Diet Therapy
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BEST PRACTICE

Acute glomerulonephritis

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Glomerulonephritis is an important cause of renal failure thought to be caused by autoimmune damage to the kidney. While each type of glomerulonephritis begins with a unique initiating stimulus, subsequent common inflammatory and fibrotic events lead to a final pathway of progressive renal damage. In this article the different forms of inflammatory glomerulonephritis and their diagnosis are discussed. In a review of therapy both immediate life saving treatment given when glomerulonephritis causes acute renal failure and more specific treatments designed to modify the underlying mechanisms of renal injury are considered.

Glomerulonephritis is an important cause of renal impairment accounting for 10%–15% of cases of end stage renal failure in the USA, following only diabetes and hypertension in importance.[1] In defining acute glomerulonephritis, we have chosen to discuss those glomerular diseases that may present with a nephritic syndrome—that is with haematuria, proteinuria, and impaired renal function together with hypertension, fluid overload, and oedema. Their pathology involves intraglomerular inflammation and cellular proliferation with secondary renal impairment over days to weeks. This definition excludes glomerular diseases without cell proliferation or nephritic presentations, such as minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis that can, none the less, chronically compromise renal function. In primary glomerulonephritis, disease is almost entirely restricted to the kidneys (as in IgA nephropathy or post-streptococcal glomerulonephritis) while in secondary glomerulonephritis it occurs in association with more diffuse inflammation (as in systemic lupus erythematosus or systemic vasculitis). Prompt diagnosis of glomerulonephritis is vital as patients with even mildly impaired renal function, hypertension, and urinary abnormalities may rapidly lose kidney function if not treated urgently.

Although our understanding of the causes of glomerulonephritis is still at a basic level, inflammation is thought to be autoimmune mediated and involve both cellular and humoral immune systems. In each case a unique initiating stimulus (occurring by one of at least four different mechanisms) is followed by a common pathway of inflammatory and subsequently fibrotic events. In antiglomerular basement membrane disease, patients produce antibodies that react directly with the specialised basement membranes of the lung and glomerulus.[2] In post-streptococcal glomerulonephritis antibodies are formed not to an endogenous antigen but to an exogenous streptococcal antigen planted in the glomerulus at the time of infection.[3] In systemic lupus erythematosus and IgA nephropathy, the antigen antibody reaction occurs not only in situ in the glomerulus but also systemically with subsequent trapping of complexes in the kidney. Finally in the glomerulonephritis seen in small vessel vasculitis, cellular rather than humoral immune responses are thought to be stimulated, with inflammation often originating in organs distant to the kidney with a subsequent renal influx of T-cells and macrophages as crescentic glomerulonephritis evolves.

Whatever the initial events, common inflammatory pathways follow with activation of the coagulation and complement cascades and production of proinflammatory cytokines.[4] Activation of complement components leads to chemotaxis of inflammatory cells and cell lysis (via the membrane attack complex). The coagulation cascade leads to fibrin deposition. Cellular proliferation of parietal epithelial cells in Bowman's space together with an influx of inflammatory cells such as macrophages and neutrophils results in acute glomerular crescent formation. Cytokine release leads to activation of the glomerular cells themselves and a change in endogenous cell phenotype results in cell proliferation, overproduction of proteases and oxidants, and laying down of extracellular matrix with subsequent fibrosis, perhaps stimulated by factors such as platelet derived growth factor and transforming growth factor beta. Failure of apoptosis (the normal mechanism allowing resolution of inflammation) is also important. Finally in a chronic phase of damage, haemodynamic alterations lead to hyperfiltration and intraglomerular hypertension[5] with subsequent development of glomerular sclerosis and chronic interstitial damage. Thus a process that is initially inflammatory with the potential to resolve may progress to fibrosis and irreversible scarring. This dynamic picture may partly explain why in post-streptococcal glomerulonephritis where antigen is rapidly cleared, even acute renal failure can be expected to resolve spontaneously. By contrast in hepatitis C associated mesangiocapillary glomerulonephritis (MCGN) where viral infection is chronic, antigen cannot be cleared and renal damage may chronically progress.

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Abbreviations: ACE, angiotensin converting enzyme; ANCA, antineutrophil cytoplasmic antibodies; HSP, Henoch-Schönlein purpura; MCGN, mesangiocapillary glomerulonephritis; RPGN, rapidly progressive glomerulonephritis; WHO, World Health Organisation

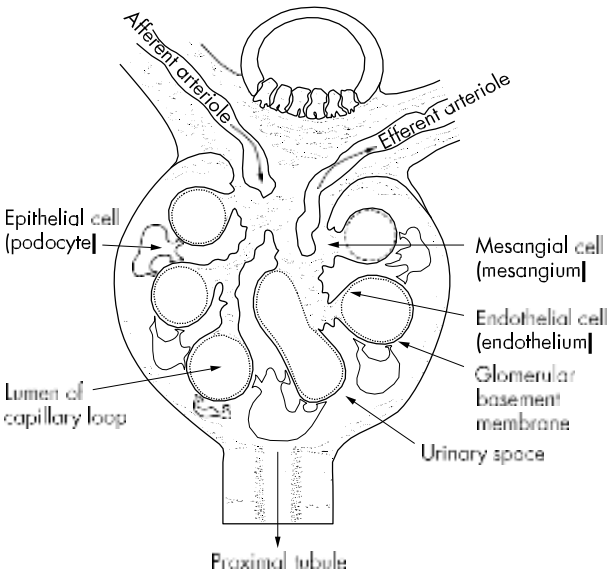

Figure 1 Section through a normal renal glomerulus. Blood is carried in to the glomerulus by an afferent arteriole and leaves by the efferent arteriole. Capillary loops that emerge from the vascular pole are supported by stalks of mesangial cells. On entering the lumen of a capillary loop, blood is filtered through a barrier consisting of a fenestrated endothelial layer, the glomerular basement membrane, and an epithelial layer. Urine emerges in to the urinary space and passes in to the proximal tubule.

To understand the histology of glomerulonephritis, we need to revisit the basic structure of the normal kidney (see fig 1). Inflammatory, proliferative, and fibrotic changes may affect specific cells of the kidney differently or may result in more global changes with particular patterns resulting in a spectrum of clinical presentations. In table 1, we have attempted to summarise the complex nomenclature that surrounds glomerulonephritis by naming each disease, describing its common renal clinical presentation and explaining its underlying histological lesion. In table 2 we have focused purely on clinical aspects which may aid rapid diagnosis. Renal biopsies are vital both in defining a diagnosis, and also in offering prognostic information by differentiating acute reversible damage from chronically scarred non-viable kidney which does not justify the risks of potentially toxic therapy. Although current treatments are, at best, crude, with greater understanding of pathological events we hope to design more specific therapy both to limit acute damage, and to prevent progression to chronic scarring with its inevitable decline in renal function.

POST-INFECTIOUS ENDOCAPILLARY GLOMERULONEPHRITIS

Post-streptococcal glomerulonephritis is the best known example of endocapillary glomerulonephritis, the most common form of acute glomerulonephritis seen after some bacterial, viral, fungal, and parasitic infections. Although this pattern of glomerular injury after a streptococcal infection remains an important cause of acute renal failure in the developing world, in Europe and the USA this lesion is increasingly seen in infections such as endocarditis after intravenous drug abuse. In post-streptococcal glomerulonephritis, children are usually affected with a male preponderance.[6] It can follow pharyngitis (commonly in winter) or skin infections (commonly in summer) with a β-haemolytic nephritogenic strain of streptococcus (often type 12) with the glomerulonephritis occurring one to 12 weeks after initial infection. It affects up to 15% of those infected, although many cases are subclinical and self resolving. In children most severely affected, presentation is with the classic nephritic picture of puffy eyelids, facial oedema, hypertension, and dark scanty urine with microscopic haematuria and proteinuria.

The pathology is that of a planted antigen where a streptococcal component is deposited in the glomerulus during infection.[3] Subsequent production of antibody by the host produces in situ immune complex formation which alters the permeability of the glomerular basement membrane and allows subsequent deposition of further pre-formed immune complexes. In addition streptococcal antigen may cross react with glomerular structures or directly activate complement with subsequent attraction of inflammatory cells.[7 8] Immune deposits initiate a diffuse proliferative glomerulonephritis particularly affecting mesangial and endothelial cells. Immunostaining shows C3 in the mesangium and along capillary walls with accompanying IgG.

Serology may show raised antistreptolysin antibody titres but its absence does not exclude the diagnosis as many nephritogenic strains do not produce streptolysin. Low C3 levels with normal C4 levels (due to alternative pathway activation) are seen acutely but should have returned to normal within two months.

MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS/ IGA NEPHROPATHY

IgA nephropathy is the commonest of all glomerulonephritides world wide. Thus although only 4%–13% of patients present with acute nephritis (the commoner presentation being with micro or macroscopic haematuria), this still represents a considerable number of cases.[9] Peak presentation is during the second and third decades showing a 2:1 male preponderance with attacks sometimes after infection (particularly pharyngitis[10 11]). The disease shows great geographic variation and is more common in the Western Pacific rim and in Asia (accounting for 50% of primary glomerular disease in Japan) but is rare in black populations.[4]

IgA nephropathy is the classic mesangioproliferative glomerulonephritis where cellular proliferation may be either diffuse or focal but affects predominantly the mesangium. Immunofluorescence shows paramesangial deposition of IgA (with some IgG and IgM) together with alternative pathway complement components, while electron microscopy shows mesangial dense deposits. Polymeric IgA1 is deposited[12] in the kidney after overproduction of systemic IgA1 polymers (possibly in response to infection) together with impaired clearance through both the hepatic and the myeloid routes. In addition abnormal glycosylation of IgA may make it more prone to self aggregate and form immune complexes with affinity for the mesangium.[12] The disease is associated with a raised serum concentrations of IgA in 50% of patients, but serum complement levels are normal as complement activation is restricted to the kidneys alone.[13]

HENOCH-SCHÖNLEIN PURPURA

The renal lesion of Henoch-Schönlein purpura (HSP) is almost identical to that of the more severe variants of IgA nephropathy. However, as a small vessel vasculitis, HSP also has the systemic features of a purpuric rash largely affecting the lower limbs, arthritis or arthralgia, and abdominal pain sometimes in association with rectal bleeding. The disease is most commonly seen in those less than 20 years of age. Renal involvement is not always present initially but its incidence increases with time and is more common in older children who have associated abdominal pain and a persisting rash.[14] Renal involvement can also occur in adults where it is thought to carry a worse prognosis. Although haematuria and proteinuria are the most common renal presentations, 8% of patients will have an acute nephritis and up to 29% may present with a combined nephritic and nephrotic picture.[9]

