clinical efficacy of Acthar in patients with persistently active SLE despite moderate dose corticosteroids.[98] The authors state that the data suggest that Acthar reduced disease activity in patients requiring corticosteroids for persistently active SLE, with improvements occurring within 8 weeks of treatment initiation.[98]

It was reported in a conference abstract that H.P. Acthar Gel demonstrated efficacy in patients with dermatomyositis refractory to treatment.[99]

F. Dermatologic Diseases: Severe erythema multiforme, Stevens-Johnson syndrome

- Refer patients with severe reactions

Guidelines

National Clinical Guideline Centre. Drug allergy: diagnosis and management of drug allergy in adults, children and young people. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 36 p. (Clinical guideline; no. 183).[100]

This set of guidelines include boxes as a guide when deciding to suspect drug allergy (when taking a history and undertaking a clinical examination). Stevens-Johnson syndrome is in the "Non-immediate Reactions with Systemic Involvement" box (excerpt from guidelines):

Signs and Allergic Patterns of Suspected Drug Allergy with Timing of Onset*

Toxic epidermal necrolysis or **Stevens–Johnson syndrome** characterised by: Painful rash and fever (often early signs) Mucosal or cutaneous erosions Vesicles, blistering or epidermal detachment Red purpuric macules or **erythema multiforme**	Onset usually 7–14 days after first drug exposure or within 3 days of second exposure

It is recommended to refer people to a specialist drug allergy service if they have had "a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome, toxic epidermal necrolysis)."

G. Allergic States: Serum sickness

- No evidence for corticotropin identified
- Limited evidence for glucocorticoids

Guidelines

No relevant guidelines were identified. UpToDate also report that no evidence-based guidelines or controlled trials upon which to base therapy recommendations exist.[56]

UpToDate:
The author state that the recommended treatment approach is based upon experience and case reports and series.[101-105] Based on a retrospective chart review of the management of children presenting with reactions to cefaclor by emergency department pediatrician, the most common treatment for serum sickness-like reactions was discontinuation of the culprit drug, combined with the prescription of both antihistamines and glucocorticoids."[56,104]
Their recommendations of glucocorticoid therapy is as follows (based upon case reports and small observational series):

- "Patients with higher fever (eg, temperature >38.5ºC), more severe arthritis and arthralgias, or more extensive rashes, including extensive vasculitic rashes, may be treated with short courses of glucocorticoids." "These agents are usually administered orally (eg, prednisone at 0.5 to 1 mg/kg per day)[106-108]. Sometimes even higher doses are used."
- "Occasionally, patients who are very uncomfortable or who appear acutely ill may be treated with intravenous methylprednisolone in the range of 1 to 2 mg/kg per day in one or two divided doses[102,109]."
- "Glucocorticoids can frequently be rapidly tapered, with the total duration of therapy less than one week."[56]

H. Ophthalmic Diseases (Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis; iritis, iridocyclitis, diffuse posterioir uveitis and choroiditis, optic neuritis, chorioretinitis; anterior segment inflammation)

- Refer patients with serious ophthalmic conditions to specialist in eye disease

Guidelines

Refer to MS NICE guidelines (heading "Optic Neuritis and Neuromyelitis Optica"). No other relevant guidelines were identified.
There are many different types and classes of eye diseases, allergic and inflammatory processes involving the eye, and eye infections and the Acthar product label states "severe". Therefore, optimal management of patients with serious ophthalmic conditions or not responsive to topical treatment necessitates consultation with an ophthalmologist or other specialist in eye disease. Up to Date for example states that oral glucocorticoids are frequently recommended for patients with uveitis that is resistant to topical therapy, and

some types of uveitis such as posterior or intermediate uveitis and panuveitis are generally not responsive to topical treatment. Initial management in these cases usually includes observation, as well as periocular and, occasionally, intraocular glucocorticoid injections.[110]

I. **Respiratory Diseases:** Symptomatic Sarcoidosis

- Lack of evidence

Guidelines

No relevant guidelines were identified. Sadek et al. in a 2013 review also report that there are no published clinical consensus guidelines or systematic evaluation supporting the use of corticosteroids for the treatment of cardiac sarcoidosis.[111]

Systematic Review(s)

- Lack of evidence for ACTH
- Lack of evidence for corticosteroids

No systematic reviews were identified for corticotropin in sarcoidosis. It is difficult to assess the benefits of glucocorticoid therapy in the treatment of sarcoidosis because patients with sarcoidosis undergo spontaneous remission or have a benign clinical course so it is difficult to know whether response to therapy is a treatment effect or the natural course of that patient's disease.[61] Also: "There is no easy way to assess disease activity or severity, and symptoms may be discordant with results of pulmonary function testing and chest imaging, which makes it difficult to interpret the results of clinical studies or the response to therapy in an individual patient. There is a concern that early administration of systemic glucocorticoid therapy may actually increase the likelihood that the patient will develop relapsing disease, rather than a sustained remission. Glucocorticoids have substantial adverse effects, particularly during long-term therapy."[61]

Paramothayan et al. (2006 Cochrane Systematic Review) reviewed the benefit of corticosteroids (oral or inhaled) in the treatment of pulmonary sarcoidosis and found that oral steroids improved the chest X-ray and a global score of CXR, symptoms and spirometry over 3-24 month (short-term benefit), but there is little evidence of an improvement in lung function, and limited data on long-term disease progression.[60] "Oral steroids may be of benefit for patients with Stage 2 and 3 disease with moderate to severe or progressive symptoms or CXR changes."[60]

Sadek et al. (2013 "Other Review" in Cochrane Library) reviewed the published data on corticosteroid treatment of cardiac sarcoidosis.[111] The authors included 10 publications and reported that there were no randomized trials and all publications were of poor to fair quality, and that there is a need for large multicentre prospective registries and trials in this patient population.[111]

J. **Edematous State (to induce diuresis or remission of proteinuria in nephrotic syndrome** without uremia of the idiopathic type or that due to **lupus erythematosus**)

- According to Goldsmith et al. there has been a re-emergence of interest in adrenocorticotropic hormone (ACTH) in patients with resistant nephrotic syndrome.[5]
- Corticosteroids are recommended in current guidelines, but corticotropin is not mentioned.[112,113]
- No systematic review evidence for corticotropin
- The authors of a recently published small open-label phase 2 study of treatment with synthetic ACTH (tetracosactide hexacetaat) in high risk patients with membranous Nephropathy (ACTHiMeN) advise

against synthetic ACTH as standard treatment in membranous nephropathy, because it was less effective than cyclophosphamide and was associated with many adverse events.[114]

- In a retrospective case series (short follow-up) where ACTH was used as 2nd, 3rd or 4th line therapy in most patients (resistant nephrotic syndrome) it was found that it may be an option for resistant nephrotic syndrome.[115]

Guidelines

Please refer to appendix 3 for guideline information regarding corticosteroids.

- *American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis (2012)*[112]
- *KDIGO clinical practice guideline for glomerulonephritis(2012)*[113]

Systematic Review(s)

- ⇨ Lack of evidence for ACTH

Adults:

- ⇨ Potential benefits, but lack of high-quality evidence and well-recognized adverse effects for treatment regime involving corticosteroids.

Children:

- ⇨ Evidence supporting:
  1) Initial episode of steroid-sensitive nephrotic syndrome (SSNS): Prednisone for two or three months (no benefit of increasing the duration)
  2) Frequently relapsing nephrotic syndrome (FRNS): Daily prednisone given for five to seven days at the onset of an upper respiratory tract or viral infection
- ⇨ Appropriate second line agent in SSNS: Additional data needed but evidence that eight-week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone.
- ⇨ Lack of evidence in children for steroid-resistant nephrotic syndrome (SRNS) for efficacy of cyclosporin (some evidence) and other regimens including high dose steroids with cyclosporin.

A recently published systematic review evaluated the safety and efficacy of immunosuppressive treatments for adult patients with IMN and nephrotic syndrome.[53] The authors (Chen et al.)[53] reported that "a combined alkylating agent and corticosteroid regimen had short- and long-term benefits on adult IMN with nephrotic syndrome", but also that "Although a six-month course of alternating monthly cycles of corticosteroids and cyclophosphamide was recommended by the KDIGO Clinical Practice Guideline 2012 as the initial therapy for adult IMN with nephrotic syndrome, clinicians should inform their patients of the lack of high-quality evidence for these benefits as well as the well-recognised adverse effects of this therapy."[53] "Whether this combined therapy should be indicated in all adult patients at high risk of progression to ESKD or only restricted to those with deteriorating kidney function still remained unclear."[53]

Hahn et al. assessed the benefits and harms of different corticosteroid regimens in children with SSNS, and reviewed the benefits and harms of therapy in 1) children in their initial episode of SSNS, and 2) children who experience a relapsing course of SSNS.[52] The authors concluded (based on more recently published low risk of bias studies) that "there is no benefit of increasing the duration of prednisone beyond two or three months in the initial episode of SSNS" (no significant differences in the risk of relapse or the development of FRNS between prednisone given for three to six months compared with two or three months).[52] Also, "Based on four studies in children with frequently relapsing nephrotic syndrome, prednisone given for five to seven days at the onset of a viral infection reduces the risk of relapse."[52]

Pravitsitthikul et al. report that about 80% to 90% of children with steroid-sensitive nephrotic syndrome (SSNS) have relapses, and that of these children, around half relapse frequently, and are at risk of adverse effects from corticosteroids.[116] "Non-corticosteroid immunosuppressive medications are used to prolong periods of remission in these children; however, these medications have significant potential adverse effects. Currently, there is no consensus about the most appropriate second line agent in children who are steroid sensitive, but who continue to relapse."[116] In this updated Cochrane review, the authors therefore evaluated the benefits and harms of non-corticosteroid immunosuppressive medications in relapsing SSNS in children.[116]
The authors found that eight-week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone, and that there is some evidence that mycophenolate mofetil and rituximab are valuable additional medications for relapsing SSNS.[116] "We found that more studies are needed that compare different drug treatments to determine how these medicines should be used in children with nephrotic syndrome."[116]

Hodson et al. report that the majority of children who present with their first episode of nephrotic syndrome achieve remission with corticosteroid therapy, and that those who fail to respond may be treated with immunosuppressive agents (cyclophosphamide, calcineurin inhibitors: cyclosporin or tacrolimus, chlorambucil) or angiotensin-converting enzyme inhibitors (ACEi).[117] In this review the authors evaluated the benefits and harms of agents used in idiopathic steroid-resistant nephrotic syndrome (SRNS) in children to help determine optimal treatment combinations with the least toxicity.[117] The authors concluded that "Further adequately powered, well designed RCTs are needed to confirm the efficacy of cyclosporin and to evaluate other regimens for idiopathic SRNS including high dose steroids with cyclosporin."[117]

Clinical Trials (clinicaltrials.gov)

Synthetic ACTH
The authors of a recently published small open-label phase 2 study of treatment with synthetic ACTH (tetracosactide hexacetaat) in high risk patients with membranous Nephropathy (ACTHiMeN) found that synthetic ACTH is less effective than cyclophosphamide in inducing a remission in high risk patients with idiopathic membranous nephropathy.[114] They also reported that the use of synthetic ACTH was associated with many adverse events.[114] "Therefore, we advise against synthetic ACTH as standard treatment in membranous nephropathy."[114]

Repository Corticotropin (H.P. Acthar Gel)
The effect of Repository Corticotropin (ACTH) in the Treatment of Various Nephrotic Syndromes was evaluated in a small, open-label (non-randomised) phase 4 prospective study to determine whether it is as effective in reducing protein in the urine as seen in synthetic ACTH in Europe (synthetic ACTH/Synacthen Depot has been used in the treatment of Nephrotic Syndrome in Europe but is not available in the United States).[118] However, no study results have been posted on ClinicalTrials.gov for this study, no publication has been provided, and a corresponding publication was not identified through a Pubmed search.

Also refer to table 7 for information on an **observational study** (retrospective case series)(2011).[115] The authors reported that ACTH was used as 2nd, 3rd or 4th line therapy in most patients (resistant nephrotic syndrome) and concluded that ACTH may be an option for resistant nephrotic syndrome.[115]

Additional Evidence

The following Cochrane reviews regarding corticotropin were also identified in the Cochrane Library.

Post-dural puncture headache (PDPH)

- ⇨ Lack of evidence

In a recent Cochrane systematic review, Basurto et al. assessed the effectiveness and safety of drugs for treating PDPH (reported as the most common complication of lumbar puncture) in adults and children, and concluded that there is a lack of conclusive evidence for adrenocorticotropic hormone.[119]

Myasthenia Gravis

- ⇨ Lack of evidence

Refer to Schneider-Gold C, et al. (2005)[120] & Benatar M, et al. (2012)[121] in appendix 2.

As a potential chemoprotective agent to prevent or limit the neurotoxicity of cisplatin and related drugs

- ⇨ Lack of evidence

Refer to Benatar M, et al. (2014)[121] in appendix 2.

Clinicaltrials.gov was searched for trials regarding corticotropin or cosyntropin and identified 3 trials (all completed). Please refer to table 6 for copies of the published abstracts (where available).

Please refer to appendix 2 for abstracts of additional studies.

The US Institute for Clinical and Economic Review (ICER)

The ICER report provides analyses of long-term cost-effectiveness and the potential budget impact of an intervention and provides a value-based price benchmark for each intervention which reflects how much better it is at improving patient outcomes.[122] The California Technology Assessment Forum (CTAF) is a core program of ICER that "reviews objective evidence and holds public meetings to develop recommendations for how stakeholders can apply evidence to improve quality and value of care."[123] No search results were obtained for Acthar, corticotropin or ACTH on the ICER website.

Safety

It has been more than 60 years since ACTH was first approved so safety data is available. Corticotropin stimulates the release of endogenous corticosteroids, so corticosteroid effects and adverse effects should be considered with its use.

"Common adverse reactions for Acthar Gel are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain."[9] Adverse reactions in children under 2 include increased risk of infections, hypertension, irritability, Cushingoid symptoms, cardiac hypertrophy and weight gain.[9] Acthar has a Medication Guide.

Please refer to appendix 1 for information on contraindications and precautions.

Pregnancy & lactation: "Studies reporting the use of corticotropin in pregnancy have not demonstrated adverse fetal effects [Ref]. However, corticosteroids have been suspected of causing malformations. Because

corticotropin stimulates the release of endogenous corticosteroids, this relationship should be considered when prescribing the drug to women in their reproductive years."[124] "No reports describing the use of corticotropin during human lactation have been located. The use of this agent during breastfeeding probably is compatible."[124]

Formulation limitations: Corticotropin is only available as an injection given IM or SC, and individual responses to therapeutic corticotropin vary considerably and doses must be adjusted accordingly. "ACTH rapidly disappears from the circulation following its IV administration; in people the plasma half-life is about 15 minutes."[9] The product label states that the pharmacokinetics of H.P. Acthar Gel have not been adequately characterized.[9]

Prolonged duration of use:

- Cushing's Syndrome may occur after prolonged therapy (generally resolve after therapy is discontinued) so it is recommended to monitor for signs and symptoms such as deposition of adipose tissue (e.g. moon face, truncal obesity), cutaneous striae, easy bruisability, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.[9]
- Children: It may inhibit growth so the product label states that if use is necessary, it should be given intermittently with careful observation.[9]
- May decrease bone density so patients should be monitored for osteoporosis.[9]
- May cause adrenal Insufficiency after prolonged therapy when medication is withdrawn/discontinued (due to hypothalamic-pituitary-axis (HPA) suppression) so it is recommended to monitor for effects of HPA suppression after stopping treatment such as weakness, hyperpigmentation, weight loss, hypotension, and abdominal pain.[9] Tapering of the dose could help minimize this. Also, it could take days to months for the adrenal gland to recover so corticosteroids should be used during a period of stress (e.g. trauma or surgery).[9]

Utah Medicaid Utilization Data

There were 15 claims for 6 patients from April 2013 to October 2015 (all pharmacy) for "corticotropin".

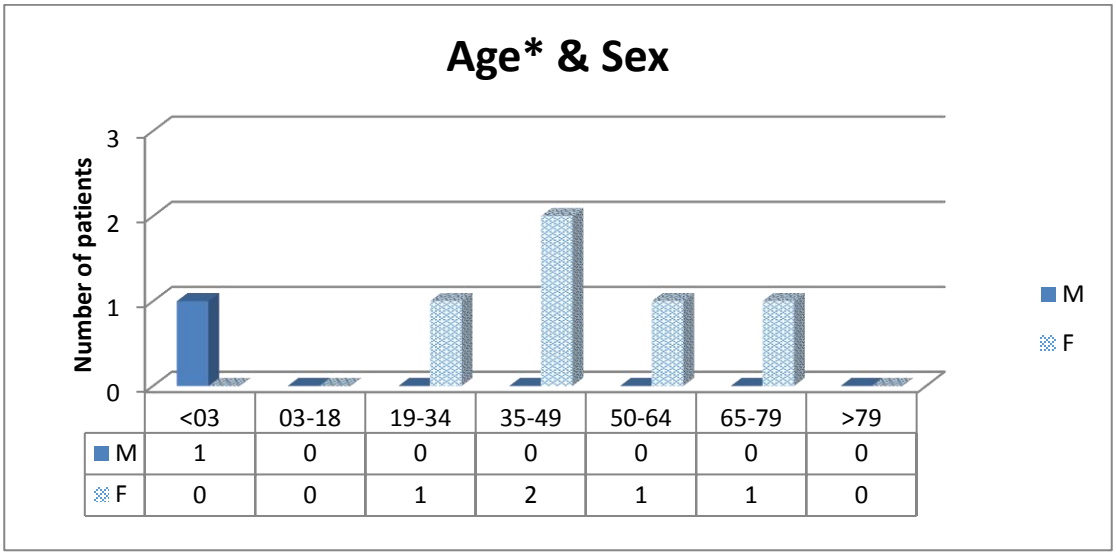
		ALL		2013		2014		2015		2016 (to date)	
GENERIC	**DESCRIPTION**	**CLAIMS**	**PATIENTS**	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Corticotropin	H.P. ACTHAR INJ 80UNIT	**15**	**6**	2	2	2	**1***	11	4	0	0
* ALSO 1 OF 2 PATIENTS IN 2013 AND <3 YEARS OLD											

No hospital/clinic/office claims were identified.

Procedure claims were searched:

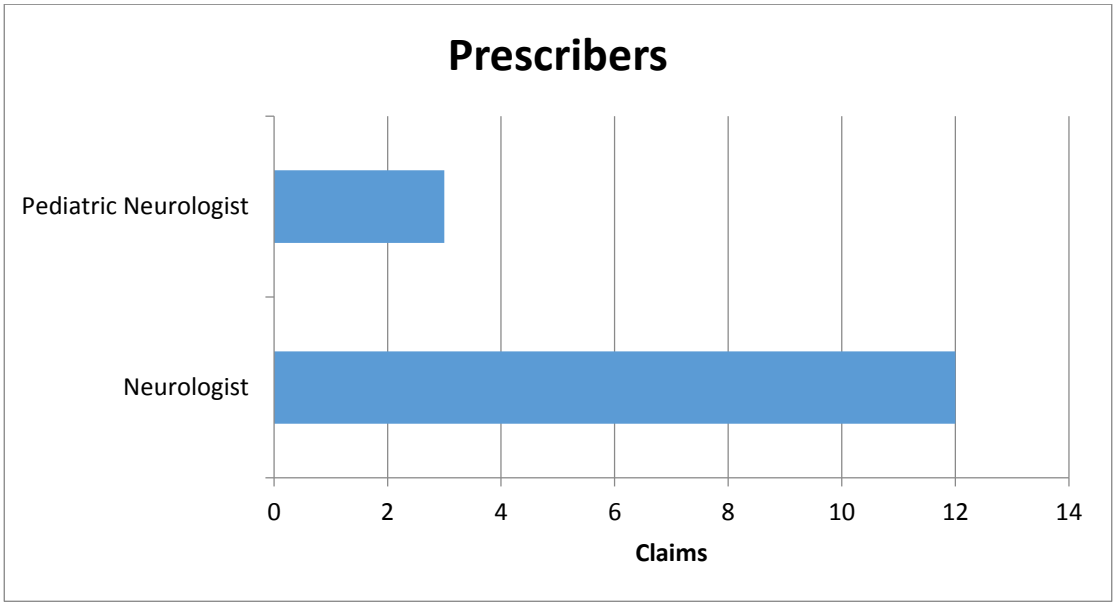
CPT J0800 (INJECTION, CORTICOTROPIN, UP TO 40 UNITS): No claims identified.