Table 1 The classification of acute glomerulonephritis by disease, renal presentation, and histological lesion (where the nephritic syndrome is a relatively rare presentation, the more usual clinical presentation is given in bold type)

Disease	Possible clinical renal presentations	Most common histological lesion
Postinfectious glomerulonephritis (Historically post-streptococcal but also seen with other bacterial, viral and parasitic infections)	Nephritic syndrome, haematuria, proteinuria	Endocapillary glomerulonephritis—a diffuse proliferative glomerulonephritis especially affecting mesangial and endothelial cells possibly provoked by in situ immune complex deposition due to a planted streptococcal antigen
IgA nephropathy	Nephritic syndrome **Macroscopic/microscopic haematuria**	Mesangioproliferative glomerulonephritis—a focal or diffuse cellular proliferation affecting predominantly the mesangium possibly stimulated by polymeric IgA deposition
Henoch-Schönlein purpura	Nephritic syndrome, haematuria, proteinuria, nephrotic syndrome	Mesangial cell proliferation may be associated with glomerular crescents, capillary necrosis and leucocytoclastic vasculitis possibly due to subtle differences in size of IgA deposits
Wegener's granulomatosis, microscopic polyangiitis, idiopathic crescentic glomerulonephritis	Rapidly progressive glomerulonephritis, nephritic syndrome	A focal or diffuse proliferative glomerulonephritis with extensive crescent formation in greater than 50% of glomeruli
Antiglomerular basement membrane disease	Rapidly progressive glomerulonephritis, nephritic syndrome	A focal segmental glomerulonephritis with necrosis which rapidly progresses to widespread crescent formation caused by antibodies to type IV collagen
Type I MCGN, idiopathic. In association with infective endocarditis, visceral abscesses, infected arteriovenous shunts	Nephritic syndrome **Nephrotic syndrome, haematuria, proteinuria**	A mesangiocapillary glomerulonephritis with intense cellular proliferation involving mesangial expansion and thickening of capillary walls due to extension of proliferation into capillary loops. Probably provoked by subendothelial immune complex deposition
Hepatitis C associated type I MCGN		May have additional intracapillary cryoglobulin deposition
Type II MCGN (sometimes seen in association with partial lipodystrophy)		Intense mesangial cell proliferation as above in the absence of immune complex deposition but in association with dense intramembranous deposits
Systemic lupus erythematosus	Nephritic syndrome, nephrotic syndrome, haematuria, proteinuria	WHO type III A focal proliferative glomerulonephritis involving cellular proliferation in mesangial and endocapillary areas affecting <50% of glomeruli WHO type IV A diffuse proliferative glomerulonephritis involving mesangial and endocapillary proliferation in >50% of glomeruli sometimes in association with necrosis and crescent formation

Patients with HSP also have systemic IgA containing immune complexes, though their size is larger than those in IgA disease. Mesangial deposition of IgA is usually seen but capillary wall staining for IgA is also frequent. Glomerular crescents and fibrin deposition are more common in HSP, as is capillary necrosis and leucocytoclastic vasculitis.[9] It is thought that subtle differences in the IgA complexes in HSP lead to greater leucocyte stimulation and thus to the small vessel vasculitis and extrarenal manifestations that define HSP.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

The rapidly progressive glomerulonephritides are the most serious of all glomerulonephritides with the potential to destroy renal function within days. Although causes are heterogeneous, they are united by the histological finding of extensive crescents (a proliferation of parietal epithelial cells and mononuclear phagocytes with possible fibroblasts in Bowman's capsule) affecting more than 50% of glomeruli. Causes fall into three broad categories with different presentations, treatments, and prognoses.

Pauci-immune glomerulonephritis caused by small vessel vasculitides accounts for about 50% of RPGN with an incidence of approximately 2 per 100 000 per year and a peak in the sixth decade with equal sex distribution. Disease may be limited to the kidney (idiopathic crescentic glomerulonephritis) or be associated with widespread systemic inflammation (Wegener's granulomatosis and microscopic polyangiitis). Overt presentation is often preceded by weight loss

Table 2 Clinical features of acute glomerulonephritides

Type of glomerulonephritis	Age and sex	Investigations	Extrarenal manifestations
Post-infectious glomerulonephritis (post- streptococcal glomerulonephritis)	Most common between 2 and 12 years; boys > girls	Low C3 (alternative complement pathway), antistreptolysin titre	Sore throat or skin infection 7 days to 12 weeks before presentation
IgA nephropathy	Commonly presents in 20s and 30s; men > women	Raised serum IgA in 50% of cases, complement normal	Macroscopic haematuria may relate to time of infections
Henoch-Schönlein purpura	<20 years of age	Complement normal	Purpuric rash on legs, arthritis, abdominal pain
Wegener's granulomatosis, microscopic polyangiitis	50s/60s; men = women	ANCA, complement normal	Weight loss, malaise, upper and lower respiratory tract symptoms, arthritis, palpable purpura
Antiglomerular basement membrane disease	Young men; 50s and 60s; both sexes	Antiglomerular basement membrane antibody, complement levels normal	Lung haemorrhage especially in smokers
MCGN:			
Type I	20s; women > men	Low C4 (classical path activation)	
Type II	teenage; women > men	Low C3 (alternative path activation), C3 nephritic factor	Gaunt face due to partial lypodystrophy
Type I with hepatitis C	Middle age	Low C4, +ve hepatitis C serology, hepatitis C RNA on polymerase chain reaction, serum cryoglobulins, +ve antinuclear antibody/ +ve Rh factor	Abnormal liver function tests (rarely cirrhosis), pupuric rash, neuropathy, polyarthralgia, leg ulcers
Lupus nephritis	Young women in 20 and 30s	Low C3, antinuclear antibody/ anti-ds DNA, anticardiolipin antibody	Arthralgia, photosensitive skin rash, pleurisy, and pericarditis

and general malaise with later features relating to individual illnesses. Microscopic polyangiitis has cutaneous (palpable purpura), neurological (mononeuritis multiplex) or gastrointestinal vasculitis as well as renal failure, with pulmonary symptoms in only 50% of cases (due to non-granulomatous arteriolar vasculitis and capillaritis). By contrast, Wegener's granulomatosis is dominated by pulmonary manifestations with upper (deafness, nasal cartilage collapse, sinusitis), and lower (pulmonary haemorrhage due to granulomatous vasculitis) respiratory tract involvement and cavitating lung lesions seen on radiography.

Biopsy shows a focal or diffuse proliferative glomerulonephritis with extensive crescents. The pathogenesis of vasculitis remains the focus of much research but direct immunoglobulin deposition in the glomerulus is not thought to play a significant part (hence the term pauci-immune). Serologically, however, these diseases are linked in about 90% of cases by the finding of antineutrophil cytoplasmic antibodies (ANCA). Antibody staining is usually directed against the neutrophil cytoplasm in Wegener's with an antigen specificity for proteinase 3 on ELISA, whereas in microscopic polyangiitis it is generally perinucleur in pattern and is directed against myeloperoxidase. A direct causative role for ANCA in small vessel vasculitis remains controversial with experimental evidence pointing towards roles for neutrophils, macrophages, and T-cells in its pathogenesis.[15]

Antiglomerular basement membrane disease accounts for 10%–20% of cases of RPGN with a frequency of 0.5 cases per million per year in a European caucasoid population.[2] The disease occurs in two peaks, one in the third decade with a male preponderance and the second in the sixth and seventh decades affecting both sexes equally.[16] Associated lung involvement is more common in young men (when the disease is known as Goodpasture's disease), while that isolated to the kidneys is commoner in older patients. A prodrome of weight loss and malaise is less common than in the vasculitides and patients often present with either acute renal failure or haemoptysis due to lung involvement.[17] Haemoptysis is commoner in smokers and in those with fluid overload or intercurrent infections (the later also making the kidney damage more severe). Lung haemorrhage is the most common cause of death during early disease and should be suspected with haemoptysis or where a chest radiograph shows alveolar shadowing without restriction by anatomical fissures and with sparing of the upper zones. Acute haemorrhage may be confirmed by a transiently raised transfer factor on pulmonary function testing.

Antiglomerular basement membrane disease is caused by antibodies that bind the apha 3 chain of type 4 collagen found in the specialised basement membranes of the kidney and lung.[18] Initially histology may show a focal segmental glomerulonephritis with necrosis and interstitial inflammation but will rapidly progress to show widespread crescent formation with all crescents at the same stage of evolution (a previously normal kidney can develop 100% crescents in as little as five days). Immunofluorescence shows the linear deposition of IgG antibodies (sometimes associated with C3) along the glomerular basement membrane. Serology is positive for antiglomerular basement membrane antibodies but in 20%–30% of patients ANCA antibodies are also detected.[19] These latter patients behave clinically more like those with vasculitis (with lethargy, malaise, weight loss) and have a better renal prognosis than those with antiglomerular basement membrane antibodies alone—this may be because they are actually affected by vasculitis with the antiglomerular basement membrane antibodies being a secondary response to the damaged basement membrane.

Some 30%–40% of RPGN is due to a group of heterogeneous conditions where renal damage is associated with immune complex deposition or other causes of basement membrane damage such as accelerated hypertension. Pathology is frequently an aggressive variant of a glomerulonephritis normally associated with a more benign course (such as post-streptococcal glomerulonephritis, or IgA nephropathy), with histology being complicated by extensive inflammation and crescent formation. It is also seen after infections such as endocarditis and shunt nephritis or in association with multisystem disease such as systemic lupus erythematosus.

MESANGIOCAPILLARY GLOMERULONEPHRITIS; ALSO KNOWN AS MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

This rare form of glomerulonephritis has enjoyed renewed interest after the discovery that a subtype of MCGN type I is associated with chronic hepatitis C infection. MCGN commonly presents as a nephrotic syndrome but in 16%–30% of patients the initial presentation is with acute nephritis. The disease can be subdivided into types I and II, with its idiopathic forms mostly seen in children and young adults with cases presenting at a younger age in type II (15 years ±11

years) than in type I (24 years ±16 years) disease, with a slight female preponderance. Type I MCGN shares some features with lupus nephritis, and a similar histological picture can also be seen with endocarditis and infected arteriovenous shunts. In type II MCGN, patients may have an associated partial lypodystrophy giving them a very gaunt facial appearance.