CPT 96372 (THRPTIC/PROPH/.DIAG INJ, SUBCUTANEOUS/INTRMSCLR): 91,854 claims for 42,540 patients, between 1/1/2013 and 2/29/2016.
29% of these claims included the substance/drug information and corticotropin was not identified in any of those claims (71% / 65000 claims did not include substance/drug information).



	<03	03-18	19-34	35-49	50-64	65-79	>79
M	1	0	0	0	0	0	0
F	0	0	1	2	1	1	0

* Age at first fill.



Conclusions

Current guidelines support the use of ACTH as a first-line treatment option for infantile spasms.[67,68] For MS exacerbations, corticosteroids appear to be appropriate first-line treatment and ACTH may be another option, but a healthcare professional with expertise in MS would be best placed to treat these patients as "not all relapses need treating with steroids"[79] Based on systematic review evidence, short-term use of corticosteroids in RA appear appropriate.[83] Current guidelines recommend corticotropin as an alternative to intraarticular corticosteroid injection or IV/IM methylprednisolone for acute gout in patients unable to take oral medications (to relieve the signs and symptoms of acute gout).[8,89] Limited evidence support the use of Acthar in patients with SLE and systemic dermatomyositis.[98] Based on NICE guidance, patients experiencing "a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson syndrome, toxic epidermal necrolysis)" should be referred to a specialist drug allergy service.[100] No evidence was identified for the use of corticotropin in serum sickness and use of glucocorticoids in patients with severe symptoms is based on limited evidence.[56] Optimal management of patients with serious ophthalmic conditions or not responsive to topical treatment necessitates consultation with an ophthalmologist or other specialist in eye disease. Corticosteroids and occasionally intraocular injections are used in some ocular conditions resistant to topical therapy, but evidence for use of corticotropin was not identified.[110] There is a lack of evidence for the use of corticotropin and corticosteroids for the treatment of cardiac sarcoidosis.[111] Current guidelines recommend corticosteroids for the treatment of nephrotic syndrome.[112,113] Corticotropin is not mentioned in these guidelines and no systematic reviews were identified for its use in this indication either. Based on Cochrane reviews, there is also a lack of evidence for corticotropin use in other indications (not FDA-approved) including post-dural puncture headache (PDPH)[119], Myasthenia Gravis[120,121], or as a potential chemoprotective agent.[121]

In the light of current guideline recommendations, the lack of high-quality evidence for corticotropin use in most indications, the well-recognized adverse effects of corticotropin, and the availability of oral and injectable corticosteroids that are better supported by current guidelines, Prior Authorization Criteria to ensure appropriate use of corticotropin, step-through therapy, and referral to an appropriate specialist (or consultation with a specialist) seems necessary. Based on utilization data for corticotropin, it does not appear to be used inappropriately. However, it is unclear whether a general CPT code was possibly used that did not specify corticotropin as the substance/drug.

Appendix 1 – Drug information

Corticotropin (From Lexi-Drugs)[8]		
Contraindications[8]	**Warnings/Precautions (related to adverse effects)**	***Disease-related concerns:***
Hypersensitivity to proteins of porcine origin Scleroderma Osteoporosis Systemic fungal infections Ocular herpes simplex Peptic ulcer Recent surgery Congestive heart failure (CHF) Uncontrolled hypertension Primary adrenocortical insufficiency Adrenocortical hyperfunction Infants with suspected congenital infections Coadministration of live or live attenuated vaccines IV administration	• "Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Symptoms of adrenal insufficiency may be difficult to detect in infants treated for infantile spasms. • Electrolyte disturbances: May increase retention of sodium and wasting of calcium and potassium; sodium restriction and/or potassium supplementation may be required. • Hypersensitivity reactions: Antibodies may develop following prolonged use and increase the risk of hypersensitivity reactions. • Immunosuppression: Prolonged use of corticosteroids may increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Close observation is required in patients with latent tuberculosis (TB) and/or TB reactivity; if therapy is prolonged, prophylaxis should be started. • Psychiatric disturbances: Corticosteroids may cause psychiatric disturbances, including depression, euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and psychotic manifestations. Preexisting psychiatric conditions (eg, emotional instability, psychotic tendencies) may be exacerbated by corticosteroid use."[8]	• "Cardiovascular disease: Use with caution in patients hypertension; use has been associated with fluid retention and hypertension; use is contraindicated with uncontrolled hypertension or congestive heart failure (CHF). • Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia. • Gastrointestinal disease: Use with caution in patients with GI disease (diverticulitis, ulcerative colitis, risk of impending perforation, fresh intestinal anastomoses) or abscess/pyogenic infections due to risk of gastric ulcer, GI perforation, and GI bleeding; use is contraindicated with peptic ulcer disease. • Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention. • Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred, especially during initial treatment with corticosteroids. • Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged corticosteroid use. Consider routine eye exams in chronic users. Contraindicated in patients with ocular herpes simplex. • Osteoporosis: Use with caution in patients of any age at risk for osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures. Use is contraindicated in patients with osteoporosis. • Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. • Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones."[8]

Appendix 2 – Systematic review(s), Trial(s), and other reviews

Table 3: Cochrane Reviews

Author(s)	Title	Objectives	Main Results	Author's Conclusions
Citterio A, et al (2000)[41] *(Assessed as up-to-date: 30 OCT 2002)*	Corticosteroids or ACTH for acute exacerbations in **multiple sclerosis**	Primary: "to determine the effects of corticosteroids and ACTH for the treatment of MS patients with acute exacerbation in terms of improvement of disability; reduction of risk of new exacerbations during follow-up; and prevention of disability progression at long-term follow-up." Secondary: "the frequency and severity of adverse effects and their acceptability in the light of benefits; the different effects of corticosteroids according to different doses and drugs, routes of administration, length of treatment and interval of time between onset of symptoms and randomisation, based on indirect comparisons; the different treatment effects according to disease course and the effect of corticosteroids or ACTH on magnetic resonance imaging as a surrogate marker of disease activity."	"Six trials, published between 1961 and 1998, contributed to this review. The current update did not identify new trials. A total of 377 participants (199 treatment, 178 placebo) were randomly assigned. The drugs analysed were methylprednisolone (MP) (four trials, 140 participants) and ACTH (two trials, 237 participants). Overall, administration of MP or ACTH favoured recovery from acute exacerbation in MS participants: use of either agent decreased by more than 60% the probability of the condition getting worse or stable within the first five weeks of treatment (odds ratio (OR) 0.37, 95% confidence interval (95% CI) 0.24 to 0.57; reduced disability of 1.5 points in the Kurtzke Expanded Disability Status Scale (EDSS) score at the first week of therapy, mean difference -1.47, 95% CI -2.25 to -0.69). The overall quality of evidence according to GRADE levels was moderate. Evidence was insufficient to show whether steroids or ACTH treatment prevented new exacerbations and worsening of long-term disability. Indirect comparisons suggest a significantly greater effect of MP versus ACTH, with MP conferring greater benefit compared with ACTH (OR 0.20, 95% CI 0.09 to 0.45 vs OR 0.46, 95% CI 0.28 to 0.77), and with intravenous MP proving more effective than oral MP (OR 0.12, 95% CI 0.04 to 0.42 vs OR 0.29, 95% CI 0.10 to 0.89) in decreasing the risk of getting worse or stable within the first five weeks of treatment. The time interval from onset of exacerbation to start of treatment administration does not seem to influence the outcome. Short-term (five days)	"We found evidence that corticosteroids, notably MP, are effective in the treatment of acute exacerbation, increasing the probability of ameliorating the episode and speeding up patient recovery. Data were insufficient to permit reliable estimation of the effects of corticosteroids on prevention of new exacerbations and long-term disability."

			courses of intravenous MP seem to be more effective than long-term treatment (15 days) (OR 0.13, 95% CI 0.02 to 0.75 vs OR 0.22, 95% CI 0.09 to 0.57). No data are available beyond one year of follow-up to allow evaluation of any effect on long-term progression. One study reported that short-term treatment with intravenous high-dose MP was not associated with adverse events. However, gastrointestinal symptoms and affective disorders were significantly more common in the oral high-dose MP group than in the placebo group. Weight gain and edema were significantly more frequent in the ACTH group than among controls."	
	Additional Information from Abstract "Background Corticosteroids are commonly used to improve the rate of recovery from acute exacerbation in multiple sclerosis (MS) patients. However, it is unclear just how effective these agents are and which is the best treatment schedule (type of drug, dose, frequency, duration of treatment and route of administration)." "This review is an update of the Cochrane Review, "Corticosteroids or ACTH for acute exacerbations in multiple sclerosis," first published in *The Cochrane Library* 2000, Issue 4."			
Mehta V, et al. (2015)[69] *(Assessed as up-to-date: 1 AUG 2014)*	Corticosteroids including ACTH for **childhood epilepsy other than epileptic spasms**	"To determine the efficacy, in terms of seizure control, improvements in cognition and in quality of life and tolerability of steroids compared to placebo or other antiepileptic drugs in children with epilepsy, excluding epileptic spasms."	"A single RCT was included that recruited five children in a double blind cross-over trial. One child was withdrawn prematurely from the study and another had infantile spasms and hence was excluded from further analysis. Adrenocorticotrophin hormone (ACTH 4-9) was administered. Of the three children analysed, one showed a reduction in seizures of 25% to 50% at both the low and higher doses of corticosteroids compared to placebo; one child showed a reduction in seizures at the higher dose only and one child showed no reduction in seizures at either dose. No adverse effects were reported."	"Since the last version of this review no new evidence has been found for the efficacy of corticosteroids in treating childhood epilepsies. Clinicians using steroids in childhood epilepsies, other than for epileptic spasms, should take this into account before using these agents."
	Additional Information from Abstract "Background This is an updated version of the original Cochrane review published in Issue 1, 2007.			

	Epilepsy is a disorder with recurrent epileptic seizures. Corticosteroids have been used in the treatment of children with epilepsy and have significant adverse effects. Their efficacy and tolerability have not been clearly established."			
Hancock EC, et al. (2013)[23]	Treatment of **infantile spasms**	"To compare the effects of single pharmaceutical therapies used to treat infantile spasms in terms of control of the spasms, resolution of the EEG, relapse rates, psychomotor development, subsequent epilepsy, side effects, and mortality."	"We found 16 small RCTs (fewer than 100 patients enrolled) and 2 larger RCTs (more than 100 patients enrolled). These 18 studies looked at a total of 916 patients treated with a total of 12 different pharmaceutical agents. Overall methodology of the studies was poor, in part because of ethical dilemmas such as giving placebo injections to children. Two studies showed that placebo was not as good as active treatment in resolving the spasms. The strongest evidence suggested that hormonal treatment (prednisolone or tetracosactide depot) leads to resolution of spasms faster and in more infants than does vigabatrin. Responses without subsequent relapse may be no different. The same study suggests that hormonal treatments might improve the long-term developmental outcome compared with vigabatrin in infants not found to have an underlying cause for their infantile spasms."	"To date, few well-designed RCTs have considered the treatment of infantile spasms, and the numbers of patients enrolled have been small. In the majority, methodology has been poor, hence it is not clear which treatment is optimal in the treatment of this epilepsy syndrome. Hormonal treatment resolves spasms in more infants than vigabatrin, but this may or may not translate into better long-term outcomes. If prednisolone or vigabatrin is used, high dosage is recommended. Vigabatrin may be the treatment of choice in tuberous sclerosis. Resolution of the EEG features may be important, but this has not been proven. Further research using large studies with robust methodology is required."
	"Background Infantile spasms (West's Syndrome) is a syndrome that includes a peculiar type of epileptic seizure—the spasms—and an electroencephalographic (EEG) abnormality often called *hypsarrhythmia*. Psychomotor retardation is frequently found at follow-up. Approximately two-thirds of affected infants will have a detectable underlying neurological abnormality, but still little is known about the pathophysiological basis for infantile spasms, and treatment remains problematic."			
Basurto Ona X, et al. (2015)[119]	Drug therapy for treating **post-dural puncture headache**	To assess the effectiveness and safety of drugs for treating PDPH in adults and children.	"We included 13 small RCTs (479 participants) in this review (at least 274 participants were women, with 118 parturients after a lumbar puncture for regional anaesthesia). In the original version of this Cochrane review, only seven small RCTs (200 participants) were included. Pharmacological drugs assessed were oral and intravenous caffeine, subcutaneous sumatriptan, oral gabapentin, oral pregabalin, oral theophylline, intravenous hydrocortisone,	"None of the new included studies have provided additional information to change the conclusions of the last published version of the original Cochrane review. Caffeine has shown effectiveness for treating PDPH, decreasing the proportion of participants with PDPH persistence and those requiring supplementary interventions, when compared with placebo. Gabapentin, hydrocortisone

		intravenous cosyntropin and intramuscular adrenocorticotropic hormone (ACTH). Two RCTs reported data for PDPH persistence of any severity at follow-up (primary outcome). Caffeine reduced the number of participants with PDPH at one to two hours when compared to placebo. Treatment with caffeine also decreased the need for a conservative supplementary therapeutic option. Treatment with gabapentin resulted in better visual analogue scale (VAS) scores after one, two, three and four days when compared with placebo and also when compared with ergotamine plus caffeine at two, three and four days. Treatment with hydrocortisone plus conventional treatment showed better VAS scores at six, 24 and 48 hours when compared with conventional treatment alone and also when compared with placebo. Treatment with theophylline showed better VAS scores compared with acetaminophen at two, six and 12 hours and also compared with conservative treatment at eight, 16 and 24 hours. Theophylline also showed a lower mean "sum of pain" when compared with placebo. Sumatriptan and ACTH did not show any relevant effect for this outcome. Theophylline resulted in a higher proportion of participants reporting an improvement in pain scores when compared with conservative treatment. There were no clinically significant drug adverse events. The rest of the outcomes were not reported by the included RCTs or did not show any relevant effect.”	and theophylline have been shown to decrease pain severity scores. Theophylline has also been shown to increase the proportion of participants that report an improvement in pain scores when compared with conventional treatment. **There is a lack of conclusive evidence for the other drugs assessed** (sumatriptan, **adrenocorticotropic hormone**, pregabalin and cosyntropin). These conclusions should be interpreted with caution, due to the lack of information to allow correct appraisal of risk of bias, the small sample sizes of the studies and also their limited generalisability, as nearly half of the participants were postpartum women in their 30s.”
Additional Information from Abstract “Background This is an updated version of the original Cochrane review published in Issue 8, 2011, on 'Drug therapy for treating post-dural puncture headache'.			

	Post-dural puncture headache (PDPH) is the most common complication of lumbar puncture, an invasive procedure frequently performed in the emergency room. Numerous pharmaceutical drugs have been proposed to treat PDPH but there are still some uncertainties about their clinical effectiveness."			
Janssens HJ et al. (2008)[92]	Systemic corticosteroids for **acute gout**	"To assess the efficacy and safety of systemic corticosteroids in the treatment of acute gout in comparison with placebo, NSAIDs, colchicine, other active drugs, other therapies, or no therapy."	"Three head to head trials involving 148 patients (74 systemic corticosteroids; 74 comparator drugs) were included. Placebo-controlled trials were not found. In the studies, different kinds of systemic corticosteroids and different kinds of control drugs were used, both administered in different routes. Intramuscular triamcinolone acetonide was compared respectively to oral indomethacine, and **intramuscular adrenocorticotropic hormone (ACTH)**; oral prednisolone (together with a single intramuscular diclophenac injection) was compared to oral indomethacine (together with a single placebo injection). Outcome measurements varied: average number of days until total relief of signs, mean decrease of pain per unit of time in mm on a visual analogue scale (VAS) - during rest and activity. In the triamcinolone-indomethacine trial the clinical joint status was used as an additional outcome. Clinically relevant differences between the studied systemic corticosteroids and the comparator drugs were not found; important safety problems attributable to the used corticosteroids were not reported. The quality of the three studies was graded as very low to moderate. Statistical pooling of results was not possible."	"There is inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids in the treatment of acute gout. Patients with gout did not report serious adverse effects from systemic corticosteroids, when used short term."
	Additional information from abstract Background "Gout is one of the most frequently occurring rheumatic diseases, worldwide. Given the well-known drawbacks of the regular treatments for acute gout (non-steroidal anti-inflammatory drugs (NSAIDs), colchicine), systemic corticosteroids might be safe alternatives."			
Schneider-Gold C, et al. (2005)[120]	Corticosteroids for **myasthenia gravis**	"To assess the efficacy of glucocorticosteroids or adrenocorticotrophic	"Seven trials involving a total of 199 participants were included. A trial of adrenocorticotrophic hormone (43 participants) did not show any	"Limited evidence from randomised controlled trials suggests that corticosteroid treatment offers short-

		hormone (ACTH) medication in autoimmune myasthenia gravis."	advantage compared with placebo for the treatment of ocular myasthenia gravis. Two double-blind trials compared prednisone with placebo for generalised myasthenia gravis. In the first (13 participants), the improvement was slightly greater in the prednisone group at six months. In the second (20 participants) which was a short-term trial, the improvement was significantly greater at two weeks. Two trials compared glucocorticosteroids with azathioprine (41 and 10 participants respectively). In one of these the rate of treatment failure was greater in the prednisone group. In a trial of glucocorticosteroids versus intravenous immunoglobulin (33 participants) no differences in treatment responses were encountered during a treatment period of 14 days. An open trial (39 participants) evaluating different corticosteroid doses revealed a shorter time to improvement in the high-dose group. None fulfilled the presently accepted standards of a high-quality trial. All these studies have risks of bias and have a weak statistical power."	term benefit in myasthenia gravis compared with placebo. This supports the conclusions of observational studies and expert opinion. Limited evidence from randomised controlled trials does not show any difference in efficacy between corticosteroids and either azathioprine or intravenous immunoglobulin."
	Additional Information "Background Although widely accepted as an appropriate immunosuppressive therapy, the efficacy of glucocorticosteroid treatment has only rarely been tested in controlled studies. This is an update of a Cochrane review first published in 2005 and previously updated in 2006 and 2007." Plain language summary "Myasthenia gravis is caused by the body's antibodies impairing transmission of nerve impulses to muscles, resulting in fluctuating weakness and fatigue. Acute attacks can be life threatening because of swallowing or breathing difficulties. Seven randomised controlled trials which included in all 199 participants are published. None fulfilled the presently accepted standards of a high-quality trial. All these studies have risks of bias and have a weak statistical power. Limited evidence from randomised controlled trials suggests that corticosteroids offer short-term benefit compared with placebo (dummy treatment). This supports the conclusions of observational studies and expert opinion. Limited evidence from randomised controlled trials does not show any difference in efficacy between corticosteroids and either azathioprine or intravenous immunoglobulin. All trials had design flaws which limit the strength of the conclusions. Further randomised controlled trials are needed."			
Benatar M, et al. (2012)[121]	Medical and surgical treatment for **ocular myasthenia**	"To assess the effects of treatments for ocular myasthenia and to answer	"In the original review, we identified two RCTs relevant to the treatment of ocular myasthenia, only one of which reported results in terms of the	"The available randomized controlled literature does not permit any meaningful conclusions about the

	three specific questions. Are there any treatments that impact the progression from ocular to generalized disease? Are there any treatments that improve symptoms of diplopia or ptosis? What is the frequency of adverse effects associated with treatments used?"	pre-specified outcome measures used in this review. This study included only three participants and was of limited methodological quality. There were no new RCTs in searches conducted for this or previous updates. In the absence of data from RCTs, we present a review of the available observational data."	efficacy of any form of treatment for ocular myasthenia. Data from several reasonably good quality observational studies suggest that corticosteroids and azathioprine may be beneficial in reducing the risk of progression to generalized myasthenia gravis."
	Additional Information "Background Approximately 50% of people with myasthenia gravis present with purely ocular symptoms, so called ocular myasthenia. Of these between 50% to 60% develop generalized disease, most within two years. Their management is controversial. This is an update of a review first published in 2006 and previously updated in 2008 and 2010." Plain Language Summary "Ocular myasthenia is a form of myasthenia gravis in which weakened eye muscles cause double vision or drooping eyelids. It accounts for approximately 50% of people with myasthenia gravis. Myasthenia gravis is an autoimmune disorder in which the body's own antibodies block the transmission of nerve impulses to muscles, causing fluctuating weakness and muscles that tire easily. Approximately half of people who have ocular myasthenia will go on to develop generalised myasthenia gravis and weakness affecting other muscles. For the majority of people this will be within the first two years of developing ocular symptoms. The aims of treatment for ocular myasthenia are to return the person to a state of clear vision and to prevent the development, or limit the severity of generalised myasthenia gravis. Treatments proposed for ocular myasthenia include drugs that suppress the immune system including corticosteroids and azathioprine, thymectomy (surgical removal of the thymus gland), and acetylcholinesterase inhibitors (which increases acetylcholine to compensate for the lack of acetylcholine receptors). Two randomised controlled trials (RCTs) relevant to the treatment of ocular myasthenia were identified in the original version of this review in 2006 and no new trials in this or previous updates. <u>One trial included 43 ocular myasthenia participants treated with corticotropin (a type of corticosteroid) or placebo.</u> The other only included three participants with ocular myasthenia and seven with generalised myasthenia gravis who were treated with intranasal neostigmine (an acetylcholinesterase inhibitor) or placebo. <u>Neither trial enabled us to draw firm conclusions regarding how effective these treatments were in preventing progression to the development of generalised myasthenia gravis or in improving ocular symptoms.</u> Several reasonably good quality non-randomised studies favor the use of corticosteroids and azathioprine but these and other agents need to be tested in well-designed RCTs."			
Benatar M, et al. (2014)[121]	Interventions for preventing neuropathy caused by cisplatin and related compounds	"To examine the efficacy and safety of purported **chemoprotective agents** to prevent or limit the neurotoxicity of cisplatin and related drugs."	"As of 2013, the review includes 29 studies describing nine possible chemoprotective agents, as well as description of two published meta-analyses. Among these trials, there were sufficient data in some instances to combine the results from different studies, most often using	"At present, the data are insufficient to conclude that any of the purported chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine,