It has recently been realised that a significant proportion of cases of type I MCGN previously labelled as idiopathic in fact occur in association with chronic hepatitis C infection[20] of which 20%–25% will present with acute nephritis.[21] There is geographical variation in this association and while hepatitis C associated renal disease appears particularly common in Japan (where the infection is found in up to 60% of cases of membranoproliferative glomerulonephritis) and Italy, it is less common in the USA (10%–20% of cases of membranoproliferative glomerulonephritis) and has been seen relatively little in France.[20 21] Patients present 10–15 years after infection in middle age and have subclinical liver disease with mild biochemical abnormalities. Renal disease is often seen in the context of cryoglobulinaemia (cold precipitable mixed immunoglobulins composed of monoclonal IgM rheumatoid factor and polyclonal IgG). Patients suffer malaise, anaemia, peripheral neuropathy, polyarthralgia, and a purpuric rash together with lower limb ulceration and Raynaud's disease. Rarely vasculitis also affects the gastrointestinal or cardiological systems.[22]

Idiopathic type I MCGN is associated with activation of the classical complement pathway (and therefore with low C4 concentrations) while in MCGN type II alternative pathway activation is seen with low C3 and the presence of the C3 nephritic factor (an antibody leading to permanent activation of the complement cascade). In hepatitis C associated MCGN in addition to low classical complement component levels, patients have positive antihepatitis C antibodies and hepatitis C RNA on polymerase chain reaction. They may also have a positive antinuclear antibody and rheumatoid factor tests (70%) and positive cryoglobulins (75%).[23]

The pathogenesis of MCGN is obscure but probably involves intense cellular proliferation particularly involving mesangial cells. Histologically both types show mesangial expansion and thickening of the capillary walls (with reduction in the capillary lumina), which in the case of MCGN type I is partly due to cellular proliferation extending between the capillary basement membranes causing thickening and giving the classic tramline effect. Mesangial and capillary loop deposition of C3 occurs in both forms of MCGN but is accompanied by immunoglobulin deposition only in type I MCGN. The distinction between the different types is based on electron microscopy findings: in type I subendothelial immune deposits are seen in the glomerular basement membrane while in type II dense intramembranous deposits are seen in glomerular, tubular, and vascular basement membranes (the nature of these deposits in type II disease remains unknown but does explain its alternative name of dense deposit disease). In hepatitis C associated type I MCGN intracapillary deposits are thought to be due to precipitation of the cryoglobulins themselves.

LUPUS NEPHRITIS

Renal involvement in systemic lupus erythematosus can present with proteinuria, haematuria, nephrotic syndrome, or with an acute nephritis. It is rarely the first manifestation of systemic lupus but usually occurs within five years and may be the first presentation leading to a definitive diagnosis.[24] Patients (most commonly women in their 20s and 30s with a black preponderance) will frequently have suffered lethargy, arthralgia or arthritis, skin rashes, and the symptoms of pleurisy and pericarditis in the months before presentation.[25] More than any other glomerulonephritis, lupus nephritis can change and evolve over time so that in a patient with an initially benign glomerular lesion, a new presentation with acute glomerulonephritis should prompt repeat biopsy and if needed more aggressive treatment. High titres of antinuclear antibodies and antidouble stranded DNA antibodies together with low complement levels are helpful in a nephritic flare, although changes in such markers often precede the actual glomerular inflammation, sometimes by months.[26]

The pathology is at least in part that of immune complex deposition, with antigen antibody complexes forming systemically or in situ and subsequently activating the inflammatory cascade. Positively charged nuclear histone antigens can also bind to the glomerular basement membrane altering function and permeability and acting as planted antigens that are then the target of anti-DNA antibodies.

Acute glomerulonephritis in lupus is seen in patients who have focal and diffuse proliferative glomerulonephritis—that is World Health Organisation (WHO) class III and IV lupus nephritis[27] (WHO class I (normal kidney) and WHO class II (mesangial proliferation) lupus nephritis do not present as acute glomerulonephritis). In class III lupus nephritis (focal proliferative glomerulonephritis) there is proliferation in the mesangial and endocapillary areas in less than 50% of glomeruli. Such patients have haematuria and proteinuria and are sometimes nephritic. More commonly nephritic syndrome and renal impairment is associated with the more aggressive class IV diffuse proliferative glomerulonephritis where mesangial and endocapillary hypercellularity affect more than 50% of glomeruli with additional necrosis and possibly crescent formation. Subendothelial deposits give thickened basement membrane with a wire loop appearance on light microscopy. Immunofluorescence shows extensive granular deposition of IgG, IgA, IgM, and complement in subendothelial and mesangial areas.

TREATMENT OF GLOMERULONEPHRITIS

The treatment of acute glomerulonephritis falls into two categories. Supportive treatment such as blood pressure control and dialysis is immediate and frequently life saving, but does not attempt to reverse the underlying pathology. Specific treatments aim to prevent and reverse glomerular inflammation and ultimately to preserve renal function—such treatments are often highly toxic and rely on non-specific suppression of the entire immune system. They carry the immediate risks of overwhelming infection and the later risk of reproductive toxicity and malignancy. In choosing such therapies, we need to select patients in whom kidney recovery is unlikely to occur spontaneously but where toxicity can be justified by the potential reversibility of the condition. On this basis we discuss current therapies and where possible present the rationale for their use (table 3). Many of these treatments together with newer therapies are the subject of ongoing clinical trials to determine optimum strategies.

The importance of supportive therapies in acute glomerulonephritis cannot be over emphasised. Tight blood pressure control, appropriate use of diuretics, and control of hyperkalaemia, uraemia and fluid overload, if necessary by dialysis, are quite literally life saving. Blood pressure control is vital not just in the short term but also later for any patient left with even mild renal impairment or proteinuria, with angiotensin converting enzyme (ACE) inhibitors having a particular place for their additional antiproteinuric and antifibrotic effects.[28]

In most cases of post-streptococcal glomerulonephritis where inflammation does resolve spontaneously, supportive therapies alone will be sufficient with improved renal function being seen between four and 14 days after the initial acute failure in 95% of patients.[29] Serum creatinine generally returns to baseline levels by four weeks but haematuria may persist for six months and mild proteinuria may be present in a few patients even at 10 years.[30] Rarely haematuria and proteinuria persist long term and are accompanied by hypertension and

Table 3 Treatment of glomerulonephritis (treatments used widely in clinical practice are in bold type while newer therapies are in normal type)

Glomerulonephritis	Specific treatments used	Rationale for treatment
Endocapillary glomerulonephritis	None required	Inflammation generally self resolving
Mesangioproliferative glomerulonephritis	**Acute nephritic phase: Blood pressure control with ACE inhibitors**	
	Pulsed intravenous steroids, cyclophosphamide, mycophenolate mofetil intravenous immunoglobulin	Reduce inflammation especially where renal function declining and crescents present
Antiglomerular basement membrane disease	**Pulsed intravenous steroids 1 g for 3/7 followed by oral steroids (60 mg/day) Cyclophosphamide orally (2–3 mg/kg/day)**	To switch off antiglomerular basement membrane antibody production
	Plasma exchange (daily for 14 or until no anti-GBM antibody)	To remove existing antiglomerular basement membrane antibody while immunosuppression takes effect **days**
ANCA positive vasculitis	**Pulsed intravenous steroids 1 g for 3/7 + oral steroids (start 60 mg), cyclophosphamide (2 mg/kg/day orally or 0.5–1 g monthly intravenous)**	Suppression of antibody and cellular immune arms
	Plasma exchange ? for creatinine >500 or pulmonary haemorrhage	Removal of ANCA/immune complexes?
	Treat underlying histological variant	Removal of proinflammatory cytokines?
Immune complex-mediated RPGN	If idiopathic as for ANCA positive vasculitis	Suppression of antibody response
MCGN type I: idiopathic	Steroids 40 mg/m^2 alternate days in children only	
	Aspirin (325 mg/day) Dipyridamole (75 – 100 mg three times a day) in adults only	As antiplatelet agents to decrease cellular proliferation
Type I: hepatitis C related	Alpha-interferon/ribavirin	To lessen viral drive
	Steroids, cyclophosphamide (plasma exchange)	To treat inflammatory component
Type II	No specific therapy shown to be helpful	
Lupus nephritis	**Intravenous steroids + oral steroids**	To suppress antibody production and reduce immune complexes
	Intravenous/oral cyclophosphamide Mycophenolate mofetil, cyclosporin	

declining renal function.[31] For most other causes of glomerulonephritis however, if renal function is to be preserved, we must aim to reverse the underlying events causing glomerular inflammation.

The exact immunological events of IgA nephropathy are unknown and therefore treatment of IgA nephropathy is extremely difficult. For patients who present acutely with macroscopic haematuria, but with normal renal function and blood pressure, regular review alone may be all that is required. For patients who follow a more accelerated clinical course, once again control of blood pressure and careful fluid management are vital. Acute inflammation on biopsy may justify the use of immunosuppressives with anecdotal reports of success with mycophenolate mofetil, cyclophosphamide and pulsed steroids, and intravenous immunoglobulin.[32–34] In the more chronic phase, use of ACE inhibitors, both in hypertensive and in non-hypertensive patients who have proteinuria (>1 g/24 hours), is emerging as increasingly important. These drugs both reduce the level of proteinuria and slow the decline in glomerular filtration rate normally seen.[35]

Prognosis is difficult to estimate for those patients presenting acutely with IgA nephropathy. Certainly hypertension, impaired renal function, and severe proteinuria at presentation are adverse prognostic features[36] with one study suggesting that a combination of a raised creatinine (>150 μmol/l) together with proteinuria (>1 g/24 hours) gave a patient only a 20% chance of independent renal function seven years later.[12] In HSP clinical presentation predicts prognosis with 15% of nephritic patients eventually reaching end stage renal failure, but up to 50% of those with a combined nephritic and nephrotic picture eventually needing renal replacement therapy.[37]

Rapidly progressive glomerulonephritis can irreversibly destroy renal function within days without treatment. Such risks therefore justify the use of significantly toxic therapies in an attempt to preserve independent renal function. In antiglomerular basement membrane disease, high dose steroids and cyclophosphamide are used to switch off B-cell production of antiglomerular basement membrane antibody with additional plasma exchange to remove existing antibody during the two weeks before the effects of cyclophosphamide as seen. In renal vasculitis (Wegener's and microscopic polyangiitis) much less is known of the pathogenesis but similar regimens aim to switch off both T-cell and B-cell function.[38]

Unless treatment is prompt, the renal prognosis in antiglomerular basement membrane disease is poor with few patients presenting with a serum creatinine greater than 600 μmol/l and requiring dialysis ever regaining independent renal function.[39] With plasma exchange and aggressive cytotoxic treatment, 80% of patients with a creatinine less than 600 μmol/l can expect improvements in renal function,[2] which are generally seen within days of starting treatment. Plasma exchange may be used even in those with irretrievably

damaged kidneys in an attempt to treat pulmonary haemorrhage.[40]

The prognosis in ANCA positive RPGN is better than that in antiglomerular basement membrane disease. With aggressive treatment using steroids, cyclophosphamide, and plasma exchange at least five times if they are dialysis dependent, even 75% of those patients initially requiring renal support may recover renal function, with 80% of these remaining dialysis independent at five years.[41] Plasma exchange is also used in ANCA positive vasculitis associated pulmonary haemorrhage.[42] Recent trial data have confirmed that, after initial induction with steroids and cyclophosphamide for three months, many of these patients may be safely converted to an oral azathioprine regimen.[43]

The prognosis in immune complex RPGN is determined by the level of glomerular inflammation and treatment is directed at underlying pathology. The few cases of truly idiopathic immune complex RPGN appear to take a similar clinical course to pauci-immune RPGN and immunosuppressive regimens similar to those used in ANCA positive disease may be appropriate.