	"We included randomised controlled trials (RCTs) or quasi-RCTs in which the participants received chemotherapy with cisplatin or related compounds, with a potential chemoprotectant (acetylcysteine, amifostine, adrenocorticotrophic hormone (ACTH), BNP7787, calcium and magnesium (Ca/Mg), diethyldithiocarbamate (DDTC), glutathione, Org 2766, oxcarbazepine, or vitamin E) compared to placebo, no treatment, or other treatments."	data from secondary non-quantitative measures. Nine of the studies were newly included at this update. Few of the included studies were at a high risk of bias overall, although often there was too little information to make an assessment. At least two review authors performed a formal review of an additional 44 articles but we did not include them in the final review for a variety of reasons. Of seven eligible amifostine trials (743 participants in total), one used quantitative sensory testing (vibration perception threshold) and demonstrated a favourable outcome in terms of amifostine neuroprotection, but the vibration perception threshold result was based on data from only 14 participants receiving amifostine who completed the post-treatment evaluation and should be regarded with caution. Furthermore the change measured was subclinical. None of the three eligible Ca/Mg trials (or four trials if a single retrospective study was included) described our primary outcome measures. The four Ca/Mg trials included a total of 886 participants. Of the seven eligible glutathione trials (387 participants), one used quantitative sensory testing but reported only qualitative analyses. Four eligible Org 2766 trials (311 participants) employed quantitative sensory testing but reported disparate results; meta-analyses of three of these trials using comparable measures showed no significant vibration perception threshold neuroprotection. The remaining trial reported only descriptive analyses. Similarly, none of the three eligible vitamin E trials (246 participants) reported quantitative sensory testing. The eligible single trials involving acetylcysteine (14 participants), diethyldithiocarbamate (195 participants), oxcarbazepine (32 participants), and retinoic acid (92 participants) did not perform quantitative	retinoic acid, or vitamin E) prevent or limit the neurotoxicity of platin drugs among human patients, as determined using quantitative, objective measures of neuropathy. Amifostine, calcium and magnesium, glutathione, and vitamin E showed modest but promising (borderline statistically significant) results favouring their ability to reduce the neurotoxicity of cisplatin and related chemotherapies, as measured using secondary, non-quantitative and subjective measures such as the NCI-CTC neuropathy grading scale. Among these interventions, the efficacy of only vitamin E was evaluated using quantitative nerve conduction studies; the results were negative and did not support the positive findings based on the qualitative measures. In summary, the present studies are limited by the small number of participants receiving any particular agent, a lack of objective measures of neuropathy, and differing results among similar trials, which make it impossible to conclude that any of the neuroprotective agents tested prevent or limit the neurotoxicity of platinum drugs."

			sensory testing. In all, this review includes data from 2906 participants. However, only seven trials reported data for the primary outcome measure of this review, (quantitative sensory testing) and only nine trials reported our objective secondary measure, nerve conduction test results. Additionally, methodological heterogeneity precluded pooling of the results in most cases. Nonetheless, a larger number of trials reported the results of secondary (non-quantitative and subjective) measures such as the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for neuropathy (15 trials), and these results we pooled and reported as meta-analysis. Amifostine showed a significantly reduced risk of developing neurotoxicity NCI-CTC (or equivalent) ≥ 2 compared to placebo (RR 0.26, 95% CI 0.11 to 0.61). Glutathione was also efficacious with an RR of 0.29 (95% CI 0.10 to 0.85). In three vitamin E studies subjective measures not suitable for combination in meta analysis each favoured vitamin E. For other interventions the qualitative toxicity measures were either negative (N-acetyl cysteine, Ca/Mg, DDTC and retinoic acid) or not evaluated (oxcarbazepine and Org 2766). Adverse events were infrequent or not reported for most interventions. Amifostine was associated with transient hypotension in 8% to 62% of participants, retinoic acid with hypocalcaemia in 11%, and approximately 20% of participantss withdrew from treatment with DDTC because of toxicity.”	
	Additional information “Background Cisplatin and several related antineoplastic drugs used to treat many types of solid tumours are neurotoxic, and most patients completing a full course of cisplatin chemotherapy develop a clinically detectable sensory neuropathy. Effective neuroprotective therapies have been sought.”			
Chen Y, et al. (2014)[53]	Immunosuppressive treatment for	“to evaluate the safety and efficacy of	“Thirty nine studies with 1825 patients were included, 36 of these could be included in our	“In this update, a combined alkylating agent and **corticosteroid** regimen had

idiopathic membranous nephropathy in adults with nephrotic syndrome	immunosuppressive treatments for adult patients with IMN and nephrotic syndrome. Moreover it was attempted to identify the best therapeutic regimen, when to start immunosuppression and whether the above therapies should be given to all adult patients at high risk of progression to ESKD or only restricted to those with impaired kidney function."	meta-analyses. The data from two studies could not be extracted and one study was terminated due to poor accrual. Immunosuppression significantly reduced all-cause mortality or risk of ESKD ((15 studies, 791 patients): RR 0.58 (95% CI 0.36 to 0.95, P = 0.03) and risk of ESKD ((15 studies, 791 patients): RR 0.55, 95% CI 0.31 to 0.95, P = 0.03), increased complete or partial remission ((16 studies, 864 patients): RR 1.31, 95% CI 1.01 to 1.70, P = 0.04), and decreased proteinuria ((9 studies,(393 patients): MD -0.95 g/24 h, 95% CI -1.81 to -0.09, P = 0.03) at the end of follow-up (range 6 to 120 months). However this regimen was associated with more discontinuations or hospitalisations ((16 studies, 880 studies): RR 5.35, 95% CI 2.19 to 13.02), P = 0.0002). Combined corticosteroids and alkylating agents significantly reduced death or risk of ESKD ((8 studies, 448 patients): RR 0.44, 95% CI 0.26 to 0.75, P = 0.002) and ESKD ((8 studies, 448 patients): RR 0.45, 95% CI 0.25 to 0.81, P = 0.008), increased complete or partial remission ((7 studies, 422 patients): RR 1.46, 95% CI 1.13 to 1.89, P = 0.004) and complete remission ((7 studies, 422 patients): RR 2.32, 95% CI 1.61 to 3.32, P < 0.00001), and decreased proteinuria ((6 studies, 279 patients): MD -1.25 g/24 h, 95% CI -1.93 to -0.57, P = 0.0003) at the end of follow-up (range 9 to 120 months). In a population with an assumed risk of death or ESKD of 181/1000 patients, this regimen would be expected to reduce the number of patients experiencing death or ESKD to 80/1000 patients (range 47 to 136). In a population with an assumed complete or partial remission of 408/1000 patients, this regimen would be expected to increase the number of patients experiencing complete or partial remission to 596/1000 patients (range 462 to 772). However this combined regimen was associated with a significantly higher risk of	short- and long-term benefits on adult IMN with nephrotic syndrome. Among alkylating agents, cyclophosphamide was safer than chlorambucil. This regimen was significantly associated with more withdrawals or hospitalisations. It should be emphasised that the number of included studies with high-quality design was relatively small and most of included studies did not have adequate follow-up and enough power to assess the prespecified definite endpoints. Although a six-month course of alternating monthly cycles of **corticosteroids** and cyclophosphamide was recommended by the KDIGO Clinical Practice Guideline 2012 as the initial therapy for adult IMN with nephrotic syndrome, clinicians should inform their patients of the lack of high-quality evidence for these benefits as well as the well-recognised adverse effects of this therapy. Cyclosporine or tacrolimus was recommended by the KDIGO Clinical Practice Guideline 2012 as the alternative regimen for adult IMN with nephrotic syndrome; however, there was no evidence that calcineurin inhibitors could alter the combined outcome of death or ESKD."

			discontinuation or hospitalisation due to adverse effects ((4 studies, 303 patients): RR 4.20, 95% CI 1.15 to 15.32, P = 0.03). Whether this combined therapy should be indicated in all adult patients at high risk of progression to ESKD or only restricted to those with deteriorating kidney function still remained unclear. Cyclophosphamide was safer than chlorambucil ((3 studies, 147 patients): RR 0.48, 95% CI 0.26 to 0.90, P = 0.02). There was no clear evidence to support the use of either corticosteroid or alkylating agent monotherapy. Cyclosporine and mycophenolate mofetil failed to show superiority over alkylating agents. Tacrolimus and adrenocorticotropic hormone significantly reduced proteinuria. The numbers of corresponding studies related to tacrolimus, mycophenolate mofetil, adrenocorticotropic hormone, azathioprine, mizoribine, and Tripterygium wilfordii are still too sparse to draw final conclusions."	
	"Background Idiopathic membranous nephropathy (IMN) is the most common form of nephrotic syndrome in adults. The disease shows a benign or indolent course in the majority of patients, with a rate of spontaneous complete or partial remission of nephrotic syndrome as high as 30% or more. Despite this, 30% to 40% of patients progress toward end-stage kidney disease (ESKD) within five to 15 years. The efficacy and safety of immunosuppression for IMN with nephrotic syndrome are still controversial. This is an update of a Cochrane review first published in 2004."			
Hahn D, et al. (2015)[52]	**Corticosteroid** therapy for **nephrotic syndrome** in children	"to assess the benefits and harms of different corticosteroid regimens in children with steroid-sensitive nephrotic syndrome (SSNS). The benefits and harms of therapy were studied in two groups of children 1) children in their initial episode of SSNS, and 2) children who experience a relapsing course of SSNS."	"Ten new studies were identified so a total of 34 studies (3033 total participants) were included in the 2015 review update. The risk of bias attributes were frequently poorly performed. Low risk of bias was reported in 18 studies for sequence generation, 16 studies for allocation concealment, seven for performance and detection bias, 15 for incomplete reporting and 16 for selective reporting. Three months or more of prednisone significantly reduced the risk of frequently relapsing nephrotic syndrome (FRNS) (6 studies, 582 children: RR 0.68, 95% CI 0.47 to 1.00) and of relapse by 12 to 24 months (8 studies, 741 children: RR 0.80, 95% CI 0.64 to	"In this 2015 update the addition of three well-designed studies has changed the conclusion of this review. Studies of long versus shorter duration of corticosteroids have heterogeneous treatment effects, with the older high risk of bias studies tending to over-estimate the effect of longer course therapy, compared with more recently published low risk of bias studies. Among studies at low risk of bias, there was no significant difference in the risk for FRNS between prednisone given for two or three months and longer

			1.00) compared with two months. Five or six months of prednisone significantly reduced the risk of relapse (7 studies, 763 children: RR 0.62, 95% CI 0.45 to 0.85) but not FRNS (5 studies, 591 children: RR 0.78, 95% CI 0.50 to 1.22) compared with three months. However there was significant heterogeneity in the analyses. Subgroup analysis stratified by risk of bias for allocation concealment showed that the risk for FRNS did not differ significantly between two or three months of prednisone and three to six months among studies at low risk of bias but was significantly reduced in extended duration studies compared with two or three months in studies at high risk or unclear risk of bias. There were no significant differences in the risk of adverse effects between extended duration and two or three months of prednisone. Four studies found that in children with FRNS, daily prednisone during viral infections compared with alternate-day prednisone or no treatment significantly reduced the rate of relapse."	durations or total dose of therapy indicating that there is no benefit of increasing the duration of prednisone beyond two or three months in the initial episode of SSNS. The risk of relapse in children with FRNS is reduced by the administration of daily prednisone at onset of an upper respiratory tract or viral infection. Three additional studies have increased the evidence supporting this conclusion. This management strategy may be considered for children with FRNS. A paucity of data on prednisone use in relapsing nephrotic syndrome remains. In particular there are no data from RCTs evaluating the efficacy and safety of prolonged courses of low dose alternate-day prednisone although this management strategy is recommended in current guidelines."
	"Background In nephrotic syndrome protein leaks from the blood to the urine through the glomeruli resulting in hypoproteinaemia and generalised oedema. While most children with nephrotic syndrome respond to corticosteroids, 80% experience a relapsing course. Corticosteroids have reduced the mortality rate to around 3%. However corticosteroids have well recognised potentially serious adverse effects such as obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and behavioural disturbances. This is an update of a review first published in 2000 and updated in 2003, 2005 and 2007."			
Pravitsitthikul N, et al. (2013)	**Non-corticosteroid immunosuppressive medications** for steroid-sensitive **nephrotic syndrome** in children	"To evaluate the benefits and harms of non-corticosteroid immunosuppressive medications in relapsing SSNS in children."	"We identified 32 studies (1443 children) of which one study is still ongoing. In the 31 studies with data, risk of bias assessment indicated that 11 (37%) and 16 (53%) studies were at low risk of bias for sequence generation and allocation concealment respectively. Six (29%) studies were at low risk of performance and detection bias. Twenty seven (87%) and 19 (60%) studies were at low risk of incomplete and selective reporting respectively. Alkylating agents (cyclophosphamide and chlorambucil) significantly reduced the risk of relapse at six to	"Eight-week courses of cyclophosphamide or chlorambucil and prolonged courses of cyclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with **corticosteroids** alone. Limited data indicate that mycophenolate mofetil and rituximab are valuable additional medications for relapsing SSNS. However clinically important differences in efficacy are possible and

			12 months (RR 0.43, 95% CI 0.31 to 0.60) and 12 to 24 months (RR 0.20, 95% CI 0.09 to 0.46) compared with prednisone alone. There was no significant difference in relapse risk at two years between chlorambucil and cyclophosphamide (RR 1.31, 95% CI 0.80 to 2.13). There was no significant difference at one year between intravenous and oral cyclophosphamide (RR 0.99, 95% CI 0.76 to 1.29). Cyclosporin was as effective as cyclophosphamide (RR 1.07, 95% CI 0.48 to 2.35) and chlorambucil (RR 0.82, 95% CI 0.44 to 1.53) at the end of therapy while levamisole (RR 0.47, 95% CI 0.24 to 0.89) was more effective than steroids alone. However the effects of cyclosporin and levamisole were not sustained once treatment was stopped. In one small study cyclosporin significantly reduced the relapse rate compared with mycophenolate mofetil (MD 0.75, 95% CI 0.01 to 1.49). Limited data from a cross-over study suggested that cyclosporin was more effective than mycophenolate mofetil in maintaining remission. In steroid- and cyclosporin-dependent disease, rituximab significantly reduced the risk of relapse at three months compared with conventional therapy. Mizoribine and azathioprine were no more effective than placebo or prednisone alone in maintaining remission."	further comparative studies are still needed."
	"Background About 80% to 90% of children with steroid-sensitive nephrotic syndrome (SSNS) have relapses. Of these children, around half relapse frequently, and are at risk of adverse effects from corticosteroids. Non-corticosteroid immunosuppressive medications are used to prolong periods of remission in these children; however, these medications have significant potential adverse effects. Currently, there is no consensus about the most appropriate second line agent in children who are steroid sensitive, but who continue to relapse. This is the third update of a review first published in 2001 and updated in 2005 and 2008."			
Hodson EM, et al. (2010)[117]	Interventions for idiopathic **steroid-resistant nephrotic syndrome** in children	"To evaluate the benefits and harms of interventions used to treat idiopathic steroid-resistant nephrotic syndrome (SRNS) in children."	"Fourteen RCTs (449 children) were included. Cyclosporin when compared with placebo or no treatment significantly increased the number of children who achieved complete remission (three studies, 49 children: RR 7.66, 95% CI 1.06 to 55.34). Cyclosporin significantly increased the	"Further adequately powered, well designed RCTs are needed to confirm the efficacy of cyclosporin and to evaluate other regimens for idiopathic SRNS including high dose steroids with cyclosporin."

			number with complete or partial remission compared with IV cyclophosphamide (one study, 32 children: RR 3.40, 95% CI 1.12 to 10.28). There was no significant difference in the number who achieved complete remission between oral cyclophosphamide with prednisone versus prednisone alone (two studies, 91 children: RR 1.06, 95% CI 0.61 to 1.87), IV versus oral cyclophosphamide (one study, 11 children: RR 3.13, 95% CI 0.81 to 12.06), IV cyclophosphamide versus oral cyclophosphamide with IV dexamethasone (one study, 49 children: RR 1.13, 95% CI 0.65 to 1.96), tacrolimus versus cyclosporin (one study, 41 children: RR 0.86, 95% CI 0.44 to 1.66) and azathioprine with prednisone versus prednisone alone (one study, 31 children: RR 0.94, 95% CI 0.15 to 5.84). ACEi significantly reduced proteinuria (two studies, 70 children). No studies were identified comparing high dose steroids and cyclosporin with single agents, placebo or no treatment."	
	"Background The majority of children who present with their first episode of nephrotic syndrome achieve remission with corticosteroid therapy. Children who fail to respond may be treated with immunosuppressive agents including calcineurin inhibitors (cyclosporin or tacrolimus) and with non-immunosuppressive agents such as angiotensin-converting enzyme inhibitors (ACEi). Optimal combinations of these agents with the least toxicity remain to be determined."			
Wechalekar MD, et al. (2013)[93]	**Intra-articular glucocorticoids** for **acute gout**	"To evaluate the safety and efficacy of intra-articular glucocorticoids in the treatment of acute gout."	"No trials were identified that evaluated the efficacy and safety of intra-articular glucocorticoids for acute gout."	"There is presently **no evidence** from randomised trials to support the use of intra-articular glucocorticoid treatment in acute gout. Evidence suggests intra-articular glucocorticoids may be a safe and effective treatment in osteoarthritis and rheumatoid arthritis. These results may be generalisable to people with acute gout, and the treatment may be especially useful in people when non-steroidal anti-inflammatory drugs or colchicine are contraindicated."

"Background
Although intra-articular glucocorticoids are a commonly used intervention in the treatment of acute gout, there is little evidence to support their safety and efficacy in this setting."

"Overall completeness and applicability of evidence
We identified two studies (one an open single arm trial, the other a case series) related to the use of local glucocorticoids in acute gout. The first (Fernandez 1999)[94] involved 19 patients all of whom received a single dose of intra-articular triamcinolone acetonide (10 mg in the knee or 8 mg in small joints). This resulted in a reduction in pain, from 88 (range 82 to 93) on a 0 to 100 mm visual analogue scale (VAS) at baseline to 0 (range 0 to 21) at 48 hours; the treatment was safe and free of side effects with no rebound attacks or need for additional therapy. The second study (Komatsu 1969)[95] involved 10 people with gout (full details of this Japanese study are awaiting translation); they were treated with 10 mg of triamcinolone acetonide infiltrated into the most painful part of the periarticular soft tissue and had complete resolution of symptoms.

In the absence of RCTs of intra-articular glucocorticoid injection for the treatment of people with acute gout, findings from systematic reviews and randomised controlled trials of intra-articular glucocorticoid injection for other acutely inflamed joints might also be informative. Intra-articular glucocorticoid therapy has previously been shown to be effective for the treatment of **knee osteoarthritis** in the short term in RCTs (Dieppe 1980; Friedman 1980; Godwin 2004) and in a Cochrane systematic review (Bellamy 2006)*, particularly in the presence of chondrocalcinosis (Bellamy 2006; Dieppe 1980). Another Cochrane review investigated intra-articular glucocorticoids for **rheumatoid arthritis** and included five RCTs of intra-articular glucocorticoids versus placebo (Wallen 2006). Pain relief was evident on day one and improvement in joint function and swelling continued over the ensuing weeks, with a suggestion that this might be dose-related.

These Cochrane reviews (Bellamy 2006; Wallen 2006) also addressed safety. No **adverse events** were reported in the trials of intra-articular glucocorticoids for rheumatoid arthritis (Wallen 2006) while very few adverse events were reported in the trials included in the osteoarthritis Cochrane review (Bellamy 2006). Potential adverse events of intra-articular glucocorticoid therapy include local effects such as post-injection flare, glucocorticoid crystal-induced synovitis, tissue atrophy, sepsis, avascular necrosis, haematoma and fat necrosis; systemic effects include hot flush, fluid retention, hyperglycaemia and hypertension. Risk of infection is minimised by adherence to an appropriate sterile technique.

In the context of **acute gout**, systemic (oral and intramuscular) glucocorticoids have been the subject of a Cochrane systematic review (Janssens 2008a) and a subsequent randomised placebo-controlled trial (Janssens 2008b). The Cochrane review included three very low to moderate quality trials and was unable to draw conclusions about the efficacy of systemic glucocorticoids, although no adverse events were reported (Janssens 2008a). The RCT included 120 participants randomised to receive either oral prednisolone or naproxen and found no difference in benefit or adverse events (abdominal pain, itching or dizziness, dyspnoea, palpitations or other) between the two treatments (Janssens 2008b)."

***Note that this Cochrane review (Bellamy et al.[96]) has been updated since and the conclusion changed (Jüni P, et al.[97] included below):**
The 2006 version by Bellamy et al. concluded: "The short-term benefit of IA corticosteroids in treatment of knee OA is well established, and few side effects have been reported. Longer term benefits have not been confirmed based on the RevMan analysis. The response to HA products appears more durable. In this review, some discrepancies were observed between the RevMan 4.2 analysis and the original publication. These are likely the result of using secondary rather than primary data and the statistical methods available in RevMan 4.2. Future trials should have standardised outcome measures and assessment times, run longer, investigate different patient subgroups, and clinical predictors of response (those associated with inflammation and structural damage)."[96]

Jüni P, et al. (2015)[97]	**Intra-articular corticosteroid** for **knee osteoarthritis**	"To determine the benefits and harms of intra-articular corticosteroids compared with sham or no intervention in people with knee osteoarthritis in terms of pain, physical function, quality of life, and safety."	"We identified 27 trials (13 new studies) with 1767 participants in this update. We graded the quality of the evidence as 'low' for all outcomes because treatment effect estimates were inconsistent with great variation across trials, pooled estimates were imprecise and did not rule out relevant or irrelevant clinical effects, and because most trials had a high or unclear risk of bias. Intra-articular corticosteroids appeared to be more beneficial in pain reduction than control interventions (SMD -0.40, 95% CI -0.58 to -0.22), which corresponds to a difference in pain scores of 1.0 cm on a 10-cm visual analogue scale between corticosteroids and sham injection and translates into a number needed to treat for an additional beneficial outcome (NNTB) of 8 (95% CI 6 to 13). An I^2 statistic of 68% indicated considerable between-trial heterogeneity. A visual inspection of the funnel plot suggested some asymmetry (asymmetry coefficient -1.21, 95%CI -3.58 to 1.17). When stratifying results according to length of follow-up, benefits were moderate at 1 to 2 weeks after end of treatment (SMD -0.48, 95% CI -0.70 to -0.27), small to moderate at 4 to 6 weeks (SMD -0.41, 95% CI -0.61 to -0.21), small at 13 weeks (SMD -0.22, 95% CI -0.44 to 0.00), and no evidence of an effect at 26 weeks (SMD -0.07, 95% CI -0.25 to 0.11). An I^2 statistic of ≥ 63% indicated a moderate to large degree of between-trial heterogeneity up to 13 weeks after end of treatment (P for heterogeneity≤0.001), and an I^2 of 0% indicated low heterogeneity at 26 weeks (P=0.43). There was evidence of lower treatment effects in trials that randomised on average at least 50 participants per group (P=0.05) or at least 100 participants per group (P=0.013), in trials that used concomittant viscosupplementation (P=0.08), and in trials that used concomitant joint lavage (P≤0.001).	"Whether there are clinically important benefits of intra-articular corticosteroids after one to six weeks remains unclear in view of the overall quality of the evidence, considerable heterogeneity between trials, and evidence of small-study effects. A single trial included in this review described adequate measures to minimise biases and did not find any benefit of intra-articular corticosteroids. In this update of the systematic review and meta-analysis, we found most of the identified trials that compared intra-articular corticosteroids with sham or non-intervention control small and hampered by low methodological quality. An analysis of multiple time points suggested that effects decrease over time, and our analysis provided no evidence that an effect remains six months after a corticosteroid injection."

		Corticosteroids appeared to be more effective in function improvement than control interventions (SMD -0.33, 95% CI -0.56 to -0.09), which corresponds to a difference in functions scores of -0.7 units on standardised Western Ontario and McMaster Universities Arthritis Index (WOMAC) disability scale ranging from 0 to 10 and translates into a NNTB of 10 (95% CI 7 to 33). An I^2 statistic of 69% indicated a moderate to large degree of between-trial heterogeneity. A visual inspection of the funnel plot suggested asymmetry (asymmetry coefficient -4.07, 95% CI -8.08 to -0.05). When stratifying results according to length of follow-up, benefits were small to moderate at 1 to 2 weeks after end of treatment (SMD -0.43, 95% CI -0.72 to -0.14), small to moderate at 4 to 6 weeks (SMD -0.36, 95% CI -0.63 to -0.09), and no evidence of an effect at 13 weeks (SMD -0.13, 95% CI -0.37 to 0.10) or at 26 weeks (SMD 0.06, 95% CI -0.16 to 0.28). An I^2 statistic of ≥ 62% indicated a moderate to large degree of between-trial heterogeneity up to 13 weeks after end of treatment (P for heterogeneity≤0.004), and an I^2 of 0% indicated low heterogeneity at 26 weeks (P=0.52). We found evidence of lower treatment effects in trials that randomised on average at least 50 participants per group (P=0.023), in unpublished trials (P=0.023), in trials that used non-intervention controls (P=0.031), and in trials that used concomitant viscosupplementation (P=0.06). Participants on corticosteroids were 11% less likely to experience adverse events, but confidence intervals included the null effect (RR 0.89, 95% CI 0.64 to 1.23, I^2=0%). Participants on corticosteroids were 67% less likely to withdraw because of adverse events, but confidence intervals were wide and included the null effect (RR 0.33, 95% CI 0.05 to 2.07, I^2=0%). Participants	

			on corticosteroids were 27% less likely to experience any serious adverse event, but confidence intervals were wide and included the null effect (RR 0.63, 95% CI 0.15 to 2.67, I^2=0%). We found no evidence of an effect of corticosteroids on quality of life compared to control (SMD -0.01, 95% CI -0.30 to 0.28, I^2=0%). There was also no evidence of an effect of corticosteroids on joint space narrowing compared to control interventions (SMD -0.02, 95% CI -0.49 to 0.46)."	
	"Background Knee osteoarthritis is a leading cause of chronic pain, disability, and decreased quality of life. Despite the long-standing use of intra-articular corticosteroids, there is an ongoing debate about their benefits and safety. This is an update of a Cochrane review first published in 2005." **"Plain language - Background** Osteoarthritis is a disease associated with a breakdown of cartilage of the joints, such as the knee. When the joint loses cartilage, the body responds by growing bone abnormally, which can result in the bone becoming misshapen and the joint painful and unstable. This can affect physical function and the ability to use the joint. Although osteoarthritis is generally thought to be of degenerative rather than inflammatory origin, an inflammatory component may be present at times. Intra-articular corticosteroids are potent anti-inflammatory agents injected inside the knee joint."			
Wallen MM, et al. (2006)[125]	**Intra-articular steroids** and splints/rest for **children with juvenile idiopathic arthritis** and **adults with rheumatoid arthritis**	"Objectives 1. Compare IA steroid injections versus no treatment or placebo. 2. Determine the effects of rest following IA steroid injection in rheumatoid or juvenile idiopathic arthritis."	"Five trials (n=346) examining IA steroid injection in the knee joint were included. It was not possible to pool data as outcome measures, timing of follow up and the methods of data reporting differed between trials. There was inconclusive conflicting evidence from two trials that walking time was reduced. There was evidence from one moderate quality trial that pain was reduced at 1-day post-injection (0-100 VAS from 28.33 to 13.46; McGill Pain Scale from 8.89 to 3.96) but not at 1 week or 7-12 weeks post-injection. There is some evidence that IA injections improved knee flexion (by 14 degrees) and reduced knee extension lag (by 20 degrees), knee circumference (median reduction = 0.3 cm) and morning stiffness (reduced from 60 mins to 7.6 mins). One trial (n=91) examined the effects of rest following injection in the knee. The rested group achieved significant improvement in pain,	"There is some evidence to support the use of IA steroid injections and resting a knee following injections but that wrists should not be rested following injections. The included studies involved adult participants so any conclusions can only cautiously applied to children. Further research is required to examine the use and type of rest and the differential responses of different joints following injections."

			stiffness, knee circumference, and walking time when compared with the non-rested group (no point estimates provided). One trial evaluated rest following injection of the wrist (n=117). Relapse rate was higher in the rested group (rest relapse rate = 24/58, no-rest group = 14/59); but there were no differences between the rested and non-rested groups on pain, joint circumference, wrist function, grip strength or ROM."	
	"Background Resting or immobilizing a joint to enhance outcomes following intra-articular (IA) steroid injection is generally advocated. This systematic review aimed to determine the efficacy of IA steroid injections and the influence of post-injection rest."			
Gøtzsche PC, et al. (2005)[83]	Short-term low-dose **corticosteroids** vs placebo and nonsteroidal antiinflammatory drugs in **rheumatoid arthritis**	"To determine whether short-term (i.e. as recorded within the first month of therapy), oral low-dose corticosteroids (corresponding to a maximum of 15 mg prednisolone daily) is superior to placebo and non-steroidal, anti-inflammatory drugs in patients with rheumatoid arthritis."	"Eleven trials, involving 462 patients, were included. Two placebo-controlled trials had adequate allocation concealment. For joint tenderness, the standardised mean difference was -0.52, 95% confidence interval (CI) -1.01 to -0.03, for pain it was -0.67, 95% CI -1.58 to 0.23, and for grip strength, 0.22, 95% CI -0.40 to 0.84. The estimates for the other trials were considerably larger. Prednisolone also had a greater effect than non-steroidal, anti-inflammatory drugs on joint tenderness (-0.63, 95% CI -1.16 to -0.11) and pain (-1.25, 95% CI -2.24 to -0.26), whereas the difference in grip strength was not significant (0.31, 95% CI -0.02 to 0.64). The main harms in long-term treatment were vertebral fractures and infections."	"Prednisolone in low doses (not exceeding 15 mg daily) may be used intermittently in patients with rheumatoid arthritis, particularly if the disease cannot be controlled by other means. The risk of harms needs to be considered, however, especially the risk of fractures and infections. Since prednisolone is highly effective, short-term placebo controlled trials studying the clinical effect of low-dose prednisolone or other oral corticosteroids are no longer necessary."
	"Background The effect of low dose corticosteroids, equivalent to 15 mg prednisolone daily or less, in patients with rheumatoid arthritis has been questioned. We reviewed the trials that compared corticosteroids with placebo or non-steroidal, anti-inflammatory drugs."			
Kirwan JR, et al. (2007)[84]	Effects of **glucocorticoids** on radiological	"To perform a systematic review of studies evaluating glucocorticoid efficacy in	"The initial search produced 217 citations, and 15 were added from experts, abstracts and review of reference lists. Authors of 4 trials being prepared	"Even in the most conservative estimate, the evidence that glucocorticoids given in addition to

	progression in **rheumatoid arthritis**	inhibiting the progression of radiological damage in rheumatoid arthritis."	for publication (and subsequently published) kindly shared their data. After application of eligibility criteria 15 studies and 1,414 patients were included. The majority of trials studied early RA (disease duration up to 2 years), and the mean cumulative dose of glucocorticoid was 2,300 mg prednisone equivalent (range 270 mg - 5,800 mg) over the first year. Glucocorticoids were mostly added to other disease modifying anti-rheumatoid drug (DMARD) treatment. The standardised mean difference in progression was 0.40 in favour of glucocorticoids (95% CI 0.27, 0.54). In studies lasting 2 years (806 patients included), the standardised mean difference in progression in favour of glucocorticoids at 1 year was 0.45 (0.24, 0.66) and at 2 years was 0.42 (0.30, 0.55). All studies except one showed a numerical treatment effect in favour of glucocorticoids. The beneficial effects of glucocorticoids were generally achieved when used in conjunction with other DMARD treatment."	standard therapy can substantially reduce the rate of erosion progression in rheumatoid arthritis is convincing. There remains concern about potential long-term adverse reactions to glucocorticoid therapy, such as increased cardiovascular risk, and this issue requires further research."
	"Background Glucocorticoid use in rheumatoid arthritis (RA) is widespread. Two Cochrane Reviews[83,126] have been published examining the short term clinical benefit of low dose glucocorticoids compared to non-steroidal anti-inflammatory drugs and demonstrate good short term and medium term clinical benefits. The possibility that glucocorticoids may have a fundamental 'disease modifying' effect in RA, which would be seen by a reduction in the rate of radiological progression, has been raised by several authors."			
Paramothayan NS, et al. (2006)	Corticosteroids for **pulmonary sarcoidosis**	"To determine the randomised controlled trial (RCT) evidence for the benefit of corticosteroids (oral or inhaled) in the treatment of pulmonary sarcoidosis."	"Thirteen RCTs of variable quality involving 1066 participants met the inclusion criteria of the review. The oral steroid dose was equivalent to prednisolone 4-40 mg/day. OCS: there was an improvement in CXR over 3-24 months (Relative Risk (RR): 1.46 [1.01 to 2.09], 3 studies), but this finding requires cautious interpretation. No other significant differences were identified on secondary outcomes. ICS: Data were inadequate to perform meaningful analysis of data on CXR. Two studies showed no improvement in lung function, In one study there was an improvement	"Oral steroids improved the chest X-ray and a global score of CXR, symptoms and spirometry over 3-24 months. However, there is little evidence of an improvement in lung function. There are limited data beyond two years to indicate whether oral steroids have any modifying effect on long-term disease progression. Oral steroids may be of benefit for patients with Stage 2 and 3 disease with moderate to severe or progressive symptoms or CXR changes."

		in diffusing capacity in the treated group. There were no data on side-effects. In one study symptoms improved at the end of six months of treatment."	
"Background Pulmonary sarcoidosis is a common condition with an unpredictable course. Oral (OCS) or inhaled steroids (ICS) are widely used in its treatment, but there is no consensus about when and in whom therapy should be initiated, what dose should be given and for how long. Corticosteroids given for several months have deleterious side-effects so it is important to know whether they have any maintained benefit in pulmonary sarcoidosis."			

Table 4. Trials for Systemic lupus erythematosus (No Systematic reviews)

Danowski et al. (2006)[54]

Flares in lupus: Outcome Assessment Trial (FLOAT), a comparison between oral methylprednisolone and intramuscular triamcinolone.

"OBJECTIVE:

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by a relapsing-remitting course. When a mild/moderate flare occurs, treatment with corticosteroids is often instituted. There are 2 methods of acutely giving a boost of steroids: triamcinolone injection or a short-term boost of oral prednisone or methylprednisolone. We investigated whether triamcinolone is superior to oral corticosteroids for mild/moderate flare in patients with lupus.

METHODS:

In a clinical trial, 50 patients with SLE presenting with a mild or moderate flare [defined using the Safety of Estrogens in Lupus Erythematosus: National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) flare instrument] were randomized to receive oral methylprednisolone with rapid tapering (medrol dose-pack) or triamcinolone 100 mg, given intramuscularly. The patients completed a Likert scale of activity and the Medical Outcomes Study Short Form-36 health status questionnaire on the randomization day, and repeated them the next day, 2 days, one week, 2 weeks, 3 weeks, and one month later.

RESULTS:

Complete improvement occurred in 0% at one day, 0% at 2 days, 8.3% at one week, 20.8% at 2 weeks, 20.8% at 3 weeks, and 25% at 4 weeks in the methylprednisolone group versus 4.3% at one day, 4.3% at 2 days, 8.6% at one week, 12.5% at 2 weeks, 30.4% at 3 weeks, and 34.7% at 4 weeks in the triamcinolone group. Improvement in health status by Week 4 occurred in 66.6% of the patients in the methylprednisolone group versus 73.9% in the triamcinolone group.

CONCLUSION:

The triamcinolone and oral methylprednisolone groups did equally well. Triamcinolone may lead to a more rapid response than the oral methylprednisolone (69.5% vs 41.6% with some improvement at day one)."

Furie et al. (2015)[98]

H.P. Acthar gel (Acthar) attenuates disease activity in patients with persistently active Systemic Lupus Erythematosus (SLE) requiring corticosteroids

11th International Congress on Systemic Lupus Erythematosus Vienna Australia. Conference Abstract

"This 8 week double-blind randomized placebo-controlled pilot study assessed clinical efficacy of Acthar in patients with persistently active SLE despite moderate dose corticosteroids. Eligibility criteria included hybrid SLEDAI (hSLEDAI) >2 with arthritis &/or skin involvement and BILAG A or B in mucocutaneous &/or musculoskeletal systems despite 7.5-30 mg prednisone daily for >4 weeks before screening. 38 subjects were randomized to SC Acthar 80U every other day (Acthar80) or 40U daily (Acthar40), or Placebo. Study medication was maintained for 4 weeks, then tapered to 2x/wk administration of the assigned dose. Change from baseline was assessed for hSLEDAI (wk 2, 4, 6 & 8), BILAG, CLASI, and tender swollen joint count (wk 4 & 8). Baseline hSLEDAI, BILAG and CLASI were similar between groups, though tender swollen joint count was higher in subjects receiving Acthar80 vs Acthar40 or Placebo ($p<0.05$). Acthar led to significant improvement in hSLEDAI and BILAG. Clinical benefit was also demonstrated by improvements in CLASI activity ($p<0.051$ for Acthar40 and combined Acthar vs Placebo at wk 4 & 8) and tender swollen joint count ($p<0.02$ for Acthar80 vs Placebo at wk 8). There were no significant differences in treatment-emergent adverse events between groups. These controlled data suggest that Acthar reduced disease activity in patients requiring corticosteroids for persistently active SLE, with improvements occuring within 8 wk of treatment initiation. (Table Presented)."