The pathology of idiopathic MCGN remains obscure and with little specific treatment of proven value, the importance of blood pressure control increases. In an attempt to limit the platelet activation associated with cellular proliferation, aspirin and dipyridamole have been used with some success and there may be a place for steroid treatment in children.[44] Type II MCGN is rare and shows little response to conventional therapies. Renal prognosis in truly idiopathic MCGN type I gives a 60% renal survival at 10 years; this figure is probably worse in MCGN type II.

Treatment of MCGN with hepatitis C infection is complex. If the disease is thought to be driven by virus-containing immune complexes, then control of viral load using alpha-interferon and ribavirin should be most effective—although this has shown some success with improvements in mild MCGN, relapse of viral load after stopping treatment is often seen.[22] Alternatively, where renal damage is more severe, the inflammatory component of the lesion might best be controlled with immunosuppressives albeit at a risk of viral activation. Some nephrologists would therefore treat an aggressive nephritic flare with pulsed methylprednisolone followed by 3–6 months of tapered oral steroids. Where disease is particularly active oral cyclophosphamide for two months has been used. With such treatments of cryoglobulinaemic vasculitis, extrarenal manifestations respond very quickly and in more than 85% of patients the plasma creatinine falls within a week, although proteinuria is much slower to respond. Long term immunosuppression is not justified and plasma exchange remains controversial.[22] Approximately 10% of patients with hepatitis C related kidney disease will develop end stage renal failure.[21]

The treatment of lupus nephritis is also complex with only part of its pathology being understood. As a disease that often strikes young women, the risks of renal disease must be weighed against possible infertility associated with immunosuppressive regimens. Renal biopsy is vital since, with an acute nephritic flare, it is important to distinguish scarred and irreversibly damaged kidneys from those that might benefit from aggressive immunosuppression. A recent study of patients with type IV lupus nephritis suggested that a combination of pulsed monthly methylprednisolone and intravenous cyclophosphamide resulted in a remission rate of approximately 85%.[45] Further quarterly doses of pulsed cyclophosphamide after the six months of monthly induction therapy also reduced the subsequent relapse rate. There may also be a place for intravenous immunoglobulin (working by solubilising immune complexes or blocking Fc receptors to prevent the inflammatory cascade) in refractory cases or mycophenolate mofetil in acute flares.[46] The most recent data suggest that with current treatment 70%–85% of patients with type III and IV lupus nephritis will retain independent renal function at five years. Repeated acute nephritic flares are a poor prognostic indicator, as are hypertension and black race.

Glomerulonephritis is an important cause of renal failure for which we currently have only non-specific and potentially toxic therapies. With increasingly prompt diagnosis and greater understanding of pathology, we must hope to improve this situation. As knowledge grows, we may prevent some glomerulonephritides altogether, for instance by successful vaccination against hepatitis C for MCGN or by designing therapies to reverse immune complex formation in systemic lupus erythematosus. For patients in whom glomerulonephritis does occur, drugs may be designed which tackle inflammation by interrupting the complement or cytokine cascades or which target the cell signalling that leads to proliferation and subsequent fibrosis. Only then can we hope to prevent the many cases of chronic renal failure caused by these diseases.

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Sources of further information

- National Kidney Federation at www.kidney.org.uk produces very helpful patient leaflets on glomerulonephritis, IgA nephropathy, and mesangiocapillary glomerulonephritis.
- Arthritis Research Campaign at www.arc.org.uk produces excellent patient leaflets on lupus and vasculitis.

SELF TEST QUESTIONS ON ACUTE GLOMERULONEPHRITIS (ANSWERS AT END OF REFERENCES)

Q1. What is the most likely diagnosis in a 15 year old boy presenting to casualty with a sore throat and macroscopic haematuria?

Q2. Which of the following statements about lupus nephritis are true?

(A)Patients with lupus nephritis may have a normal serum creatinine value

(B)Patients with lupus nephritis may require multiple sequential biopsies

(C)In lupus nephritis a fall in C3 levels and a rise in antidouble stranded DNA levels may precede actual glomerular inflammation

(D)Patients with lupus nephritis often develop infertility as a result of their treatment

Q3. Plasma exchange is a recognised treatment in which of the following forms of glomerulonephritis?

(A) Lupus nephritis

(B) Antiglomerular basement membrane disease

(C) ANCA positive vasculitis

(D) IgA nephropathy

Q4. Immune complex deposition is thought to be important in the pathogenesis of which of the following forms of glomerulonephritis?

(A) Lupus nephritis

(B) IgA nephropathy

(C) ANCA positive vasculitis

(D) MCGN type II

Q5. Which of the following diseases, which can present as an acute nephritic syndrome, also commonly present with a nephrotic picture?

(A) Lupus nephritis

(B) IgA nephropathy

(C) Antiglomerular basement membrane disease

(D) Mesangioproliferative glomerulonephritis

(E) Post-streptococcal glomerulonephritis

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ANSWERS

Q1. IgA nephropathy. Q2. A, B, C. Q3. B, C. Q4. A, B. Q5. A, D.

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EDUCATIONAL REVIEW

The nephrotic syndrome: pathogenesis and treatment of edema formation and secondary complications

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Abstract Nephrotic syndrome is an important clinical condition affecting both children and adults. Studies suggest that the pathogenesis of edema in individual patients may occur via widely variable mechanisms, i.e., intravascular volume underfilling versus overfilling. Managing edema should therefore be directed to the underlying pathophysiology. Nephrotic syndrome is also associated with clinically important complications related to urinary loss of proteins other than albumin. This educational review focuses on the pathophysiology and management of edema and secondary complications in patients with nephrotic syndrome.

Keywords Nephrotic syndrome · Edema · Secondary complications · Underfill · Overfill

Introduction

Nephrotic syndrome is defined by proteinuria (>3–3.5 g/day in adults or >1 g/m^2/day in children), hypoalbuminemia (<3.0 g/dL), and edema. Hyperlipidemia is also present in many patients with nephrotic syndrome. Numerous glomerular conditions can result in nephrotic syndrome, and certain patients with glomerular disease may manifest nephrotic range proteinuria without significant hypoalbuminemia or edema. In the present review the pathogenesis and management of the edema and metabolic complications of nephrotic syndrome will be discussed.

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Pathogenesis of edema in nephrotic syndrome

Two major pathophysiologic mechanisms have been proposed to explain the development of edema in nephrotic syndrome, including the "underfilling" hypothesis [1] and the "overfilling" hypothesis [2]. In the underfill hypothesis (Fig. 1) [3], high-grade proteinuria results in hypoalbuminemia with an associated decrease in plasma oncotic pressure. This in turn leads to increased net capillary ultrafiltration and edema. In the early phase of this process, the edema may be attenuated by increases in interstitial hydrostatic pressure and lymphatic drainage which enhance the return of interstitial fluid into the intravascular compartment. Ultimately, however, this compensatory mechanism is overwhelmed, and edema forms. The diminished intravascular volume is exacerbated, resulting in clinical symptoms such as tachycardia, peripheral vasoconstriction, low blood pressure, oliguria, and urinary sodium retention. While the resultant fall in glomerular filtration rate (GFR) is generally of a prerenal nature, acute tubular necrosis may occur if these hemodynamic effects are prolonged. Such patients also manifest activation of the renin–angiotensin–aldosterone system (RAAS) and increased plasma norepinephrine and arginine vasopressin (AVP) concentrations [4, 5]. While activation of the RAAS or sympathetic nervous system is observed with both renal parenchymal disease and intravascular hypovolemia, the non-osmotic increase in plasma AVP suggests that the primary derangement is hypovolemia, particularly in the arterial component of the circulation, i.e., arterial underfilling [6]. Similarly, suppression of RAAS may indicate volume expansion but can also be observed with renal parenchymal disease

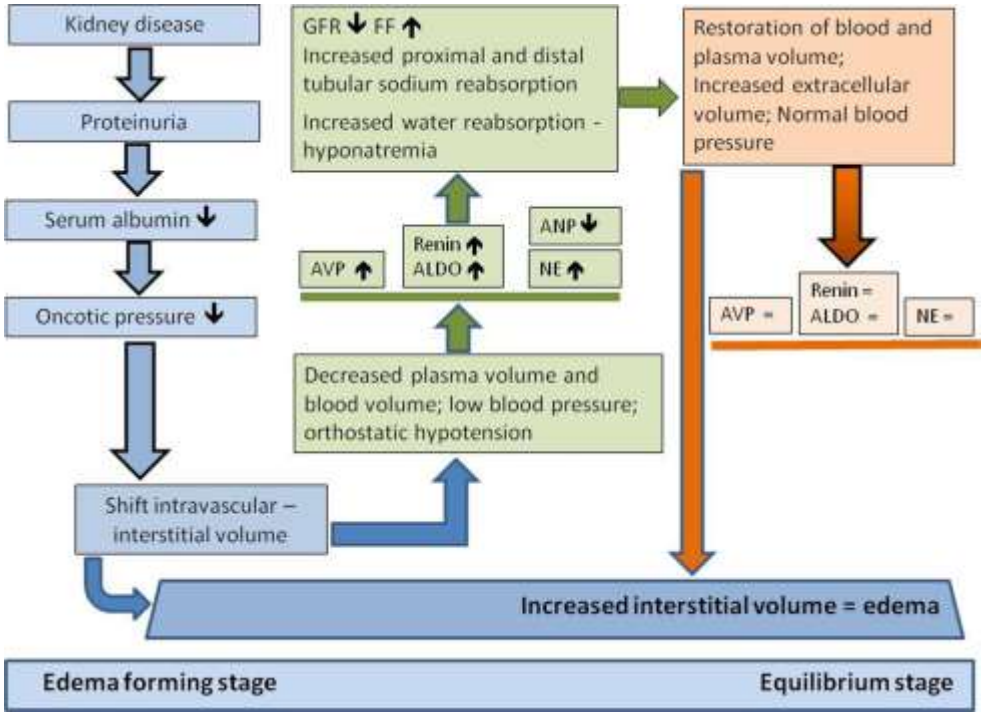

Fig. 1 The "Underfilling" theory of sodium retention in the nephrotic syndrome. *AVP* Arginine vasopressin, *ALDO* aldosterone, *ANP* atrial natriuretic peptide, *NE* norepinephrine, *GFR* glomerular filtration rate, *FF* filtration fraction. Reproduced with permission [3]

(e.g., diabetic nephropathy) independent of volume status [7, 8]. It should be emphasized that these characteristics of underfilling edema can occur in adults as well as children with nephrotic syndrome. This is believed to be the most common mechanism of edema formation in minimal change disease.