Aggarwal R, et al. (2015)[99]
Efficacy and safety of adrenocorticotropic hormone gel (acthar gel) in refractory dermatomyositis or polymyositis
American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2015 San Francisco, CA United States. Conference Abstract
"Background/Purpose: Adrenocorticotropic hormone (ACTH) gel (repository corticotropin injection) is a long-acting full sequence ACTH that may include other pro-opiomelanocortin peptides thought to have anti-inflammatory and immunomodulatory effects through melanocortin receptors. Its approval by FDA for polymyositis (PM) and dermatomyositis (DM) in 1952 was based on few case reports. We sought to evaluate the efficacy, safety, tolerability and steroid-sparing effect of ACTH gel in refractory adult PM and DM patients in a 6 month prospective, open-label uncontrolled pilot trial. Methods: 12 adult patients (5 PM; 7 DM) were enrolled at 2 centers. ACTH gel was given as 80 U twice weekly by selfinjection. One DM patient withdrew consent before study drug. The primary outcome was the proportion of patients meeting definition of improvement (DOI), defined by IMACS as improvement of > 20% in 3 of 6 core set measures (CSM) with no more than 2 worsening by >25% [(which cannot include the manual muscle testing (MMT)]. CSM include MD global, patient global, MMT, health assessment questionnaire (HAQ), muscle enzymes and extra-muscular global assessment. Secondary endpoints included steroid-sparing effect, safety, tolerability and recently proposed myositis response criteria. Results: Eleven patients (5 PM; 6 DM) were analyzed. Median age was 51 (IQR 37.9, 58.7), with 91% females and 46% Caucasians. All patients "failed" prednisone and a median (IQR) of 2 (2-3) additional immunosuppressive agents. Although the trial is ongoing, 8 patients completed 6 months on the drug and 3 have completed 1, 2 and 4 months in the trial, respectively. One patient stopping drug due to heart block at 2 months is considered a treatment failure. 91% (10/11) of subjects met the primary outcome by a median (IQR) of 3 (2-4) months, but the response was not sustained in 2 patients (on drug). Sustained improvement (DOI at subsequent visits) was seen in 8 (73%) patients. Median relative % improvement in MD global was 73%, 38% in patient global, 14% in MMT, 78% in extra muscular global, 13% in HAQ, 7% in muscle enzymes (Figure 1). Regarding the new myositis response criteria, 9 patients achieved minimal, 6 moderate and 4 major improvement with a median (IQR) total improvement score of 40 (25-65) on scale of 0-100. ACTH gel was safe, well-tolerated, and steroid-sparing with a drop in the median (IQR) prednisone dose from 15 mg (7.5-30) at baseline to 1.25 mg (0-4) at last visit (p=0.001). There were 4 serious adverse events in 3 patients: 2 with herpes zoster related to drug and 1 with musculoskeletal chest pain and 1 with heart block, both unrelated to study drug. <>Conclusion: ACTH gel improved most enrolled myositis patients and was steroid sparing, safe and well tolerated. Viral infections require monitoring. A randomized controlled trial should be considered to further assess its efficacy in myositis. (Figure Presented)***."***

Table 5: Other Reviews from PubMed (Used by Gettig as evidence for infantile spasms)

Haines ST, Casto DT (1994)
Treatment of infantile spasms.
"OBJECTIVE:
To summarize and evaluate the literature regarding the clinical features, epidemiology, etiology, pathophysiology, and treatment of infantile spasms.
DATA SOURCES:
A literature search of articles from January 1966 to July 1993 using MEDLINE, EM-Base, and Current Concepts/Life Sciences, as well as bibliographies of relevant articles.
STUDY SELECTION:
All identified original and review publications regarding the clinical features, epidemiology, etiology, pathophysiology, and treatment of infantile spasms were reviewed. Emphasis was placed on original studies published since 1975.
DATA EXTRACTION:
Data from published research were extracted and evaluated according to study design, sample size, dosing regimen, outcome measures, and treatment efficacy and safety.
DATA SYNTHESIS:
Infantile spasms constitute a rare epileptic syndrome with a poor long-term prognosis for normal intellectual development. The spasms are characterized by a brief symmetric contraction of the muscles of the neck, trunk, and/or extremities, often occurring in a series of 2 to more than 100 spasms during a single episode. The disorder is age-specific, with the peak onset of symptoms occurring between 2 and 8 months of age. Spasms of no identifiable cause in infants with normal

development prior to the onset of infantile spasms are classified as cryptogenic or idiopathic, whereas those with an identifiable cause are classified as symptomatic. Long-term prognosis is best in cryptogenic cases, with 30-70 percent attaining normal intellect compared with 5-19 percent in symptomatic cases. The etiology and pathophysiology are not well understood. Recent theory postulates that infantile spasms may be caused by an excess of corticotropin-releasing hormone activity during infancy. The suspected association between the whole-cell pertussis vaccine and infantile spasms is coincidental. Few well-designed, prospective, controlled clinical trials for the treatment of infantile spasms have been conducted.
CONCLUSIONS:
Standard anticonvulsants such as phenytoin, the barbiturates, carbamazepine, and the succinimides have been ineffective. Of the anticonvulsants, only the benzodiazepines, valproic acid, and vigabatrin have shown efficacy in reducing spasm frequency and severity. Hormonal therapy with adrenocorticotropic hormone (ACTH) and/or prednisone has been the most frequently studied treatment modality and appears to be the most effective. Hormonal therapy achieves complete spasm control in 50-75 percent of infants within four weeks of initiation. Opinions differ regarding the relative efficacy between ACTH and prednisone, the need for early initiation of hormonal treatment, and the benefits of high dosages of ACTH (> 40 units/d). No treatment has been shown conclusively to improve the long-term intellectual development of these infants. Neurosurgery may be the treatment of choice in select cases when a localized central nervous system abnormality can be demonstrated. Well-designed, blind, prospective clinical trials are needed to answer definitively many lingering questions regarding the treatment of infantile spasms."

Mackay M, et al. (2002) *Note this is the 2nd author of the Am Ac Neurol (2012) guidelines Go et al. and 1st author of 2004 practice parameter report*
Treatment of infantile spasms: an evidence-based approach
"The object of this work was to subject established empirical medical treatment regimens for infantile spasms to evidence-based medicine analysis in order to determine the current best practice for the treatment of infantile spasms in children. Clinical studies of infantile spasms reported during the presteroid era were reviewed critically to define the natural history of the disorder. Treatment trials of infantile spasms conducted since 1958 were rigorously assessed using MEDLINE and hand searches of the English language literature. Inclusion criteria were the documented presence of infantile spasms and hypsarrhythmia. Outcome measures included complete cessation of spasms, resolution of hypsarrhythmia, relapse rate, developmental outcome, the presence or absence of epilepsy, and/or an epileptiform electroencephalogram. Evidence was defined as class I, II, or III, and practice parameter recommendations were made using the framework devised by the American Academy of Neurology. Class I and III evidence support a standard of practice recommendation for the use of vigabatrin in the treatment of infantile spasms in children with tuberous sclerosis. Class I and III evidence support a guidelines recommendation for the use of either ACTH or vigabatrin in infantile spasms in nontuberous sclerosis patients. There is no strong evidence that successful treatment of infantile spasms improves the long-term prognosis for cognitive outcome or decreases the incidence of later epilepsy. A practice option recommendation for the use of oral corticosteroids in the treatment of infantile spasms is supported by limited and inconclusive class I and III data. Based on the evidence, no recommendation can be made for the use of pyridoxine, benzodiazepines, or the newer antiepileptic drugs in the treatment of infantile spasms. ACTH and vigabatrin are the most effective agents in the treatment of infantile spasms, but concerns remain about the risk/benefit profiles of these drugs."[26]

Mackay MT, et al. (2004)
Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society
"OBJECTIVE:
To determine the current best practice for treatment of infantile spasms in children.
METHODS:
Database searches of MEDLINE from 1966 and EMBASE from 1980 and searches of reference lists of retrieved articles were performed. Inclusion criteria were the documented presence of infantile spasms and hypsarrhythmia. Outcome measures included complete cessation of spasms, resolution of hypsarrhythmia, relapse rate, developmental outcome, and presence or absence of epilepsy or an epileptiform EEG. One hundred fifty-nine articles were selected for detailed review. Recommendations were based on a four-tiered classification scheme.

RESULTS:
Adrenocorticotropic hormone (ACTH) is probably effective for the short-term treatment of infantile spasms, but there is insufficient evidence to recommend the optimum dosage and duration of treatment. There is insufficient evidence to determine whether oral corticosteroids are effective. Vigabatrin is possibly effective for the short-term treatment of infantile spasm and is possibly also effective for children with tuberous sclerosis. Concerns about retinal toxicity suggest that serial ophthalmologic screening is required in patients on vigabatrin; however, the data are insufficient to make recommendations regarding the frequency or type of screening. There is insufficient evidence to recommend any other treatment of infantile spasms. There is insufficient evidence to conclude that successful treatment of infantile spasms improves the long-term prognosis.
CONCLUSIONS:
ACTH is probably an effective agent in the short-term treatment of infantile spasms. Vigabatrin is possibly effective."[27]

Riikonen R (2004)
Infantile spasms: therapy and outcome
"Up-to date information about corticotropin (ACTH) in the treatment of infantile spasms and evaluation of the long-term outcome was provided to answer questions about (1) the efficacy of doses of ACTH in comparison with other drugs, especially with vigabatrin, and the efficacy in patients with tuberous sclerosis; (2) tolerability; and (3) long-term outcome. In two studies, high doses were not more effective than low doses but were more effective in another study. In the follow-up of the studies, there was no difference. In an open, randomized, prospective study, the efficacy and relapse rates of ACTH and vigabatrin treatment did not differ significantly. The high response rates in tuberous sclerosis complex were similar. Both drugs had severe side effects. In the long-term follow-up of 20 to 35 years, one third of the patients died, the intellectual outcome of the remaining patients was normal or slightly subnormal, and one quarter and one third of the patients were seizure free. ACTH should be the first choice for treatment of infantile spasms. The side effects of ACTH, unlike those of vigabatrin, are well known, treatable, and reversible. However, an open, prospective study to compare the efficacy, relapse rate, and long-term outcome of treatment with ACTH and vigabatrin is urgently needed. The frequency of visual field defects after vigabatrin therapy should be evaluated."[29]

Table 6. Abstracts of Trials identified through Clinicaltrials.gov (or study information if no publication)

van de Logt AE, et al. (2015)[114]
Synthetic ACTH in High Risk Patients with Idiopathic Membranous Nephropathy: A Prospective, Open Label Cohort Study.
"New therapeutic agents are warranted in idiopathic membranous nephropathy. Synthetic ACTH may be advantageous with reported remission rates up to 85% and few side effects. We conducted a prospective open label cohort study from 2008 till 2010 (NCT00694863). We prospectively selected patients with idiopathic membranous nephropathy and high risk for progression (defined as βeta-2-microglobulin (β2m) excretion of >500 ng/min). For comparison, we selected matched historical controls treated with cyclophosphamide. The prospectively selected patients received intramuscular injections of synthetic ACTH during 9 months (maximal dose 1 mg twice a week). The primary endpoints concerned the feasibility and incidence of remissions as a primary event. Secondary endpoints included side effects of treatment and the incidence of remissions and relapses at long-term follow-up. Twenty patients (15 men) were included (age 54±14 years, serum creatinine 104 µmol/l [IQR 90–113], urine protein:creatinine ratio 8.7 g/10 mmol creatinine [IQR 4.3–11.1]). Seventeen patients (85%) completed treatment. 97% of injections were administered correctly. Cumulative remission rate was 55% (complete remission in 4 patients, partial remission 7 patients). In a group of historical controls treated with cyclophosphamide and steroids, 19 of 20 patients (95%) developed a remission (complete remission in 13 patients, partial remission in 6 patients) ($p<0.01$). The main limitation of our study is its small size and the use of a historical control group. We show that treatment with intramuscular injections of synthetic ACTH is feasible. Our data suggest that synthetic ACTH is less effective than cyclophosphamide in inducing a remission in high risk patients with idiopathic membranous nephropathy. The use of synthetic ACTH was also associated with many adverse events. Therefore, we advise against synthetic ACTH as standard treatment in membranous nephropathy."

No corresponding publication listed or identified via PubMed
Prospective Study Evaluating the Effect of Repository Corticotropin in the Treatment of Various Nephrotic Syndromes (ACTH)
ClinicalTrials.gov Identifier: NCT01021540
Sponsor: Arizona Kidney Disease and Hypertension Center

Information from Clinicaltrials.gov
"Detailed Description:
Synthetic ACTH (Synacthen Depot) has been used in the treatment of Nephrotic Syndrome in Europe. It has been proven effective in treating idiopathic membranous nephropathy and other various diagnoses involving the kidneys. However, Synacthen is not available in the United States. The only preparation available is the H.P. Acthar Gel (repository corticotrophin) which has been widely used in the treatment of infantile spasms and has been available longer than Synacthen. Therefore, we are conducting this study to determine if H.P. Acthar Gel (repository corticotrophin) is as effective in reducing protein in the urine as seen in synthetic ACTH in Europe.
Primary Outcome Measures:

- Acthar has the same anti-proteinuric effects in a wide range of glomerulonephropaties as seen with synthetic ACTH (Synacthen) in Europe [Time Frame: 6 months] [Designated as safety issue: No]

Secondary Outcome Measures:

- Acthar has similar anti-lipid effects as seen with Synacthen. [Time Frame: 6 months] [Designated as safety issue: No]

Estimated Enrollment: 18
Study Start Date: December 2009
Study Completion Date: October 2010
Primary Completion Date: October 2010 (Final data collection date for primary outcome measure)"[118]

Gan EH, et al. (2014)
Residual adrenal function in autoimmune Addison's disease: improvement after tetracosactide (ACTH1-24) treatment. NCT01371526
"CONTEXT:
Despite lifelong steroid hormone replacement, there is excess morbidity and mortality associated with autoimmune Addison's disease. In health, adrenocortical cells undergo continuous self-renewal from a population of subcapsular progenitor cells, under the influence of ACTH, suggesting a therapeutic possibility.
OBJECTIVE:
We aimed to determine whether tetracosactide (synthetic ACTH1-24) could revive adrenal steroidogenic function in autoimmune Addison's disease.
DESIGN, SETTING, AND PATIENTS:
Thirteen patients (aged 16-65 y) with established autoimmune Addison's disease for more than 1 year were recruited at the Newcastle University Clinical Research Facility.
INTERVENTION:
The intervention included a 20-week study of regular sc tetracosactide (ACTH1-24) therapy.
MAIN OUTCOME MEASURES:
Serum and urine corticosteroids were measured during medication withdrawal at baseline and every 5 weeks during the study.
RESULTS:
Serum cortisol levels remained less than 100 nmol/L in 11 of 13 participants throughout the study. However, two women achieved peak serum cortisol concentrations greater than 400 nmol/L after 10 and 29 weeks of tetracosactide therapy, respectively, allowing withdrawal of corticosteroid replacement. Concurrently, urine glucocorticoid and mineralocorticoid metabolite excretion increased from subnormal to above the median of healthy controls. One of these responders remains well

with improving peak serum cortisol (672 nmol/L) 28 months after stopping all treatments. The other responder showed a gradual reduction in serum cortisol and aldosterone over time, and steroid therapy was recommenced after a 28-week period without glucocorticoid replacement.
CONCLUSION:
This is the first study to demonstrate that established autoimmune Addison's disease is amenable to a regenerative medicine therapy approach."[127]

Table 7: Abstracts of observational studies

Interpret with caution due to limitations.

Bomback AS, et al. (2011)[115]
Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel
(A retrospective case series; majority of these patients received ACTH as second-, third-, or fourth-line therapy for resistant nephrotic syndrome).
"Purpose:
A synthetic adrenocorticotropin (ACTH) analog has shown efficacy in Europe as primary and secondary therapy for nephrotic syndrome, but there is no published experience using the natural, highly purified ACTH gel formulation, available in the United States, for nephrotic syndrome. We therefore investigated the use of ACTH gel for nephrotic syndrome in the United States.
Patients and methods:
Twenty-one patients with nephrotic syndrome treated with ACTH gel outside of research settings in the United States, with initiation of therapy by December 31, 2009, allowing a minimum 6 months follow-up. We defined complete remission as stable renal function with proteinuria falling to <500 mg/day, and partial remission as stable renal function with >50% reduction in proteinuria from 500 to 3500 mg/day.
Results:
Twenty-one patients with nephrotic syndrome were treated: 11 with idiopathic membranous nephropathy (iMN), 4 with membranoproliferative glomerulonephritis (MPGN), 1 with focal segmental glomerulosclerosis (FSGS), 1 with minimal change disease (MCD), 1 with immunoglobulin A (IgA) nephropathy, 1 with class V systemic lupus erythematosus (SLE) glomerulonephritis, 1 with monoclonal diffuse proliferative glomerulonephritis, and 1 with unbiopsied nephrotic syndrome. ACTH was used as primary therapy for 3 patients; the remaining patients had previously failed a mean 2.3 immunosuppressive regimens. Eleven patients achieved a complete or partial remission, with 4 (19%) in complete remission. Of the 11 patients who achieved remission, 9 had iMN, 1 had FSGS, and 1 had IgA nephropathy. Of the 11 patients with iMN, 3 (27%) achieved complete remission and 6 (55%) achieved partial remission despite having previously failed a mean 2.4 therapies. Five patients reported steroid-like adverse effects, but there were no severe infections. The limitations were retrospective data analysis with short-term follow-up.
Conclusion:
ACTH gel may be a viable treatment option for resistant nephrotic syndrome due to membranous nephropathy. Short-term data suggest that remission rates may approach 80%.
Keywords: nephrotic syndrome, membranous nephropathy, chronic kidney disease"

Introduction
"Patients with nephrotic syndrome often require immunosuppression to achieve remission, yet many patients either relapse after remission or are resistant to therapy. For example, while up to 90% of adults with minimal change disease (MCD) will respond to initial therapy with prednisone, approximately one-third of these same patients will relapse within 6 months and require further immunosuppression.1,2 With diseases such as idiopathic membranous nephropathy (iMN) and focal

segmental glomerulosclerosis (FSGS), for which first-line therapies produce substantially lower response rates than for MCD, physicians are often compelled to use second-, third-, and even fourth-line therapies to achieve remission.3–8
In several European studies, tetracosactide, a synthetic adrenocorticotropic hormone (ACTH) analog, has shown efficacy as primary and secondary therapy for nephrotic syndrome. The initial reports came in a case series of patients with various etiologies of nephrotic range proteinuria, including MCD, iMN, FSGS, and membranoproliferative glomerulonephritis (MPGN).9 Subsequently, a randomized, controlled study by Ponticelli et al reported similar remission rates in patients with iMN randomized to synthetic ACTH or to therapy with alternating months of steroids and cyclophosphamide.10 These reports have generated renewed interest in using ACTH as treatment for nephrotic syndrome, particularly in patients who are resistant to conventional therapies. Synthetic ACTH is not currently available for use in the United States, but a natural, highly purified ACTH gel formulation (H.P. Acthar® Gel [repository corticotropin injection], Questcor Pharmaceuticals, Inc, Union City, CA, USA; abbreviated ACTH gel) is both available and approved for use in nephrotic syndrome.
To date, however, there is no modern published experience on using ACTH gel in nephrotic patients. We therefore explored the initial use of ACTH gel for nephrotic syndrome in nonresearch settings (ie, by prescription), collecting data from treating nephrologists of all known patients in the United States whose treatment with this agent was initiated by the end of 2009. We describe their clinical course before and after treatment with ACTH gel."

McElhaney JL (1989)[66]
Repository corticotropin injection as an adjunct to smoking cessation during the initial nicotine withdrawal period: results from a family practice clinic
"Fifteen white patients participated in this study of a family-practice-based smoking cessation program in which corticotropin (ACTH) was used to assist patients during the first one to two weeks of abstinence from nicotine. All patients were habitual smokers who had made one or more attempts to quit smoking before entering this program. Treatment consisted of three single intramuscular injections of ACTH. In most cases, declining doses of 160, 80, and 40 U were administered at three-day intervals. The decision to provide additional treatment was based on the response by each volunteer and the investigator's judgment. The mean duration of follow-up was 33 days (range, 17 to 49 days), with the exception of two patients, who have just recently completed therapy. Evidence supporting complete smoking cessation or a significant reduction (80% to greater than 90%) in the number of cigarettes smoked per day was achieved in 13 of the 15 patients. The single nonresponder expressed an initial interest in the program, but showed a lack of motivation thereafter. There was insufficient follow-up on one other patient, who has not been available for monitoring since completion of therapy. Symptoms associated with the tobacco withdrawal syndrome that were reported by the patients included mild irritability and restlessness."

Appendix 3 – Additional Guidelines

American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis (2012)[112]

"Major Recommendations
The levels of evidence supporting the recommendations (A-C) are defined at the end of the "Major Recommendations" field.
Renal Biopsy and Histology
The Task Force Panel recommended that all patients with clinical evidence of active lupus nephritis (LN), previously untreated, undergo renal biopsy (unless strongly contraindicated) so that glomerular disease can be classified by current International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (level C evidence) (see Table 1 in the original guideline document for ISN/RPS classification of LN). In addition, disease can be evaluated for activity and chronicity and for tubular and vascular changes. Finally, biopsies may identify additional or alternative causes of renal disease, such as tubular necrosis related to medications, hypovolemia, or hypotension. Biopsy is most highly recommended in patients with the characteristics indicated in the following table.
Table. Indications for Renal Biopsy in Patients with Systemic Lupus Erythematosus

	Level of Evidence
Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication)	C
Confirmed proteinuria of ≥1.0 gm per 24 hours (either 24-hour urine specimens or spot protein/creatinine ratios are acceptable)	C
Combinations of the following, assuming the findings are confirmed in at least two tests done within a short period of time and in the absence of alternative causes: a. Proteinuria ≥0.5 gm per 24 hours plus hematuria, defined as ≥5 RBCs per hpf b. Proteinuria ≥0.5 gm per 24 hours plus cellular casts	C

RBCs = red blood cells; hpf = high-power field.
The Task Force Panel recommended that treatment be based in large part on the classification of type of LN by these ISN/RPS criteria. As a result, the following recommendations are presented according to the histologic classification of nephritis. *The Task Force Panel agreed that class I* (minimal mesangial immune deposits on immunofluorescence with normal light microscopy) *and class II* (mesangial hypercellularity or matrix expansion on light microscopy with immune deposits confined to mesangium on immunofluorescence) *generally do not require immunosuppressive treatment (level C evidence)*. In general, patients with class III (subendothelial immune deposits and proliferative changes in <50% of glomeruli) and class IV (subendothelial deposits and proliferative glomerular changes involving ≥50% of glomeruli) require aggressive therapy with glucocorticoids and immunosuppressive agents. Class V (subepithelial immune deposits and membranous thickening of glomerular capillaries) when combined with class III or IV should be treated in the same manner as class III or IV. Class V alone ("pure membranous LN") may be approached somewhat differently, as indicated below under "Recommendations for Induction of Improvement in Patients with Class V 'Pure Membranous' LN". Histologic class VI (sclerosis of ≥90% of glomeruli) generally requires preparation for renal replacement therapy rather than immunosuppression. The designations "A" and "C" indicate whether active or chronic changes are present; the higher the chronicity the less likely that the nephritis will respond to immunosuppression. However, A or C classifications were not included in the entry criteria for clinical trials in LN published to date, and therefore they are not considered in the recommendations.
Adjunctive Treatments
The Task Force Panel recommended that all systemic lupus erythematosus (SLE) patients with nephritis be treated with a background of hydroxychloroquine (HCQ; level C evidence), unless there is a contraindication.
All LN patients with proteinuria ≥0.5 gm per 24 hours (or equivalent by protein/creatinine ratios on spot urine samples) should have blockade of the renin–angiotensin system, which drives intraglomerular pressure (level A evidence for nondiabetic chronic renal disease). Treatment with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces proteinuria by approximately 30%, and significantly delays doubling of serum creatinine and progression to end-stage renal disease in patients with nondiabetic chronic renal disease. These classes of medications are contraindicated in pregnancy. The use of combination ACE inhibitors/ARB therapies is controversial. ACE inhibitors or ARB treatments are superior to calcium-channel blockers and diuretics alone in preserving renal function in chronic kidney disease.
The Task Force Panel recommended that careful attention be paid to control of hypertension, with a target of ≤130/80 mm Hg (level A evidence for nondiabetic chronic renal disease). The Task Force Panel also recommended that statin therapy be introduced in patients with low-density lipoprotein cholesterol >100 mg/dl (level C evidence). Note that a glomerular filtration rate <60

ml/minute/1.73 m^2 (equivalent to a serum creatinine level >1.5 mg/dl or 133 µmoles/liter) is a risk factor for accelerated atherosclerosis. SLE itself is also an independent risk factor for accelerated atherosclerosis.
Finally, the Task Force Panel recommended that women of child-bearing potential with active or prior LN receive counseling regarding pregnancy risks conferred by the disease and its treatments (level C evidence).

Recommendations for Induction of Improvement in Patients with ISN Class III/IV Lupus Glomerulonephritis

The Task Force Panel recommended mycophenolate mofetil (MMF) (2–3 gm total daily orally) or intravenous (IV) cyclophosphamide (CYC) along with glucocorticoids (level A evidence) (see Figure 2 in the original guideline document). MMF and CYC are considered equivalent based on recent high-quality studies, a meta-analysis, and expert opinion. Long-term studies with MMF are not as abundant as those with CYC; data show good results for induction therapy with MMF of 3 gm total dose daily for 6 months, followed by maintenance with lower doses of MMF for 3 years. MMF has been similar in efficacy in all races studied to date (whites, Asians, African Americans, and Latin/Hispanic Americans). The Aspreva Lupus Management Study (ALMS) trial comparing response rates of LN to MMF plus glucocorticoids showed similar improvement in whites, Asians, and other races (primarily African Americans and Hispanics). However, *The Task Force Panel voted that Asians compared to non-Asians might require lower doses of MMF for similar efficacy (level C evidence).* Therefore, the physician might aim for 3 gm per day total daily highest dose in non-Asians and 2 gm per day in Asians. There is evidence that African Americans and Hispanics with LN respond less well to IV CYC than do patients of white or Asian races. MMF/mycophenolic acid (MPA) may be an initial choice more likely to induce improvement in patients who are African American or Hispanic.
The exact suggested dose of MMF varied based on the clinical scenario: for those with class III/IV without cellular crescents and for those with proteinuria and a stable creatinine for whom a renal biopsy sample cannot be obtained, both 2 gm and 3 gm total daily doses were acceptable to the Task Force Panel, while a dose of 3 gm daily was favored for those with class III/IV and crescents and for those with proteinuria and a recent significant rise in creatinine.
Some evidence suggests that MPA and enteric-coated mycophenolate sodium are less likely than MMF to cause nausea and diarrhea, but this is controversial, and the exact equivalency of the preparations is not firmly established. *The Core Expert Panel recommended that MMF and MPA are likely to be equivalent in inducing improvement of LN, with 1,440–2,160 mg total daily dose of MPA roughly equivalent to 2,000–3,000 mg total daily dose of MMF.* Some investigators have suggested that serum levels of MPA, the active metabolite of MMF, should be measured at the trough or peak (1 hour after a dose), and treatment of SLE should be guided by these levels. However, there are not enough data at this time to make recommendations for monitoring of drug levels.
There are two regimens of IV CYC recommended by the Task Force Panel: 1) low-dose "Euro-Lupus" CYC (500 mg IV once every 2 weeks for a total of 6 doses), followed by maintenance therapy with daily oral azathioprine (AZA) or daily oral MMF (level B evidence), and 2) high-dose CYC (500–1,000 mg/m^2 IV once a month for 6 doses), followed by maintenance treatment with MMF or AZA (level A evidence) (see Figure 2 in the original guideline document). If CYC is being considered for treatment, the Core Expert Panel recommended IV CYC at the low "Euro-Lupus" dose for white patients with Western European or Southern European racial/ethnic backgrounds (level B evidence). In European study patients, the low- and high-dose regimens were equivalent in efficacy, and serious infections were less frequent with the lower doses. The low- and high-dose regimens have not been compared in nonwhite racial groups. Ten years of followup comparing low- and high-dose regimens showed similar rates of LN flares, end-stage renal disease, and doubling of the serum creatinine.
Pulse IV glucocorticoids (500–1,000 mg methylprednisolone daily for 3 doses) in combination with immunosuppressive therapy is recommended by the Task Force Panel, followed by daily oral glucocorticoids (0.5–1 mg/kg/day), followed by a taper to the minimal amount necessary to control disease (level C evidence). There are insufficient data to recommend a specific steroid taper because the nephritis and extrarenal manifestations vary from patient to patient. There was no consensus reached regarding the use of monthly IV methylprednisolone with monthly IV CYC.
Although AZA has been used to treat LN, the Task Force Panel did not recommend it as one of the first choices for induction therapy.
The panel recommends that most patients be followed for 6 months after initiation of induction treatment with either CYC or MMF before making major changes in treatment other than alteration of glucocorticoid doses, unless there is clear evidence of worsening at 3 months (50% or more worsening of proteinuria or serum creatinine; level A evidence).
Fertility issues are often a concern for young SLE patients with nephritis. In a discussion, the Task Force Panel recommended that MMF was preferable to CYC for patients who express a major concern with fertility preservation, since high-dose CYC can cause permanent infertility in both women and men (level A evidence of gonadal toxicity). Six months of high-dose IV CYC was associated with approximately 10% sustained infertility in young women, and higher rates in older women. If 6 months of CYC were followed by quarterly doses, there was a higher rate of infertility. The Task Force Panel did not reach a consensus on the use of leuprolide in patients with SLE receiving CYC as a means to preserve fertility. They also noted that MMF is teratogenic (class D in US Food and Drug Administration [FDA] ranking). Therefore, the physician should be sure that a patient is not pregnant before prescribing MMF or MPA, and the medications should be stopped for at least 6 weeks before pregnancy is attempted.

Recommendations for Induction of Improvement in Patients with Class IV or IV/V Plus Cellular Crescents

The Task Force Panel recommended either CYC or MMF for induction of improvement in this type of LN (level C evidence), along with IV pulses of high-dose glucocorticoid and initiation of oral glucocorticoids at the higher-range dosage, 1 mg/kg/day orally (see Figure 2 in the original guideline document). For the purpose of these recommendations statements, the presence of any crescents on a renal biopsy sample was considered crescentic LN. Until recently, experts have favored high-dose IV CYC for treatment of LN with cellular crescents. In general, the presence of crescents indicates a poorer prognosis, even with appropriate treatment.

Further recommendations for a pregnant patient with crescentic glomerulonephritis are provided in the section on "Treatment of LN in Patients Who Are Pregnant," below.

Recommendations for Induction of Improvement in Patients with Class V "Pure Membranous" LN

The Task Force Panel recommends that patients with pure class V LN and with nephrotic range proteinuria be started on prednisone (0.5 mg/kg/day) plus MMF 2–3 gm total daily dose (level A evidence) (see Figure 3 in the original guideline document).

Other therapies for membranous LN have been reported; however, the Task Force Panel did not reach consensus on a recommendation regarding those therapies.

Recommendations for Maintaining Improvement in Patients Who Respond to Induction Therapy

The Task Force Panel recommended that either AZA or MMF be used for maintenance therapy (level A evidence) (see Figure 2 in the original guideline document). The Task Force Panel did not vote on the rate of medication taper during the maintenance phase; to date, there are no adequate data to inform the physician regarding how rapidly AZA or MMF can be tapered or withdrawn.

Recommendations for Changing Therapies in Patients Who Do Not Respond Adequately to Induction Therapy

In patients who fail to respond after 6 months of treatment (based on the treating physician's clinical impression) with glucocorticoids plus MMF or CYC, the Task Force Panel recommends a switch of the immunosuppressive agent from either CYC to MMF, or from MMF to CYC, with these changes accompanied by IV pulses of glucocorticoids for 3 days (level C evidence) (see Figure 2 in the original guideline document). For CYC, either low dose or high dose can be used in white individuals, as discussed above in the section on "Recommendations for Induction of Improvement in Patients with ISN Class III/IV Lupus Glomerulonephritis," above. Evidence to support these opinions is not as strong as evidence for the efficacy of initial induction therapy. *The panel also voted that in some cases rituximab can be used in patients whose nephritis fails to improve or worsens after 6 months of one induction therapy, or after the patient has failed both CYC and MMF treatments (level C evidence).* The Task Force Panel did not reach consensus regarding the use of calcineurin inhibitors in this setting; however, there is evidence for their efficacy as an induction agent and in refractory disease.

There is evidence in open-label trials that LN may respond to rituximab treatment. Prospective, randomized, placebo-controlled trials did not show a significant difference between rituximab and placebo (on a background of MMF and glucocorticoids) after 1 year of treatment.

Evidence to support the use of cyclosporine or tacrolimus in LN is from open trials and recent prospective clinical trials; additional prospective trials are in progress. In a recent prospective trial, tacrolimus was equivalent to high-dose IV CYC in inducing complete and partial remissions of LN over a 6-month period. In another 4-year–long prospective trial, cyclosporine was similar to AZA in preventing renal flares in patients receiving maintenance therapy.

If nephritis is worsening in patients treated for 3 months with glucocorticoids plus CYC or MMF, the Task Force Panel recommended that the clinician can choose any of the alternative treatments discussed (level C evidence). Although combinations of MMF and calcineurin inhibitors and of rituximab and MMF are being studied and might be considered for those who have failed the recommended induction therapies, data are not robust enough at this time to include them for voting scenarios.

The FDA has approved belimumab for use in seropositive patients with SLE who have active disease in spite of prior therapies.

Identification of Vascular Disease in Patients with SLE and Renal Abnormalities

Several types of vascular involvement can occur in renal tissue of SLE, including vasculitis, fibrinoid necrosis with narrowing of small arteries/arterioles ("bland" vasculopathy), thrombotic microangiopathy, and renal vein thrombosis. In general, vasculitis is treated similarly to the more common forms of LN discussed above. Bland vasculopathy is highly associated with hypertension; it is not clear which comes first, SLE or hypertension. Thrombotic microangiopathy can be associated with a thrombotic thrombocytopenia–like picture. *The Task Force Panel recommended that thrombotic microangiopathy be treated primarily with plasma exchange therapy (level C evidence)*

Treatment of LN in Patients Who Are Pregnant

The Task Force Panel recommended several approaches for management of LN in women who are pregnant (all level C evidence) (see Figure 4 in the original guideline document). In patients with prior LN but no current evidence of systemic or renal disease activity, no nephritis medications are necessary. Patients with mild systemic activity may be treated with HCQ; this probably reduces activity of SLE during pregnancy. If clinically active nephritis is present, or there is substantial extrarenal disease activity, the clinician may prescribe glucocorticoids at doses necessary to control disease activity, and if necessary AZA can be added. High-dose glucocorticoid therapy in patients with SLE is associated with a high risk of maternal complications such as hypertension and diabetes mellitus. MMF, CYC, and methotrexate should be avoided because they are teratogenic in humans. Although AZA is listed as pregnancy category D in Micromedex, cross-sectional studies have shown that the risk of fetal abnormalities is low. The dose of AZA should not exceed 2 mg/kg in a pregnant woman. *For patients with a persistently active nephritis with documented or suspected class III or IV with crescents, consideration of delivery after 28 weeks for a viable fetus is recommended.*

Monitoring Activity of LN

Recommendations for monitoring LN are shown in the following table, and result from votes of the Task Force Panel (level C evidence).

Table. Recommended Monitoring of Lupus Nephritis*

	Blood Pressure	Urinalysis	Protein/Creatinine Ratio	Serum Creatinine	C3/C4 Levels	Anti-DNA
Active nephritis at onset of treatment	1	1	1	1	2†	3
Previous active nephritis, none currently	3	3	3	3	3	6
Pregnant with active GN at onset of treatment	1	1	1	1	1	1
Pregnant with previous nephritis, none currently	1	1	3	3	3	3
No prior or current nephritis	3	6	6	6	6	6

*Values are the monthly intervals suggested as the minimum frequency at which the indicated laboratory tests should be measured in the systemic lupus erythematosus scenarios shown in the left-hand column. GN = glomerulonephritis.
†Opinion of authors based on a study published after the Task Force Panel had voted.

Definitions:

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care

Clinical Algorithm(s)

The original guideline document contains clinical algorithms for:

- Class III/IV induction therapy for lupus nephritis (LN)
- Treatment of class V LN without proliferative changes and with nephrotic range proteinuria (>3 gm/24 hours)
- Treatment of class III, IV, and V LN in patients who are pregnant"[128]

KDIGO clinical practice guideline for glomerulonephritis(2012)[113]

"Limiting the long-term adverse effects of treatment is an important objective. Children with frequently relapsing (FR) or steroid-dependent steroid-sensitive nephrotic syndrome (SD SSNS) require prolonged corticosteroid therapy, which is associated with significant adverse effects, including impaired linear growth, behavioral changes, obesity, Cushing's syndrome, hypertension, ophthalmological disorders, impaired glucose tolerance, and reduced bone mineral density. Adverse effects may persist into adult life in young people, who continue to relapse after puberty. To reduce the risk of corticosteroid related adverse effects, children with FR or SD SSNS may require other agents, including alkylating agents (cyclophosphamide, chlorambucil) and calcineurin inhibitors (CNI) (cyclosporine, tacrolimus). Adverse effects of these agents include increased risk of infection and reduced fertility (alkylating agents) and kidney dysfunction and hypertension (CNI)."

"Major Recommendations

Definitions of the strength of recommendation (Level 1, Level 2, or Not Graded), and the quality of the supporting evidence (A-D) are provided at the end of the 'Major Recommendations' field.

Steroid-Sensitive Nephrotic Syndrome in Children (SSNS)

Treatment of the Initial Episode of SSNS

- The Work Group recommends that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (*1B*)
  - The Work Group recommends that oral prednisone be administered as a single daily dose (*1B*) starting at 60 mg/m^2/d or 2 mg/kg/d to a maximum 60 mg/d. (*1D*)
  - The Work Group recommends that daily oral prednisone be given for 4–6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2–5 months with tapering of the dose. (*1B*)

Treatment of Relapsing SSNS with Corticosteroids

- Corticosteroid therapy for children with infrequent relapses of SSNS:
  - The Work Group suggests that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m^2 or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. (*2D*)
  - The Work Group suggests that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m^2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (*2C*)

- Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:
    - The Work Group suggests that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (*2C*)
    - The Work Group suggests that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (*2D*)
    - The Work Group suggests that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (*2D*)
    - The Work Group suggests that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (*2C*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in randomized controlled trials (RCTs) depending on the country of origin. All later references to prednisone in this section refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Treatment of FR and SD SSNS with Corticosteroid-Sparing Agents

- The Work Group recommends that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (*1B*)
- The Work Group recommends that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for FR SSNS. (*1B*) The Work Group suggests that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (*2C*)
    - The Work Group suggests that cyclophosphamide (2 mg/kg/d) be given for 8–12 weeks (maximum cumulative dose 168 mg/kg). (*2C*)
    - The Work Group suggests that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (*2D*)
    - The Work Group suggests that chlorambucil (0.1–0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (*2C*)
    - The Work Group suggests that second courses of alkylating agents not be given. (*2D*)
- The Work Group recommends that levamisole be given as a corticosteroid-sparing agent. (*1B*)
    - The Work Group suggests that levamisole be given at a dose of 2.5 mg/kg on alternate days (*2B*) for at least 12 months (*2C*) as most children will relapse when levamisole is stopped.
- The Work Group recommends that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (*1C*)
    - The Work Group suggests that cyclosporine be administered at a dose of 4–5 mg/kg/d (starting dose) in two divided doses. (*2C*)
    - The Work Group suggests that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (*2D*)
    - Monitor CNI levels during therapy to limit toxicity. (*Not Graded*)
    - The Work Group suggests that CNIs be given for at least 12 months, as most children will relapse when CNIs are stopped. (*2C*)
- The Work Group suggests that mycophenolate mofetil (MMF) be given as a corticosteroid-sparing agent. (*2C*)
    - The Work Group suggests that MMF (starting dose 1200 mg/m^2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (*2C*)
- The Work Group suggests that rituximab be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (*2C*)
- The Work Group suggests that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*2C*)
- The Work Group recommends that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*1B*)

Indication for Kidney Biopsy

- Indications for kidney biopsy in children with SSNS are (*Not Graded*):
    - Late failure to respond following initial response to corticosteroids
    - A high index of suspicion for a different underlying pathology
    - Decreasing kidney function in children receiving CNIs

Immunizations in Children with SSNS

- To reduce the risk of serious infections in children with SSNS (*Not Graded*):
    - Give pneumococcal vaccination to the children.
    - Give influenza vaccination annually to the children and their household contacts.

- Defer vaccination with live vaccines until prednisone dose is below either 1 mg/kg daily (<20 mg/d) or 2 mg/kg on alternate days (<40 mg on alternate days).
- Live vaccines are contraindicated in children receiving corticosteroid-sparing immunosuppressive agents.
- Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child but avoid direct exposure of the child to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.
- Following close contact with Varicella infection, give nonimmune children on immunosuppressive agents varicella zoster immune globulin, if available.