Usberti and colleagues studied 16 pediatric and adult patients with nephrotic syndrome who had normal renal function [9]. These patients had decreased plasma sodium concentration, increased plasma AVP concentration, impaired excretion of an acute water load, and elevation of plasma renin activity (PRA) and urinary norepinephrine levels as compared to controls. A highly significant inverse correlation between plasma AVP concentration and blood volume was demonstrated in these nephrotic patients (Fig. 2) [9]. Isotonic albumin infusion decreased plasma AVP concentration and increased water diuresis.

In contrast, Dorhout-Mees et al. have observed an overfill mechanism of edema formation in nephrotic syndrome (Reviewed in [10]). This interpretation necessitates an intrarenal mechanism of increased renal sodium and water reabsorption as the initiating factor in volume expansion and edema (Fig. 3) [3]. These authors observed that after prednisone-induced remission in 13 episodes of nephrotic syndrome in ten subjects with minimal change disease, blood pressure fell in 12 cases and plasma volume fell in ten cases. Gur et al. evaluated plasma and blood volume in 88 patients with nephrotic syndrome [11]. In support of vascular overfilling, they reported higher plasma and blood volumes corrected for estimated lean body mass as compared to controls. It should be emphasized, however, that the use of radioactive-labeled albumin to measure plasma or blood volume has an accuracy of ±10 % [12]. An additional source of variability comes from the correction of these volumes for body mass in the setting of significant edema. Nonetheless, it must be acknowledged that nephrotic syndrome, particularly when associated with various glomerulonephritides, may be characterized by hypertension, decreased kidney function, and volume expansion, i.e., vascular overfilling.

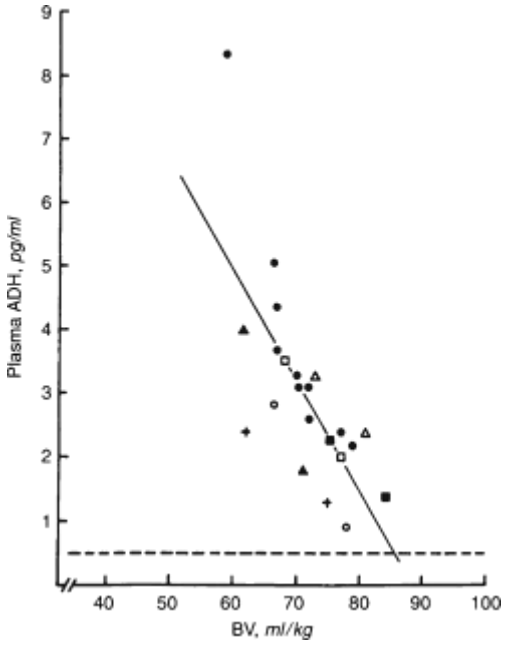

Fig. 2 Relationship between plasma antidiuretic hormone (*ADH*) and blood volume (*BV*) in nephrotic syndrome. *Solid circles* Basal values of nonexpanded patients, *other symbols* individual patients who underwent the BV expansion with 20 % plasma albumin. Reproduced with permission [9]

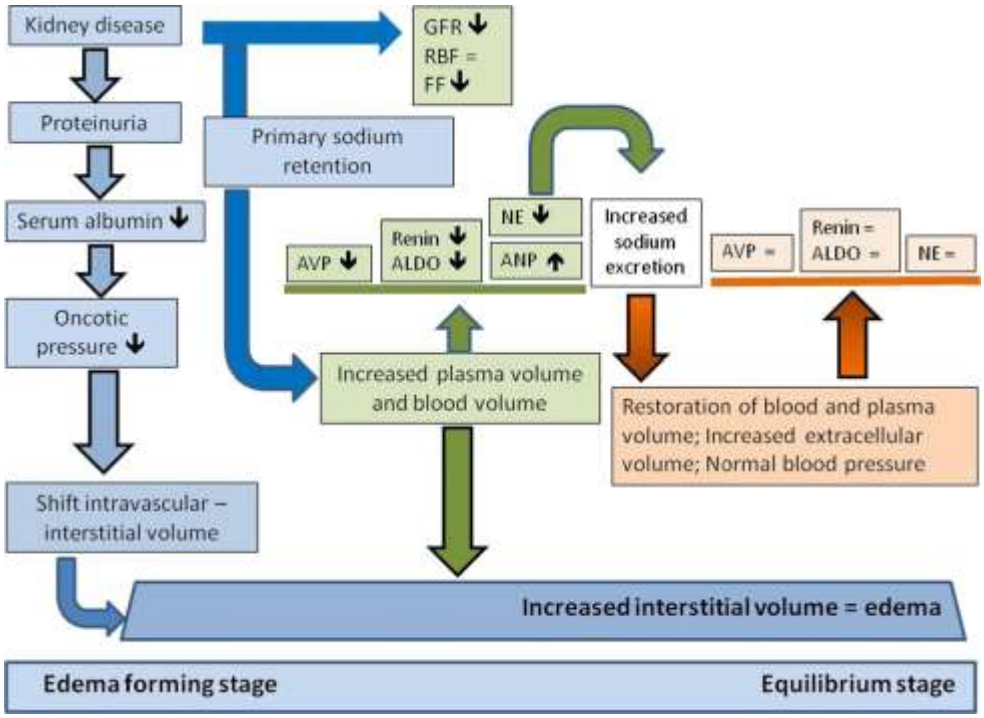

Fig. 3 The "Overfilling" theory of sodium retention in the nephrotic syndrome. Reproduced with permission [3]

Studies in which an angiotensin-converting enzyme inhibitor (ACEI) decreased plasma aldosterone concentration without inducing negative sodium balance have been used to support the overfilling hypothesis [13]. It is important to note, however, that blood pressure and thus renal perfusion pressure decreased with ACEI treatment which could have obscured any natriuretic response. In this regard, the mineralocorticoid receptor antagonist spironolactone has been shown to induce natriuresis in nephrotic patients in the absence of a fall in blood pressure [14].

Usberti et al. have described two groups of adult nephrotic patients differentiated by their plasma albumin concentration [15]. Those with plasma albumin concentrations of <1.7 g/dL had low blood volume, low plasma atrial natriuretic peptide (ANP) concentration, increased plasma angiotensin II concentration, and increased proximal tubule sodium reabsorption as estimated by lithium clearance. Alternatively, nephrotic patients with a plasma albumin concentration of >1.7 g/dL exhibited normal blood pressure and hormone concentrations. An analysis of all patients demonstrated that plasma albumin concentration was positively correlated with blood volume, while PRA was inversely correlated with blood volume and plasma albumin concentration. In children with nephrotic syndrome and severe edema, Kapur et al. [16] were able to differentiate underfilled and overfilled subjects by the fractional excretion of sodium (FENa). Those with a FENa of <0.2 % appeared to be volume contracted with significantly elevated blood urea nitrogen (BUN), elevated BUN/creatinine ratio, decreased urine sodium concentration, and increased plasma renin activity, serum aldosterone and plasma antidiuretic hormone concentrations as compared to the group with a FENa of >0.2 %.

Several mechanisms have been proposed to explain primary renal sodium and water retention in nephrotic patients with overfilling of the intravascular compartment, leading to edema. Such patients show resistance to ANP which has been attributed to increased activity of cyclic guanosine 3′,5′-monophosphate (cGMP) phosphodiesterase. This enzyme catabolizes the second messenger cGMP which is normally formed when ANP interacts with its biologically active natriuretic peptide A receptors, thereby leading to blunted ANP responsiveness [17–19]. It has also been suggested that intrarenal sodium retention in overfilled nephrotic patients is due to activation of the epithelial sodium channel (ENaC) in the collecting duct. Modification of extracellular loops of ENaC by proteinases such as plasmin is known to enhance channel activation [20, 21]. In this regard, Svenningsen et al. have shown that nephrotic urine activates ENaC channels expressed in cell culture and that such activation can be prevented by inhibitors of plasmin [22]. More recently, Andersen et al. studied 20 children with idiopathic nephrotic syndrome, reporting that urine obtained during relapsed nephrotic syndrome contains an increased amount of plasminogen–plasmin compared with urine collected during remission and that the relapse urine activated ENaC in a collecting duct cell line while remission urine did not [23].

Management of edema in nephrotic syndrome

Treatment of nephrotic syndrome should be directed at the primary disease. Guidelines for treatment in specific conditions

are detailed elsewhere [24–26]. When there are no specific evidence-based therapies, treatments aimed at mechanisms common to a variety of glomerular diseases can be considered. For example, proteinuria is considered to be an important risk factor for progression of chronic kidney disease [27]. Thus, inhibition of the RAAS with either an ACEI or angiotensin receptor blocker (ARB) is often utilized in order to decrease proteinuria and to hopefully delay the progression of chronic kidney disease.

Diet

Many of the symptoms in patients with nephrotic syndrome relate to the edema caused by renal sodium and water retention. Thus dietary sodium intake should be restricted to 2 g per day in adults or 35 mg/kg/day in children. Restriction of water intake can be reserved for patients with hyponatremia. If edema persists, diuretic treatment should be considered.

Diuretics

It is important to distinguish the potential contributions of underfilling versus overfilling in individual patients prior to the initiation of diuretic therapy (Table 1) [3]. Aggressive use of high-dose diuretics in "overfilled" nephrotic patients is indicated for management of edema and intravascular volume excess. In contrast, the use of diuretics in nephrotic syndrome with vascular underfilling should be undertaken judiciously with careful monitoring of renal and systemic hemodynamics given the potential to exacerbate intravascular hypovolemia. In this regard, Kapur et al. have demonstrated that diuretic therapy alone is safe and effective for the management of severe edema in nephrotic children who are overfilled while underfilled nephrotics may require both albumin and diuretics [16].