Steroid-Resistant Nephrotic Syndrome (SRNS) in Children

Evaluation of Children with SRNS

- The Work Group suggests a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (*2D*)
- The following are required to evaluate the child with SRNS (*Not Graded*):
  - A diagnostic kidney biopsy
  - Evaluation of kidney function by glomerular filtration rate (GFR) or estimated GFR (eGFR)
  - Quantitation of urine protein excretion

Treatment Recommendations for SRNS

- The Work Group recommends using a CNI as initial therapy for children with SRNS. (*1B*)
  - The Work Group suggests that CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. (*2C*)
  - The Work Group suggests CNIs be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. (*2C*)
  - The Work Group suggests that low-dose corticosteroid therapy be combined with CNI therapy. (*2D*)
- The Work Group recommends treatment with angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARBs) for children with SRNS. (*1B*)
- In children who fail to achieve remission with CNI therapy:
  - The Work Group suggests that mycophenolate mofetil (*2D*), high-dose corticosteroids (*2D*), or a combination of these agents (*2D*) be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids.
  - The Work Group suggests that cyclophosphamide not be given to children with SRNS. (*2B*)
- In patients with a relapse of nephrotic syndrome after complete remission, the Work Group suggests that therapy be restarted using any one of the following options: (*2C*)
  - Oral corticosteroids (*2D*)
  - Return to previous successful immunosuppressive agent (*2D*)
  - An alternative immunosuppressive agent to minimize potential cumulative toxicity (*2D*)

Minimal-Change Disease (MCD) in Adults

Treatment of Initial Episode of Adult MCD

- The Work Group recommends that corticosteroids be given for initial treatment of nephrotic syndrome. (*1C*)
- The Work Group suggests prednisone or prednisolone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg). (*2C*)
- The Work Group suggests the initial high dose of corticosteroids, if tolerated, be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. (*2C*)
- In patients who remit, the Work Group suggests that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission. (*2D*)
- For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis), the Work Group suggests oral cyclophosphamide or CNIs as discussed in frequently relapsing MCD. (*2D*)
- The Work Group suggests using the same initial dose and duration of corticosteroids for infrequent relapses as in the recommendations above. (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this section refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

FR/SD MCD

- The Work Group suggests oral cyclophosphamide 2–2.5 mg/kg/d for 8 weeks. (*2C*)
- The Work Group suggests CNI (cyclosporine 3–5 mg/kg/d or tacrolimus 0.05–0.1 mg/kg/d in divided doses) for 1–2 years for FR/SD MCD patients who have relapsed despite cyclophosphamide, or for people who wish to preserve their fertility. (*2C*)

- The Work Group suggests MMF 500–1000 mg twice daily for 1–2 years for patients who are intolerant of corticosteroids, cyclophosphamide, and CNIs. (*2D*)

Corticosteroid-Resistant MCD

- Re-evaluate patients who are corticosteroid-resistant for other causes of nephrotic syndrome. (*Not Graded*)

Supportive Therapy

- The Work Group suggests that MCD patients who have acute kidney injury (AKI) be treated with renal replacement therapy as indicated, but together with corticosteroids, as for a first episode of MCD. (*2D*)
- The Work Group suggests that, for the initial episode of nephrotic syndrome associated with MCD, statins not be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria. (*2D*)

Idiopathic Focal Segmental Glomerulosclerosis in Adults

Initial Evaluation of FSGS

- Undertake thorough evaluation to exclude secondary forms of FSGS. (*Not Graded*)
- Do not routinely perform genetic testing. (*Not Graded*)

Initial Treatment of FSGS

- The Work Group recommends that corticosteroid and immunosuppressive therapy be considered only in idiopathic FSGS associated with clinical features of the nephrotic syndrome. (*1C*)
- The Work Group suggests prednisone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). (*2C*)
- The Work Group suggests the initial high dose of corticosteroids be given for a minimum of 4 weeks; continue high-dose corticosteroids up to a maximum of 16 weeks, as tolerated, or until complete remission has been achieved, whichever is earlier. (*2D*)
- The Work Group suggests corticosteroids be tapered slowly over a period of 6 months after achieving complete remission. (*2D*)
- The Work Group suggests CNIs be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis). (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this section refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Treatment for Relapse

- The Work Group suggests that a relapse of nephrotic syndrome is treated as per the recommendations for relapsing MCD in adults (see recommendations above). (*2D*)

Treatment for Steroid-Resistant FSGS

- For steroid-resistant FSGS, the Work Group suggests that cyclosporine at 3–5 mg/kg/d in divided doses be given for at least 4–6 months. (*2B*)
- If there is a partial or complete remission, the Work Group suggests continuing cyclosporine treatment for at least 12 months, followed by a slow taper. (*2D*)
- The Work Group suggests that patients with steroid-resistant FSGS, who do not tolerate cyclosporine, be treated with a combination of mycophenolate mofetil and high-dose dexamethasone. (*2C*)

Idiopathic Membranous Nephropathy (IMN)

Evaluation of MN

- Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven membranous nephropathy. (*Not Graded*)

Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents (see the recommendations for children with IMN in the section below).

- The Work Group recommends that initial therapy be started only in patients with nephrotic syndrome AND when at least one of the following conditions is met:
    - Urinary protein excretion persistently exceeds 4 g/d AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and antiproteinuric therapy during an observation period of at least 6 months (*1B*)
    - The presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome (*1C*)
    - Serum creatinine (SCr) has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min/1.73 m^2 AND this change is not explained by superimposed complications. (*2C*)
- Do not use immunosuppressive therapy in patients with a SCr persistently >3.5 mg/dl (>309 µmol/l) (or an eGFR <30 ml/min per 1.73 m^2) AND reduction of kidney size on ultrasound (e.g., <8 cm in length) OR those with concomitant severe or potentially life-threatening infections. (*Not Graded*)

Initial Therapy of IMN

- The Work Group recommends that initial therapy consist of a 6-month course of alternating monthly cycles of oral and intravenous (i.v.) corticosteroids, and oral alkylating agents (see Table 15 in the original guideline document). (*1B*)
- The Work Group suggests using cyclophosphamide rather than chlorambucil for initial therapy. (*2B*)
- The Work Group recommends patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present (see 'Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents,' above). (*1C*)
- Perform a repeat kidney biopsy only if the patient has rapidly deteriorating kidney function (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria (>15 g/d). (*Not Graded*)
- Adjust the dose of cyclophosphamide or chlorambucil according to the age of the patient and eGFR. (*Not Graded*)
- The Work Group suggests that continuous daily (noncyclical) use of oral alkylating agents may also be effective, but can be associated with greater risk of toxicity, particularly when administered for >6 months. (*2C*)

Alternative Regimens for the Initial Therapy of IMN: CNI Therapy

- The Work Group recommends that cyclosporine or tacrolimus be used for a period of at least 6 months in patients who meet the criteria for initial therapy (as described in 'Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents,') but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen (see Table 18 in the original guideline document for specific recommendations for dosage during therapy). (*1C*)
- The Work Group suggests that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. (*2C*)
- The Work Group suggests that the dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months. (*2C*)
- The Work Group suggests that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr (>20%) during therapy. (*Not Graded*) (See Table 18 in the original guideline document for specific CNI-based regimen dosage recommendations.)

Regimens Not Recommended or Suggested for Initial Therapy of IMN

- The Work Group recommends that corticosteroid monotherapy not be used for initial therapy of IMN. (*1B*)
- The Work Group suggests that monotherapy with MMF not be used for initial therapy of IMN. (*2C*)

Treatment of IMN Resistant to Recommended Initial Therapy

- The Work Group suggests that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (*2C*)
- The Work Group suggests that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (*2C*)

Treatment for Relapses of Nephrotic Syndrome in Adults with IMN

- The Work Group suggests that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (*2D*)
- The Work Group suggests that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy (see 'Initial Therapy of IMN,' above), the regimen be repeated only once for treatment of a relapse. (*2B*)

Treatment of IMN in Children

- The Work Group suggests that treatment of IMN in children follows the recommendations for treatment of IMN in adults. (*2C*) (See 'Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents' and 'Initial Therapy on IMN,' above.)
- The Work Group suggests that no more than one course of the cyclical corticosteroid/alkylating-agent regimen be given in children. (*2D*)

Prophylactic Anticoagulants in IMN

- The Work Group suggests that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin (<2.5 g/dl [<25 g/l]) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin. (*2C*)

Idiopathic Membranoproliferative Glomerulonephritis (MPGN)

Evaluation of MPGN

- Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20 in the original guideline document). (*Not Graded*)

Treatment of Idiopathic MPGN

- The Work Group suggests that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate day or daily corticosteroids with initial therapy limited to less than 6 months. (*2D*)

Infection-Related Glomerulonephritis (GN)

- For the following infection-related GN, the Work Group suggests appropriate treatment of the infectious disease and standard approaches to management of the kidney manifestations: (*2D*)
    - Poststreptococcal GN
    - Infective endocarditis-related GN
    - Shunt nephritis

Hepatitis C Virus (HCV) Infection–Related GN

- For HCV-infected patients with CKD Stages 1 or 2 and GN, the Work Group suggests combined antiviral treatment using pegylated interferon and ribavirin as in the general population. (*2C*)
    - Titrate ribavirin dose according to patient tolerance and level of renal function. (*Not Graded*)
- For HCV-infected patients with CKD Stages 3, 4, or 5 and GN not yet on dialysis, the Work Group suggests monotherapy with pegylated interferon, with doses adjusted to the level of kidney function. (*2D*)
- For patients with HCV and mixed cryoglobulinemia (immunoglobulin G [IgG]/immunoglobulin M [IgM]) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia, the Work Group suggests either plasmapheresis, rituximab, or cyclophosphamide, in conjunction with i.v. methylprednisolone, and concomitant antiviral therapy. (*2D*)

Hepatitis B Virus (HBV) Infection–Related GN

- The Work Group recommends that patients with HBV infection and GN receive treatment with interferon-α or with nucleoside analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (see Table 23 in the original guideline document). (*1C*)
- The Work Group recommends that the dosing of these antiviral agents be adjusted to the degree of kidney function. (*1C*)

Human Immunodeficiency Virus (HIV) Infection–Related Glomerular Disorders

- The Work Group recommends that antiretroviral therapy be initiated in all patients with biopsy-proven HIV-associated nephropathy, regardless of CD4 count. (*1B*)

Schistosomal, Filarial, and Malarial Nephropathies

- The Work Group suggests that patients with GN and concomitant malarial, schistosomal, or filarial infection be treated with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. (*Not Graded*)
- The Work Group suggests that corticosteroids or immunosuppressive agents not be used for treatment of schistosomal-associated GN, since the GN is believed to be the direct result of infection and the attendant immune response to the organism. (*2D*)
- The Work Group suggests that blood culture for *Salmonella* be considered in all patients with hepatosplenic schistosomiasis who show urinary abnormalities and/or reduced GFR. (*2C*)
    - The Work Group suggests that all patients who show a positive blood culture for *Salmonella* receive anti-*Salmonella* therapy. (*2C*)

<u>Immunoglobulin A Nephropathy (IgAN)</u>

Initial Evaluation Including Assessment of Risk of Progressive Kidney Disease

- Assess all patients with biopsy-proven IgAN for secondary causes of IgAN. (*Not Graded*)
- Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (*Not Graded*)
- Pathological features may be used to assess prognosis. (*Not Graded*)

Antiproteinuric and Antihypertensive Therapy

- The Work Group recommends long-term ACE-I or ARB treatment when proteinuria is >1 g/d, with up-titration of the drug depending on blood pressure. (*1B*)
- The Work Group suggests ACE-I or ARB treatment if proteinuria is between 0.5 to 1 g/d (in children, between 0.5 to 1 g/d per 1.73 m^2). (*2D*)
- The Work Group suggests the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (*2C*)
- In IgAN, use blood pressure treatment goals of <130/80 mmHg in patients with proteinuria <1 g/d, and <125/75 mmHg when initial proteinuria is >1 g/d (see Chapter 2 in the original guideline document). (*Not Graded*)

Corticosteroids

- The Work Group suggests that patients with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR <50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

Immunosuppressive Agents (Cyclophosphamide, Azathioprine, MMF, Cyclosporine)

- The Work Group suggests not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see 'Crescentic IgAN,' below). (*2D*)
- The Work Group suggests not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see 'Atypical Forms of IgAN,' below). (*2C*)
- The Work Group suggests not using MMF in IgAN. (*2C*)

Other Treatments

Fish Oil Treatment

- The Work Group suggests using fish oil in the treatment of IgAN with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). (*2D*)

Antiplatelet Agents

- The Work Group suggests not using antiplatelet agents to treat IgAN. (*2C*)

Tonsillectomy

- The Work Group suggests that tonsillectomy not be performed for IgAN. (*2C*)

Atypical Forms of IgAN

MCD with Mesangial IgA Deposits

- The Work Group recommends treatment as for MCD (see 'Minimal-Change Disease in Adults,' above) in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. (*2B*)

AKI Associated with Macroscopic Hematuria

- Perform a repeat kidney biopsy in IgAN patients with AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. (*Not Graded*)
- The Work Group suggests general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing only acute tubular necrosis (ATN) and intratubular erythrocyte casts. (*2C*)

Crescentic IgAN

- Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. (*Not Graded*)
- The Work Group suggests the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (see 'Pauci-Immune Focal and Segmental Necrotizing Glomerulonephritis,' below). (*2D*)

Henoch-Schönlein Purpura (HSP) Nephritis

Treatment of HSP Nephritis in Children

- The Work Group suggests that children with HSP nephritis and persistent proteinuria, >0.5–1 g/d per 1.73 m^2, are treated with ACE-I or ARBs. (*2D*)
- The Work Group suggests that children with persistent proteinuria, >1 g/d per 1.73 m^2, after a trial of ACE-I or ARBs, and GFR >50 ml/min per 1.73 m^2, be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see 'Immunoglobulin A Nephropathy,' above). (*2D*)

Treatment of Crescentic HSP Nephritis in Children

- The Work Group suggests that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN (see 'Crescentic IgAN,' above). (*2D*)

Prevention of HSP Nephritis in Children

- The Work Group recommends not using corticosteroids to prevent HSP nephritis. (*1B*)

HSP Nephritis in Adults

- The Work Group suggests that HSP nephritis in adults be treated the same as in children. (*2D*)

Lupus Nephritis (LN)

Class I LN (Minimal-Mesangial LN)

- The Work Group suggests that patients with class I LN be treated as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

Class II LN (Mesangial-Proliferative LN)

- Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (*2D*)
- The Work Group suggests that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (see 'Minimal-change Disease in Adults,' above). (*2D*)

Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Initial Therapy

- The Work Group recommends initial therapy with corticosteroids (*1A*), combined with either cyclophosphamide (*1B*) or MMF (*1B*).
- The Work Group suggests that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (*2D*)

Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Maintenance Therapy

- The Work Group recommends that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent). (*1B*)
- The Work Group suggests that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (*2C*)

- The Work Group suggests that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)
- If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)
- While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, the Work Group suggests that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

Class V LN (Membranous LN)

- The Work Group recommends that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)
- The Work Group suggests that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF (*2D*), or azathioprine (*2D*).

General Treatment of LN

- The Work Group suggests that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (*2C*)

Class VI LN (Advanced Sclerosis LN)

- The Work Group recommends that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

Relapse of LN

- The Work Group suggests that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (*2B*)
    - If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then the Work Group suggests a non–cyclophosphamide-based initial regimen be used (see Regimen D, Table 28 in the original guideline document). (*2B*)
- Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (*Not Graded*)

Treatment of Resistant Disease

- In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (*Not Graded*)
- Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens (see 'Class III LN [Focal LN] and Class IV LN [Diffuse LN]—Initial Therapy,' above). (*Not Graded*)
- The Work Group suggests that nonresponders who have failed more than one of the recommended initial regimens (see 'Class III LN [Focal LN] and Class IV LN [Diffuse LN]—Initial Therapy,' above) may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (*2D*)

Systemic Lupus and Thrombotic Microangiopathy

- The Work Group suggests that the antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target international normalized ratio [INR] 2–3). (*2D*)
- The Work Group suggests that patients with systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange as for patients with TTP without systemic lupus. (*2D*)

Systemic Lupus and Pregnancy

- The Work Group suggests that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (*2D*)
- The Work Group recommends that cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy. (*1A*)
- The Work Group suggests that hydroxychloroquine be continued during pregnancy. (*2B*)
- The Work Group recommends that LN patients who become pregnant while being treated with MMF be switched to azathioprine. (*1B*)
- The Work Group recommends that, if LN patients relapse during pregnancy, they receive treatment with corticosteroids and, depending on the severity of the relapse, azathioprine. (*1B*)
- If pregnant patients are receiving corticosteroids or azathioprine, the Work Group suggests that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (*2D*)
- The Work Group suggests administration of low-dose aspirin during pregnancy to decrease the risk of fetal loss. (*2C*)

LN in Children

- The Work Group suggests that children with LN receive the same therapies as adults with LN, with dosing based on patient size and GFR. (*2D*)

<u>Pauci-Immune Focal and Segmental Necrotizing Glomerulonephritis</u>

Initial Treatment of Pauci-Immune Focal and Segmental Necrotizing GN

- The Work Group recommends that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)
- The Work Group recommends that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

Special Patient Populations

- The Work Group recommends the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)
- The Work Group suggests the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)
- The Work Group suggests the addition of plasmapheresis for patients with overlap syndrome of antineutrophil cytoplasmic antibodies (ANCA) vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see 'Treatment of Anti-Glomerular Basement Membrane Antibody Glomerulonephritis,' below) (*2D*)
- The Work Group suggests discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis dependent and who do not have any extrarenal manifestations of disease. (*2C*)

Maintenance Therapy

- The Work Group recommends maintenance therapy in patients who have achieved remission. (*1B*)
- The Work Group suggests continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (*2D*)
- The Work Group recommends no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (*1C*)

Choice of Agent for Maintenance Therapy

- The Work Group recommends azathioprine 1–2 mg/kg/d orally as maintenance therapy. (*1B*)
- The Work Group suggests that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. (*2C*)
- The Work Group suggests trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (*2B*)
- The Work Group suggests methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2. (*1C*)
- The Work Group recommends not using etanercept as adjunctive therapy. (*1A*)

Treatment of Relapse

- The Work Group recommends treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see 'Initial Treatment of Pauci-Immune Focal and Segmental Necrotizing GN,' above). (*1C*)
- The Work Group suggests treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

Treatment of Resistant Disease

- In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, the Work Group recommends the addition of rituximab (*1C*), and suggest i.v. immunoglobulin (*2C*) or plasmapheresis (*2D*) as alternatives.