The extent of diuretic support required depends on the degree of edema and the individual's clinical response. In nephrotic patients with mild edema and normal GFR, an oral thiazide diuretic may be a reasonable first choice. With more severe edema, a loop diuretic should be considered, with intravenous administration more effective than oral administration [28]. When using oral loop diuretics, bioavailability of the drug must be considered (Table 2). While furosemide is the most commonly used loop diuretic, particularly in children, it has the greatest variation in oral bioavailability. In one study the oral bioavailability of furosemide in nephrotic children was found to be 58 % [29]. Because of the short duration of action of loop diuretics they must be administered at least twice per day. Poor diuretic response may be overridden by increasing the oral dose of the loop diuretic and/or by administering the agent intravenously. One study in nephrotic children demonstrated that 1 mg/kg of intravenous furosemide was twice as effective as 2 mg/kg of oral furosemide [28]. Torsemide and ethacrynic acid are less commonly utilized in children. As ethacrynic acid is the only loop diuretic which does not contain a sulfhydryl moiety, it may be useful in patients with significant sulfa allergy.

Table 1 Factors which help to differentiate overfill and underfill edema in nephrotic syndrome[a]

Factors	Overfill	Underfill
GFR <50 % of normal	+	−
GFR >75 % of normal	−	+
Serum albumin >2 g/dL	+	−
Serum albumin <2 g/dL	−	+
Minimal change histology	−	+
Hypertension	+	−
Postural hypotension	−	+

GFR, Glomerular filtration rate

[a] Table is reproduced from reference [12] with permission

Loop diuretics are highly protein bound and must be secreted into the lumen of the nephron in order to block the Na-K-2Cl cotransporter in the thick ascending limb of the loop of Henle. Thus, it has been suggested that insufficient tubular secretion of the loop diuretic occurs in nephrotic patients with severe hypoalbuminemia, , resulting in a need for higher doses to achieve the desired effect. In fact, however, urinary protein binding of loop diuretics does not appear to be a major mechanism of diuretic resistance in nephrotic syndrome [30]. Poor compliance with prescribed medications and/or dietary salt intake should be excluded as causes of apparent resistance to loop diuretics. True resistance to loop diuretics in edematous disorders is multifactorial (Fig. 4) [31]. Diuretic-induced intravascular volume depletion and negative sodium balance stimulate neurohormonal systems, including RAAS, the sympathetic nervous system, and AVP, leading to renal vasoconstriction and sodium and water retention. The associated decrease in distal sodium delivery leads to loop diuretic resistance. Resistance by this mechanism can be addressed with concomitant use of a thiazide or amiloride. Chronic administration of loop diuretics in animals has also been shown to cause hypertrophy and hyperplasia in epithelial cells of the distal convoluted tubule with increased expression of the sodium chloride cotransporter, thereby blunting the natriuretic effect [32, 33]. Resistance by this mechanism can be overcome by concomitant use of a mineralocorticoid receptor antagonist. Limited data suggest that similar adaptations also occur in humans [34].

Combination therapy with loop and thiazide or thiazide like-diuretics (e.g., metolazone) can enhance diuresis as compared to a loop diuretic alone—but the patient needs to be carefully monitored to avoid severe hypokalemia and alkalosis. The administration of amiloride or a mineralocorticoid receptor antagonist with the loop diuretic can minimize hypokalemia although the diuretic effect of these

Table 2 Pharmacology of loop diuretics

Pharmacology parameters	Furosemide	Bumetanide	Torsemide
Relative IV potency (mg)	40	1	20
Bioavailability (%)	10–100 (50)	80–100	80–100
Average effect duration (h)	6–8	4–6	6–8
Oral to IV conversion	2:1	1:1	1:1
30-day cost (USD $)	4	4	19–23

IV, Intravenous

medications alone at routine doses appears to be minimal [35, 36]. However, high-dose spironolactone (200 mg twice a day) has been shown to induce significant natriuresis in nephrotic adults as compared to controls [14]. Although it has been suggested that increased activity of ENaC may be a mechanism of primary sodium retention in nephrotic syndrome, there is no current clinical evidence to support the use of amiloride as a first-line diuretic in nephrotic syndrome. Whether the diuretic effect of amiloride is blunted by enhanced distal sodium delivery secondary to the frequent concomitant use of a loop diuretic is not known.

Albumin support

If diuretic therapy has not been effective, the intravenous administration of loop diuretics in combination with albumin may induce an effective although short-lived and relatively expensive diuresis [37]. The transient increase in blood volume associated with improved oncotic pressure is anticipated to improve renal hemodynamics and increase diuresis. With such treatment it is particularly important to determine the patient's intravascular volume status. In nephrotic patients with underfilling associated with severe hypoalbuminemia (<2 g/dL), an enhanced diuresis can be obtained with intravenous co-administration of 1 g/kg of 25 % albumin and furosemide. Alternatively, the administration of 25 % albumin to nephrotic patients who are overfilled may further exacerbate hypervolemia, contributing to systemic hypertension and generation or exacerbation of pulmonary edema. A 25 % solution of albumin must also be used with caution in patients with oliguria or significantly impaired renal function due to increased risk of pulmonary edema, while 5 % albumin is not helpful for management of edema due to the large volume required to provide a significant colloid load in an already edematous patient.

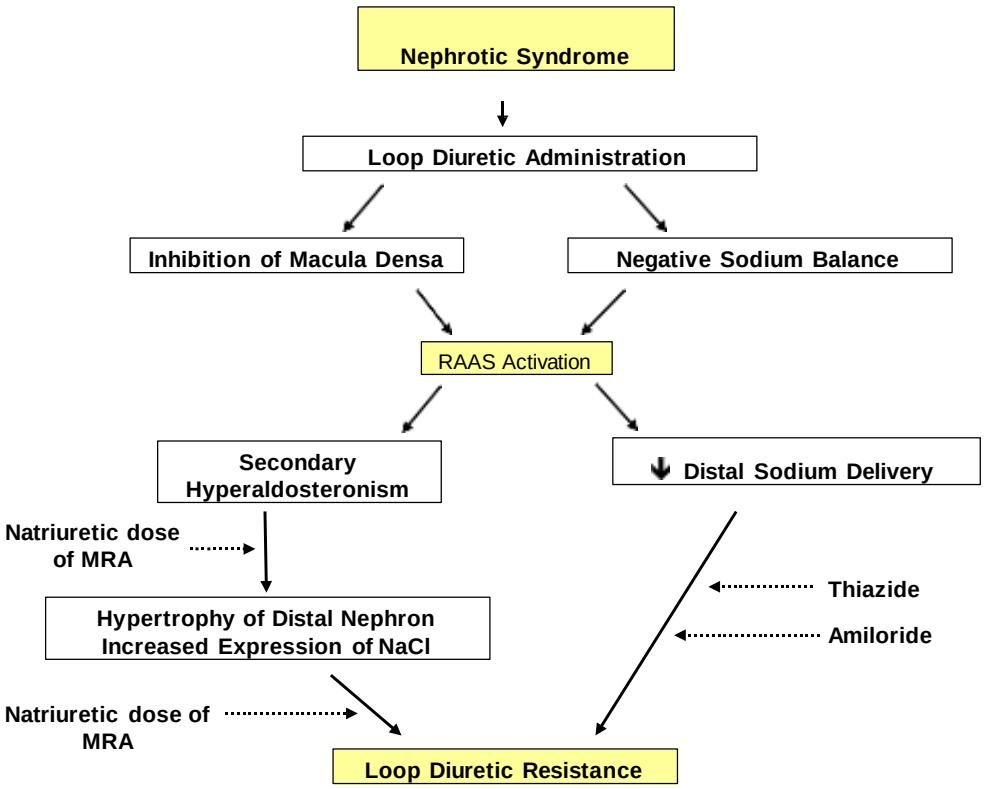

Fig. 4 Mechanisms of loop diuretic resistance in nephrotic syndrome. Loop diuretic administration induces intravascular volume depletion and negative sodium balance which result in activation of the renin–angiotensin–aldosterone system (*RAAS*). Loop diuretics also block sodium chloride transport at the macula densa, which directly stimulates RAAS independent of renal sodium loss. Elevated serum aldosterone concentration also results in hypertrophy of the distal nephron and increased expression of the sodium chloride cotransporter. These effects can be addressed with the use of a mineralocorticoid receptor antagonist (*MRA*). Decreased distal sodium delivery also contributes to resistance to loop diuretics. This effect can be mitigated with use of a thiazide or amiloride. Reproduced with permission [31]

Secondary complications of nephrotic syndrome

Increased urinary losses of protein and protein-bound molecules contribute to several complications in patients with nephrotic syndrome. The loss of albumin and thyroid binding globulin may reduce the binding capacity for total triiodothyronine and thyroxine. However, due to a rise in thyroid stimulating hormone (TSH), overt hypothyroidism is only rarely observed [38, 39]. Both subclinical and overt hypothyroidism may be more prevalent among treatment-resistant nephrotic children [40, 41]. Therefore, this subpopulation may warrant routine monitoring of thyroid function tests although no specific guidelines are available.

Both transferrin and erythropoietin (EPO) may be lost in the urine of nephrotic patients. Since transferrin transports iron to red blood cells, severely decreased transferrin levels can produce a microcytic anemia which is poorly responsive to iron supplementation [42]. EPO therapy has been shown to increase hemoglobin levels in anemic nephrotic patients with normal renal function and iron repletion[43].

Patients with nephrotic syndrome also may have reduced 25-hydroxy-vitamin D levels secondary to urinary loss of vitamin D binding protein [44]. In this setting, decreased serum ionized calcium levels may occur secondary to decreased free serum calcitriol, possibly leading to secondary hyperparathyroidism and only rarely to severe complications such as osteitis fibrosis and osteomalacia [45]. Vitamin D supplementation as cholecalciferol or ergocalciferol should be instituted when vitamin D deficiency is documented.