Monitoring

- The Work Group suggests not changing immunosuppression based on changes in ANCA titer alone. (*2D*)

Transplantation

- The Work Group recommends delaying transplantation until patients are in complete extrarenal remission for 12 months. (*1C*)
- The Work Group recommends not delaying transplantation for patients who are in complete remission but are still ANCA-positive. (*1C*)

<u>Treatment of Anti-Glomerular Basement Membrane Antibody Glomerulonephritis (GBM GN)</u>

Treatment of Anti-GBM GN

- The Work Group recommends initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis (see Table 31 in the original guideline document) in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage. (*1B*)
- Start treatment for anti-GBM GN without delay once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis (Table 31 in the original guideline document) while waiting for confirmation. (*Not Graded*)
- The Work Group recommends no maintenance immunosuppressive therapy for anti-GBM GN. (*1D*)
- Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months. (*Not Graded*)

<u>Definitions</u>:

Nomenclature and Description for Grading Recommendations

	Implications		
Grade[a]	**Patients**	**Clinicians**	**Policy**
Level 1 'The Work Group recommends'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'The Work Group suggests'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

[a]The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Clinical Algorithm(s)

A management algorithm for patients with acute kidney injury (AKI) associated with macroscopic hematuria is provided in the original guideline document."[113]

References

1. Prescribing Data. http://www.cdc.gov/drugoverdose/data/prescribing.html. Accessed 6 June 2016.
2. Gasbarro R. Titration and Conversion of Opioid Analgesics – Getting Chronic Pain under Control while Minimizing Adverse Effects. http://www.freece.com/FreeCe/CECatalog_Details.aspx?ID=e46065fa-41b0-4a94-899c-cf897b213a9c.
3. Fudin J. What Is the Maximum Safe Dose of Opioids? February 21, 2008. http://www.medscape.com/viewarticle/569913.
4. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. *J Pain Symptom Manage.* Jan 2000;19(1):53-62.
5. Goldsmith CJ, Hammad S. A review of the re-emergence of adrenocorticotrophic hormone therapy in glomerular disease, more than a drug of last resort? *Clin Kidney J.* Aug 2015;8(4):430-432.
6. Gettig J, Cummings JP, Matuszewski K. H.P. Acthar gel and cosyntropin review: clinical and financial implications. *P T.* May 2009;34(5):250-257.
7. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database of Systematic Reviews.* 2006(3).
8. Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department. . http://www.guideline.gov/content.aspx?id=38439&search=opioid*.
9. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician.* Jul 2012;15(3 Suppl):S67-116.
10. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Reviews.* 2010(1).
11. Product Information: Meperidine HCl oral tablets solution, meperidine HCl oral tablets solution. Roxane Laboratories, Inc. (per DailyMed), 2011.
12. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* Jan 2013;41(1):263-306.
13. Micromedex. http://www.micromedexsolutions.com/micromedex2/librarian/CS/40177F/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/330F6A/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/pf.HomePage?navitem=topHome&isToolPage=true.
14. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis.* Dec 2003;62(12):1145-1155.
15. International Association for the Study of Pain, Subcommittee on Taxonomy. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Pain 1986; Vol. Suppl 3:S1-S225. .
16. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Cmaj.* May 23 2006;174(11):1589-1594.
17. Stannard C, Gaskell H, Derry S, et al. Hydromorphone for neuropathic pain in adults. *Cochrane Database of Systematic Reviews.* 2016(5).
18. Chronic Pain Management (Lexi-Drugs). http://online.lexi.com.ezproxy.lib.utah.edu/lco/action/doc/retrieve/docid/patch_f/5261.
19. Overview of the treatment of chronic pain http://www.uptodate.com.ezproxy.lib.utah.edu/contents/overview-of-the-treatment-of-chronic-pain?source=machineLearning&search=chronic+non-cancer+pain&selectedTitle=1%7E150&sectionRank=2&anchor=H195876576#H195876576.

20. Hamano S, Yamashita S, Tanaka M, Yoshinari S, Minamitani M, Eto Y. Therapeutic efficacy and adverse effects of adrenocorticotropic hormone therapy in west syndrome: differences in dosage of adrenocorticotropic hormone, onset of age, and cause. *J Pediatr.* Apr 2006;148(4):485-488.

21. Oguni H, Yanagaki S, Hayashi K, et al. Extremely low-dose ACTH step-up protocol for West syndrome: maximum therapeutic effect with minimal side effects. *Brain Dev.* Jan 2006;28(1):8-13.

22. Ndegwa S, Banks R. Methadone for the management of pain in patients with opioid addiction: a review of the evidence and guidelines for dosing recommendations. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2009. https://www.cadth.ca/media/pdf/L0110_Methadone_Maximum_Dose_final.pdf. Accessed 27 July 2016.

23. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database of Systematic Reviews.* 2011(11).

24. Haines ST, Casto DT. Treatment of infantile spasms. *Ann Pharmacother.* Jun 1994;28(6):779-791.

25. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews.* 2013(8).

26. Mackay M, Weiss S, Snead OC, 3rd. Treatment of infantile spasms: an evidence-based approach. *Int Rev Neurobiol.* 2002;49:157-184.

27. Mackay MT, Weiss SK, Adams-Webber T, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology.* May 25 2004;62(10):1668-1681.

28. Hancock E, Osborne JP, Milner P. Treatment of infantile spasms. *Cochrane Database Syst Rev.* 2002(2):CD001770.

29. Riikonen R. Infantile spasms: therapy and outcome. *J Child Neurol.* Jun 2004;19(6):401-404.

30. Goodin DS, Hauser SL. Chapter 380. Multiple Sclerosis and Other Demyelinating Diseases. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012: http://www.accessmedicine.com/content.aspx?aID=9147780. Accessed February 3, 2013.

31. Ropper AH, Samuels MA. Chapter 36. Multiple Sclerosis and Allied Demyelinating Diseases. In: Ropper AH, Samuels MA, eds. *Adams and Victor's Principles of Neurology*. 9th ed. New York: New York; 2009: http://www.accessmedicine.com/content.aspx?aID=3638768. Accessed February 3, 2013.

32. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. *Curr Opin Neurol.* Jun 2006;19(3):248-254.

33. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain.* Apr 2014;155(4):654-662.

34. Killestein J, Rudick RA, Polman CH. Oral treatment for multiple sclerosis. *Lancet Neurol.* Nov;10(11):1026-1034.

35. Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. *CNS Drugs.* Jan;25(1):37-52.

36. Compston A, Coles A. Multiple sclerosis. *Lancet.* Oct 25 2008;372(9648):1502-1517.

37. Fox RJ, Bethoux F, Goldman MD, Cohen JA. Multiple sclerosis: advances in understanding, diagnosing, and treating the underlying disease. *Cleve Clin J Med.* Jan 2006;73(1):91-102.

38. Keegan BM, Noseworthy JH. Multiple sclerosis. *Annu Rev Med.* 2002;53:285-302.

39. Siva A. The spectrum of multiple sclerosis and treatment decisions. *Clin Neurol Neurosurg.* Mar 2006;108(3):333-338.

40. Weinstock-Guttman B, Ramanathan M. Multiple sclerosis in 2011: Advances in therapy, imaging and risk factors in MS. *Nat Rev Neurol.* Feb;8(2):66-68.

41. Alviar MJM, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. *Cochrane Database of Systematic Reviews.* 2011(12).

42. MedlinePlus - Rheumatoid arthritis. http://www.nlm.nih.gov/medlineplus/ency/article/000431.htm. Accessed 27 August 2014.
43. Mayo Clinic Diseases and Conditions - Rheumatoid arthritis. http://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/basics/definition/con-20014868. Accessed 27 August 2014.
44. Arthritis Foundation - Rheumatoid Arthritis. http://www.arthritis.org/conditions-treatments/disease-center/rheumatoid-arthritis/. Accessed 27 August 2014.
45. AHRQ Drug Therapy for Rheumatoid Arthritis: Comparative Effectiveness. Clinician Summary Nov 20, 2012.
46. Gastroenterologists Publish Recommendations on IBS Treatment. http://www.medpagetoday.com/Gastroenterology/IrritableBowelSyndrome/12232. Accessed 21 May 2013.
47. Musher DM, Logan N, Bressler AM, Johnson DP, Rossignol JF. Nitazoxanide versus vancomycin in Clostridium difficile infection: a randomized, double-blind study. *Clin Infect Dis.* Feb 15 2009;48(4):e41-46.
48. Model for End-Stage Liver Disease (MELD). http://www.mayoclinic.org/meld/. Accessed 21 May 2013.
49. AHRQ Drug Therapy for Rheumatoid Arthritis: Comparative Effectiveness. Clinician Summary Nov 20, 2012. http://effectivehealthcare.ahrq.gov/ehc/products/203/1315/rheum_arth_clin_fin_to_post.pdf.
50. CDC Grand Rounds: Prescription Drug Overdoses — a U.S. Epidemic. Weekly January 13, 2012 / 61(01);10-13. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm.
51. Nephrotic syndrome. https://en.wikipedia.org/wiki/Nephrotic_syndrome. Accessed 23 March 2016.
52. Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD001533. DOI: 10.1002/14651858.CD001533.pub5. .
53. Chen Y, Schieppati A, Chen X, Cai G, Zamora J, Giuliano GA, Braun N, Perna A. Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD004293. DOI: 10.1002/14651858.CD004293.pub3. .
54. Danowski A, Magder L, Petri M. Flares in lupus: Outcome Assessment Trial (FLOAT), a comparison between oral methylprednisolone and intramuscular triamcinolone. *J Rheumatol.* Jan 2006;33(1):57-60.
55. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *Jama.* May 14 2003;289(18):2370-2378.
56. Serum sickness and serum sickness-like reactions http://www.uptodate.com.ezproxy.lib.utah.edu/contents/serum-sickness-and-serum-sickness-like-reactions?source=preview&search=Serum+sickness+and+serum+sickness-like+reactions&language=en-US&anchor=H4&selectedTitle=1~150#H4. Accessed 25 March 2016.
57. Heterologous proteins causing serum sickness. http://www.uptodate.com.ezproxy.lib.utah.edu/contents/image?imageKey=ALLRG%2F51122&topicKey=ALLRG%2F2078&rank=1%7E150&source=see_link&search=Serum+sickness+and+serum+sickness-like+reactions&utdPopup=true. Accessed 25 March 2016.
58. Peles E, Schreiber S, Gordon J, Adelson M. Significantly higher methadone dose for methadone maintenance treatment (MMT) patients with chronic pain. *Pain.* Feb 2005;113(3):340-346.
59. Manfredi PL, Gonzales GR, Cheville AL, Kornick C, Payne R. Methadone analgesia in cancer pain patients on chronic methadone maintenance therapy. *J Pain Symptom Manage.* Feb 2001;21(2):169-174.
60. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med.* Jan 17 2006;144(2):127-134.

61. Blinderman CD, Sekine R, Zhang B, Nillson M, Shaiova L. Methadone as an analgesic for patients with chronic pain in methadone maintenance treatment programs (MMTPs). *J Opioid Manag.* Mar-Apr 2009;5(2):107-114.

62. Kennedy-Hendricks A, Gielen A, McDonald E, McGinty EE, Shields W, Barry CL. MEdication sharing, storage, and disposal practices for opioid medications among us adults. *JAMA Internal Medicine.* 2016.

63. Lerman P, Lerman-Sagie T, Kivity S. Effect of early corticosteroid therapy for Landau-Kleffner syndrome. *Dev Med Child Neurol.* Mar 1991;33(3):257-260.

64. Schulz R, Nink M, Werner GS, et al. Human corticotropin-releasing hormone and thyrotropin-releasing hormone modulate the hypercapnic ventilatory response in humans. *Eur J Clin Invest.* Nov 1996;26(11):989-995.

65. Taylor CT, Brooks NC, Kelley KW. Corticotropin for acute management of gout. *Ann Pharmacother.* Mar 2001;35(3):365-368.

66. McElhaney JL. Repository corticotropin injection as an adjunct to smoking cessation during the initial nicotine withdrawal period: results from a family practice clinic. *Clin Ther.* 1989;11(6):854-861.

67. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* Jun 12 2012;78(24):1974-1980.

68. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia.* Oct 2010;51(10):2175-2189.

69. Mehta V, Ferrie CD, Cross JH, Vadlamani G. Corticosteroids including ACTH for childhood epilepsy other than epileptic spasms. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD005222. DOI: 10.1002/14651858.CD005222.pub3. .

70. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet.* Nov 13-19 2004;364(9447):1773-1778.

71. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *The Lancet. Neurology.* Nov 2005;4(11):712-717.

72. Ito M, Aiba H, Hashimoto K, et al. Low-dose ACTH therapy for West syndrome: initial effects and long-term outcome. *Neurology.* Jan 8 2002;58(1):110-114.

73. Wiffen PJ, Derry S, Moore RA, et al. Buprenorphine for neuropathic pain in adults. *Cochrane Database of Systematic Reviews.* 2015(9).

74. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database of Systematic Reviews.* 2012(7).

75. Jensen TS, Baron R, Haanpaa M, et al. A new definition of neuropathic pain. *Pain.* Oct 2011;152(10):2204-2205.

76. Oderda GM, Lake J, Rudell K, Roland CL, Masters ET. Economic Burden of Prescription Opioid Misuse and Abuse: A Systematic Review. *J Pain Palliat Care Pharmacother.* 2015;29(4):388-400.

77. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. *Epilepsia.* Aug 2015;56(8):1185-1197.

78. Korff CM, Nordli DR, Jr. The clinical-electrographic expression of infantile seizures. *Epilepsy Res.* Aug 2006;70 Suppl 1:S116-131.

79. Oral methadone for chronic noncancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness, and side effects (Structured abstract). Centre for Reviews and Dissemination. Database of Abstracts of Reviews of Effects 2015 Issue 2. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12005006372/frame.html. Accessed 27 July 2016.

80. Goodin DS, Frohman EM, Garmany GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology.* Jan 22 2002;58(2):169-178.

81. Kalb R. *Overview of Multiple Sclerosis*: National Multiple Sclerosis Society Professional Resource Center;2012.

82. (CADTH) CAfDaTiH. *Recommendation for drug therapies for relapsing-remitting multiple sclerosis.* National Guideline Clearinghouse2013.

83. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids (Structured abstract). Centre for Reviews and Dissemination. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12006003361/frame.html.

84. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther.* 2005;7(5):R1046-1051.

85. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum.* Oct 2013;65(10):2499-2512.

86. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Canada: National Opioid Use Guideline Group (NOUGG); 2010 http://nationalpaincentre.mcmaster.ca/opioid/cgop_b02_conducting_an_opioid_trial.html. Accessed 22 June 2016.

87. Katz MH. Opioid Prescribing for Chronic Pain: Not for the Faint of Heart. *JAMA Internal Medicine.* May 1 2016;176(5):599-601.

88. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis care & research.* May 2012;64(5):625-639.

89. Jackman R, Purvis J. Effectiveness and Safety of High-Dose Opioids for Chronic Pain. American Family Physician, 2010-03-15, Volume 81, Issue 6, Pages 693-693. https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0002838X10601189.

90. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken).* Oct 2012;64(10):1447-1461.

91. Chou R. 2009 Clinical Guidelines from the American Pain Society and the American Academy of Pain Medicine on the use of chronic opioid therapy in chronic noncancer pain: what are the key messages for clinical practice? *Pol Arch Med Wewn.* Jul-Aug 2009;119(7-8):469-477.

92. Shaw K, Fudin J. Evaluation and Comparison of Online Equianalgesic Opioid Dose Conversion Calculators. Practical Pain Management. 2013 August. http://www.practicalpainmanagement.com/treatments/pharmacological/opioids/evaluation-comparison-online-equianalgesic-opioid-dose-conversion.

93. Wright AP, Becker WC, Schiff GD. Strategies for Flipping the Script on Opioid Overprescribing. *JAMA Internal Medicine.* Jan 2016;176(1):7-8.

94. Fernandez C, Noguera R, Gonzalez JA, Pascual E. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J Rheumatol.* Oct 1999;26(10):2285-2286.

95. Komatsu T. [Treatment of acute gouty attack with local infiltration of Kenacort-A and the study of gout and hyperuricemia at the Tanabe National Hospital during 1967]. *Iryo.* Jan 1969;23(1):54-61.

96. McCabe SE, West BT, Boyd CJ. Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study. *J Adolesc Health.* Apr 2013;52(4):480-485.

97. Adult use of prescription opioid pain medications - Utah, 2008. *MMWR Morb Mortal Wkly Rep.* Feb 19 2010;59(6):153-157.

98. Furie R, Das M, Li D, et al. H.P. Acthar gel (Acthar) attenuates disease activity in patients with persistently active Systemic Lupus Erythematosus (SLE) requiring corticosteroids. *Clinical and*

experimental rheumatology. 2015(3 suppl. 90):S31. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/840/CN-01107840/frame.html.

99. Aggarwal R, Marder G, Loganathan P, et al. Efficacy and safety of adrenocorticotropic hormone gel (acthar gel) in refractory dermatomyositis or polymyositis. *Arthritis and Rheumatology.* 2015(no pagination). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/731/CN-01126731/frame.html.

100. Zimmermann M, Richarz U. End-of-dose pain in chronic pain: does it vary with the use of different long-acting opioids? *Pain Pract.* Nov 2014;14(8):757-769.

101. Vial T, Pont J, Pham E, Rabilloud M, Descotes J. Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother.* Jul-Aug 1992;26(7-8):910-914.

102. Finger E, Scheinberg M. Development of serum sickness-like symptoms after rituximab infusion in two patients with severe hypergammaglobulinemia. *J Clin Rheumatol.* Apr 2007;13(2):94-95.

103. LoVecchio F, Welch S, Klemens J, Curry SC, Thomas R. Incidence of immediate and delayed hypersensitivity to Centruroides antivenom. *Ann Emerg Med.* Nov 1999;34(5):615-619.

104. Joubert GI, Hadad K, Matsui D, Gloor J, Rieder MJ. Selection of treatment of cefaclor-associated urticarial, serum sickness-like reactions and erythema multiforme by emergency pediatricians: lack of a uniform standard of care. *Can J Clin Pharmacol.* Winter 1999;6(4):197-201.

105. Grammer LC. Cefaclor serum sickness. *Jama.* Apr 17 1996;275(15):1152-1153.

106. Clark BM, Kotti GH, Shah AD, Conger NG. Severe serum sickness reaction to oral and intramuscular penicillin. *Pharmacotherapy.* May 2006;26(5):705-708.

107. Rana JS, Sheikh J. Serum sickness-like reactions after placement of sirolimus-eluting stents. *Ann Allergy Asthma Immunol.* Feb 2007;98(2):201-202.

108. Tatum AJ, Ditto AM, Patterson R. Severe serum sickness-like reaction to oral penicillin drugs: three case reports. *Ann Allergy Asthma Immunol.* Mar 2001;86(3):330-334.

109. Lundquist AL, Chari RS, Wood JH, et al. Serum sickness following rabbit antithymocyte-globulin induction in a liver transplant recipient: case report and literature review. *Liver Transpl.* May 2007;13(5):647-650.

110. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review (Provisional abstract). Centre for Reviews and Dissemination. Database of Abstracts of Reviews of Effects 2015 Issue 2. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12003002362/frame.html.

111. Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. *Can J Cardiol.* Sep 2013;29(9):1034-1041.

112. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken).* Jun 2012;64(6):797-808.

113. Nerenberg DM, Fudin J. Maximum daily dose of hydrocodone. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* [Letter]. 2010; 2010/09/21:1588-1589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20852155 and http://paindr.com/wp-content/uploads/2012/07/nerenberg-fudin_maximum-daily-dose-of-hydrocodone.pdf.

114. van de Logt AE, Beerenhout CH, Brink HS, van de Kerkhof JJ, Wetzels JF, Hofstra JM. Synthetic ACTH in High Risk Patients with Idiopathic Membranous Nephropathy: A Prospective, Open Label Cohort Study. *PLoS One.* 2015;10(11):e0142033.

115. Bomback AS, Tumlin JA, Baranski J, et al. Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel. *Drug Des Devel Ther.* 2011;5:147-153.

116. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* Feb 2009;10(2):113-130.

117. Hodson EM, Willis NS, Craig JC. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003594. DOI: 10.1002/14651858.CD003594.pub4. .

118. Bohnert AS, Logan JE, Ganoczy D, Dowell D. A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain. *Med Care.* May 2016;54(5):435-441.

119. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* Dec 2004;112(3):372-380.

120. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain.* May 2007;23(4):287-299.

121. Fudin J. Opioid Conversion: New Perspectives on Dosing Calculations. Published Online: Wednesday, September 9, 2015. http://www.pharmacytimes.com/contributor/jeffrey-fudin/2015/09/opioid-conversion-new-perspectives-on-dosing-calculations.

122. Webster LR, Fine PG. Overdose deaths demand a new paradigm for opioid rotation. *Pain Medicine.* Apr 2012;13(4):571-574.

123. Passik SD. Opioid Rotation: What Is the Rush? *Pain Medicine.* 2012-04-01 00:00:00 2012;13(4):487-488.

124. Lembke A, Humphreys K, Newmark J. Weighing the Risks and Benefits of Chronic Opioid Therapy. American Family Physician, 2016-06-15, Volume 93, Issue 12, Pages 982-990. https://www.clinicalkey.com/#!/content/1-s2.0-S0002838X16301587.

125. Opioids in chronic non-cancer pain: systematic review of efficacy and safety (Structured abstract). Centre for Reviews and Dissemination. http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12004006872/frame.html.

126. Criswell L, Saag K, Sems KM, Welch V, Shea B, Wells GA, Suarez-Almazor ME. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. Cochrane Database of Systematic Reviews 1998, Issue 3. Art. No.: CD001158. DOI: 10.1002/14651858.CD001158.

127. Gan EH, MacArthur K, Mitchell AL, et al. Residual adrenal function in autoimmune Addison's disease: improvement after tetracosactide (ACTH1-24) treatment. *J Clin Endocrinol Metab.* Jan 2014;99(1):111-118.

128. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Ann Intern Med.* Sep 6 2011;155(5):325-328.