Patients with nephrotic syndrome have an increased risk of thromboembolic events [46]. Such events are associated with increased procoagulants, such as fibrinogen, factor VIII, and plasminogen activity factor-1, and decreased anticoagulants due to urinary losses of antithrombin III, plasminogen, and protein S [47]. A procoagulant state is favored and is further exacerbated by low intravascular volume observed in underfilled nephrotic patients or induced by diuretic therapy. A retrospective review reported that 9 % of 326 children with nephrotic syndrome of any cause had experienced at least one thromboembolic event, with a median time to the first event of 70.5 days following the diagnosis of nephrotic syndrome [48]. This is similar to adults in whom the majority of venous thromboembolism events occur within the first 6 months after diagnosis of nephrotic syndrome [46]. Independent predictors of thromboembolic events in the children of this study included age at onset of nephrotic syndrome of over 12 years, severity of proteinuria, and history of thromboembolic event prior to diagnosis of nephrotic syndrome [48]. Children with congenital nephrotic syndrome and membranous nephropathy are known to have a higher risk of thrombotic events [48]. The role of prophylactic anticoagulation in this setting is still debated [49]. Some have suggested primary pharmacologic prophylaxis with appropriately dosed low-molecular-weight heparin or other anticoagulant for nephrotic patients at the highest risk of thromboembolic events, such as those with additional thrombotic risk factors including surgery, malignancy, or pregnancy, those with a prior history of thromboembolism, or patients with membranous nephropathy [50]. However, there are no controlled clinical trials to support this recommendation.

Patients with nephrotic syndrome are prone to serious bacterial infection, notably pneumonia, sepsis, and peritonitis secondary to *Streptococcus pneumoniae*, *Escherichia coli*, and *Hemophilus* bacteria. Infection was the major cause of death in nephrotic children prior to the introduction of prednisone and antibiotics. The predisposition to infections with nephrotic syndrome has been associated with urinary immunoglobulin losses leading to low serum immunoglobulin G levels [51]. Treatment with intravenous immunoglobulin may be considered in the setting of acute serious bacterial infection or recurrent severe bacterial infections, but the protective effects are short-lived and routine administration is costly. Vaccination against pneumococcus with 13-valent conjugate vaccine and 23-valent polysaccharide vaccine is indicated and should be provided according to patient age and prior immunization history [52]. Studies suggest that an adequate serologic response can be induced in many subjects despite high-dose corticosteroid treatment [53, 54].

Nephrotic patients have abnormalities of lipid metabolism which predispose to cardiovascular disease [55, 56]. Adults with nephrotic syndrome have a significantly increased relative risk of myocardial infarction (5.5; 95 % confidence interval 1.6–18.3) as compared to controls despite adjustment for hypertension and smoking status [57]. The lipid abnormalities which occur with nephrotic syndrome include: (1) an increase in low-density lipoprotein (LDL) cholesterol due to reduced hepatic cholesterol uptake associated with acquired LDL-receptor deficiency; (2) increased lipoprotein(a) concentration due to increased rate of synthesis; (3) hypertriglyceridemia secondary to an inability to clear very low density lipoprotein, chylomicrons, and remnant particles. The defect in triglyceride clearance involves reduced endothelial lipoprotein lipase (LPL) and decreased ability of lipoproteins to bind to LPL. Acute myocardial infarction has been rarely reported in children with chronic nephrotic syndrome [58, 59]. Although previous data suggest no increased risk of cardiovascular events in adulthood associated with resolved childhood steroid-responsive nephrotic syndrome [60], concern for premature atherosclerosis and associated early cardiovascular events still exists. Adults with a history of steroid-responsive childhood nephrotic syndrome demonstrate increased total cholesterol, LDL, homocysteine, and apolipoprotein B and A1 levels as compared to controls, and there is a significant correlation between carotid intima-media wall thickness (IMT) and the number of recurrences of nephrotic syndrome [61]. In adults with childhood onset systemic lupus erythematosus, nephrotic range proteinuria has been associated with significantly higher levels of total cholesterol, LDL,

apolipoprotein B, and fibrinogen as well as higher IMT as compared to patients with lupus and lesser degrees of proteinuria or with controls [62]. Further study in this area is needed. Decreasing proteinuria and hypoalbuminemia with ACEI or ARB therapy may improve lipid abnormalities as well as control blood pressure in nephrotic patients (reviewed in [63]). In chronic nephrotic syndrome with persistent hyperlipidemia, statin therapy should be considered in both children and adults.

In adults, if proteinuria in nephrotic patients remains ≥1 g per day, a blood pressure goal of ≤125/75 mmHg is recommended, whereas with a decrease to <1 g per day a goal of ≤130/80 mmHg is satisfactory. In children with nephrotic syndrome, the goal blood pressure should be at or below the 90th percentile for age, sex, and height with a maximum for teenagers of 120/80 mmHg. Moderate protein restriction (0.8–1 g/kg per day) is recommended in adults with nephrotic syndrome while affected children require normal caloric and protein intake for their age to allow for appropriate growth. High dietary protein intake should be avoided in both pediatric and adult nephrotic patients.

In conclusion, in addition to treatment of the underlying glomerular disease, management of edema should include assessment of an underfilled versus overfilled intravascular space. This assessment may guide clinical decision-making with respect to diuretic and albumin support. Given the urinary losses of multiple proteins in addition to albumin, it is important to monitor affected patients for secondary metabolic complications and to treat these complications appropriately. Children with treatment-resistant nephrotic syndrome are at particular risk for these secondary complications. Further study into the long-term effects of childhood nephrotic syndrome on adult kidney and cardiovascular health are needed.

Multiple choice questions (answers are provided following the Reference list)

1) The following are more suggestive of underfilling than overfilling in nephrotic syndrome EXCEPT:

   a. Serum albumin concentration below 2 g/dL
   b. Minimal change histology
   c. Hypertension
   d. Postural hypotension

2) The following should be considered in the management of severe anasarca and mild pulmonary edema in a hypertensive nephrotic child with serum albumin concentration 2.7 g/dL and other findings consistent with the overfill hypothesis EXCEPT:

   a. Loop diuretics
   b. Addition of a thiazide or metolazone to enhance diuresis
   c. Daily intravenous administration of 25 % albumin
   d. Fluid restriction

3) The following are commonly known secondary complications of active nephrotic syndrome EXCEPT:

   a. Subclinical hypothyroidism
   b. Thromboembolism
   c. Hypogammaglobulinemia
   d. Hepatitis

4) A teenage girl with membranous nephropathy presents with left flank pain, gross hematuria, and thrombocytopenia. The most likely etiology related to her nephrotic syndrome is:

   a. Urolithiasis
   b. Left renal vein thrombosis
   c. Urinary tract infection
   d. Wilms tumor

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Nutritional Management of Kidney Stones (Nephrolithiasis)

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The incidence of kidney stones is common in the United States and treatments for them are very costly. This review article provides information about epidemiology, mechanism, diagnosis, and pathophysiology of kidney stone formation, and methods for the evaluation of stone risks for new and follow-up patients. Adequate evaluation and management can prevent recurrence of stones. Kidney stone prevention should be individualized in both its medical and dietary management, keeping in mind the specific risks involved for each type of stones. Recognition of these risk factors and development of long-term management strategies for dealing with them are the most effective ways to prevent recurrence of kidney stones.

Key Words: Nephrolithiasis, Calcium oxalate, Uric acid stone, Hypercalciuria, Hyperoxaluria, Risk factors for kidney stones, Prevention of kidney stone

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Introduction

Nephrolithiasis, or kidney stone, is the presence of renal calculi caused by a disruption in the balance between solubility and precipitation of salts in the urinary tract and in the kidneys. The incidence is at peak among white males age 20 and 30 years old. The National Health and Nutrition Examination Survey (NHANES) III (1988-1994) reported that there was a 5% prevalence of stone formation among adults in the United States and this represented a 4% increase from the NHANES II (1976-1980) [1,2]. Nephrolithiasis is considered to be a disease of affluence like obesity, hypertension, and type 2 diabetes because it is so prevalent in wealthy countries [3,4]. Urologic intervention is required in as many as 20% of patients with renal colic [5] and more than $2 billion is spent on treatment each year. The lifetime prevalence of kidney stones in the United States is 12% among men and 7% among women [6,7]. Kidney stones develop when urine becomes "supersaturated" with insoluble compounds containing calcium, oxalate (CaOx), and phosphate (CaP), resulting from dehydration or a genetic predisposition to over-excrete these ions in the urine. About 5-10% of Americans have this predisposition.

Kidney stone formation

When CaOx concentration is 4 times above the normal solubility a crystal starts to form. If the CaOx concentration is 7 to 11 times higher than normal solubility the nucleation begins. In low urine volume, the presence of high calcium, high oxalate the supersaturation (SS) of CaOx is increased. Citrate in the urine forms soluble complex with urinary Ca. If urine has low citrate concentration SSCaOx is promoted to form CaOx stone. If urine pH is > 6.5, proportion of divalent and trivalent ions are increased then SSCaP is favorable. The levels of urinary supersaturation of the different solutes determine the specific types of stones [8-10].

Kidney stones tend to recur. Approximately 50% people who form one stone form another within 10 years. The risk of recurrence ranges from 30-50% at 5 years in observational studies. The control groups in recent randomized controlled trials have a 2-5% annual recurrence rate after an incident calcium oxalate stone. Recurrence rates also depend on the stone type. When nuclei of uric acid form, they lower the metastable limit (e.g. susceptibility to perturbation) and favor further stone precipitation. Decreased supersaturation of the urine filtrate will decrease the risk of recurrence of kidney stone [11].

Types of Kidney Stones

Table 1 describes the various types of kidney stones and their prevalence. Approximately 70-80% of kidney stones are composed of calcium oxalate and calcium phosphate. Of the rest, 10% are struvite, 10% of uric acid; and less than 1% are composed of cystine or are diagnosed as drug-related stones. Calcium and uric acid stones are more common in men; women have more struvite stones. Figure 1 shows the appearance of the different types of stones.

Calcium stones

Most calcium stones are composed of calcium oxalate, either by itself or much more commonly in combination with calcium phosphate or calcium urate [9,13]. Hypercalciuria, low urine volume and hypocitraturia all predispose to the development of calcium stones. Hypercalciuria often occurs with diseases associated with hypercalcemia like hyperparathyroidism, malignancy, sarcoidosis and vitamin D excess [14,15]. When no other cause is found the hypercalcuria is known as "idiopathic hypercalciuria". Idiopathic hypercalciuria is familial and is likely a polygenic trait, although there are some rare monogenic causes of hypercalciuria and kidney stones such as Dent's disease, an X-linked disorder characterized by hypercalciuria, nephrocalcinosis, and the development of renal failure. Alkaline urine is a risk factor for the development calcium phosphate stones [11,16,17]. Another risk factor for calcium oxalate stone is hyperoxaluria, which occurs due to bowel disease (enteric hyperoxaluria) and genetic disorders of oxalate metabolism (primary hyperoxaluria) [18].

Dietary oxalate may be important in stone development; spinach, beets and rhubarb in particular, contain large amounts of oxalate and they may increase urinary oxalate excretion and predispose to the development of calcium oxalate stones. High dose vitamin C therapy can also lead to increased oxalate generation as vitamin C (ascorbic acid) is metabolized. Oxalate reabsorption in the colon is reduced by the formation of insoluble calcium oxalate [19-24].

This is very important in planning therapy because restricting dietary calcium results in less calcium being available in the intestinal lumen to bind the oxalate. This leads to increased oxalate absorption and therefore increased urinary oxalate excretion [21,25-27]. Therefore, dietary calcium should not be restricted in malabsorption syndromes such as small bowel disease, following surgical small bowel resection, jejuno-ileal bypass surgery and inflammatory bowel disease (IBD) in which there is malabsorption of fatty acids and bile salts. Intestinal

Table 1. Type of stones

Type	Frequency (%)	Sex	Crystals	Radiography
Calcium oxalate/ mix	75	M	Envelope	Round, radiodense, sharply outlined
Calcium phosphate (brushite)	5	F>M	Amorphous: Alkaline urine	Small, radiodense, sharply outlined
Uric acid	5–15	M=F	Diamond; Acid urine	Round/ staghorn, radiolucent, filling defect
Struvite (Mg ammonium phosphate)	10–20	F	Coffin lid; Infection/ urea splitter	Staghorn, laminated radiodense
Cystine	1	M=F	Hexagon	Staghorn, radiodense

Courtesy from Dr. J. Seifter, Harvard Medical School, Renal Division Brigham and Women's Hospital, Boston

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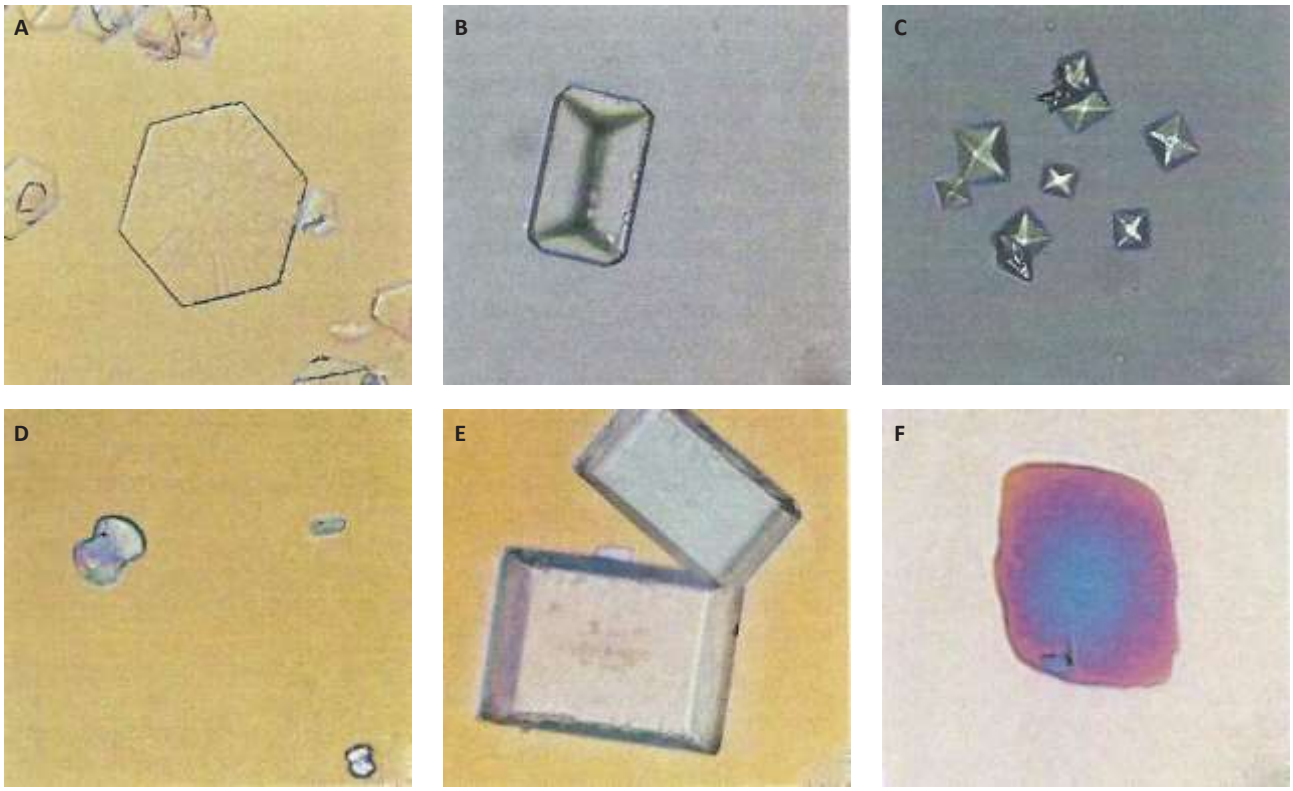

Figure 1. Type of stones. Light microscopy of urine crystals. (A) Hexagonal cystine crystal (200X); (B) coffin-lid shaped struvite crystals (200X); (C) pyramid-shaped calcium oxalate dehydrate crystals (200X); (D) dumbbell-shaped calcium oxalate monohydrate crystal (400X); (E) rectangular uric acid crystals (400X); and (F) rhomboidal uric acid crystals (400X). Reprinted with permission by Elsevier and reference [12].

calcium binds to fatty acids, causing less binding to oxalate. Non-absorbed bile salts in the colon will also cause increased colonic permeability to oxalate. Bariatric (weight loss) surgical techniques that create a malabsorptive state are being performed more frequently today than ever before. Calcium oxalate stone formation is an increasingly common complication with the more restrictive procedures, due to the highly restrictive forms of bariatric surgery such as the Roux-en-Y gastric bypass, sleeve gastrectomies and duodental switches with biliopancreatic diversion that generate malabsorption syndromes. Diarrheal losses cause volume depletion and decreased urine volume. Bicarbonate loss in the stool can cause a metabolic acidosis which can in turn lead to a low urinary pH and hypocitraturia (due to enhanced proximal reabsorption) which will predispose to the development uric acid and calcium oxalate stone formation [28,29].

Uric acid stones

Pure uric acid calculi are radiolucent on plain radiographs but visible on ultrasonography or computerized tomography (CT). These stones tend to form in individuals with hyperuricosuria. Approximately 15-20% of patients with uric acid stones have a history of gout [30-33]. A diet rich in animal protein, because of its high purine content, which produces uric acid in its catabolism, may increase the risk of uric acid stone formation [32,34,35]. At a urinary pH of less than 5.5, uric acid is poorly soluble, but solubility increases at a pH greater than 6.5.

Cystine stones

These stones tend to form only in patients with cystinuria, an autosomal recessive disorder affecting 1 in 15,000 adults in the USA that accounts for only 1% of patients with nephrolithiasis. In cystinuria, nephrolithiasis is the only clinical manifestation and it arises as a result of abnormal renal tubule transport which in turn leads to large amounts of urinary cystine excretion. Cystinuria occurs equally in males and females, although males are more severely affected. Stones begin to form in the 1st to 4th decades of life and tend to be large, multiple and bilateral. The diagnosis can be made by finding typical hexagonal crystals in the urine [36,37]. Urinary tract

infection and obstruction are common, as is stone recurrence every 1-4 years.

Struvite stones

Struvite stones are also called triple phosphate stones, or infection stones. They form in the presence of upper urinary tract infections with urease-producing bacteria (most commonly Proteus and Klebsiella). Normal urine is undersaturated with ammonium phosphate; struvite stone formation occurs only when ammonia production is increased and the urine pH is elevated, which decreases the solubility of phosphate. Bacterial urease is essential for the development of struvite stones because it leads to an elevation in ammonium, carbonate and urinary pH all at the same time. In this setting phosphate combines with ammonium, magnesium and carbonate to form a stone composed of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite.

Urease breaks down urinary urea into ammonia and carbon dioxide:

$Urea \rightarrow 2NH_3 + CO_2$

The ammonia produced by this reaction then combines with water:

$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$

Resulting in increased availability of ammonium in an alkaline urine.

Struvite stones commonly occur in patients with recurrent urinary tract infections, especially if they have abnormal urinary tract anatomy, or require frequent bladder catheterization. The stones may also occur on infected calcium, uric acid or cystine stones, especially after instrumental procedures. Struvite stones are three times more common in women than men, presumably because urinary tract infections are more common in women. They are typically very large and may be so large as to fill the renal pelvis (forming a "Staghorn calculus"). Their growth is rapid and they often grow back after surgical removal because infected fragments of stone have been left behind [38-40].

Clinical Diagnosis of Kidney Stones

Non-obstructing kidney stones produce no symptoms or signs apart from hematuria. However, the kidney stone may cause severe pain, usually accompanied by nausea, vomiting and hematuria (renal colic) when it passes into the ureter. Patients may also complain of urinary frequency and urgency. These signs and symptoms lead to many emergency department visits and hospitalization. The pattern of the pain from stone depends on its location: a stone in the upper ureter leads to pain in the flank that may radiate to the upper abdomen.

When the stone is in the lower ureter, pain may radiate to the ipsilateral testicle in men or labium in women. If the stone is lodged at the ureterovesical junction, the main symptoms will be urinary frequency or urgency. Symptoms quickly improve after passing the stone. On physical examination, the patient is often in excruciating pain, and is unable to achieve a comfortable position. Ipsilateral costovertebral angle tenderness may also be present.

Laboratory tests may show a leukocytosis which may be due to a stress response or infection. Serum creatinine is often elevated if the patient is volume depleted, or if there is bilateral ureteral obstruction or unilateral obstruction in a patient with a solitary kidney. The urinalysis will have red blood cells, white blood cells and occasionally crystals. However, because of the often non-specific physical examination and laboratory findings, imaging studies are critical in making the diagnosis.

Initial evaluation includes obtaining a non-contrast helical CT, which can accurately visualize the size and location of the stones. A kidney, ureter and bladder (KUB) film, although it is insensitive to uric acid stones since they are radiolucent and therefore are not visualized. However, it can visualize calcium–containing, struvite and cystine stones in the kidney or ureter. Complete ureteral obstruction and upper urinary tract infection (UTI) are indications for stone removal by extracorporeal shock wave lithotripsy (ESWL) or surgery [9,12,16,31,41].

Medical and nutrition evaluation of kidney stones

A comprehensive history should be taken by one of the health care providers, and the following items should be covered: prior kidney stones, composition of prior stones if known, dietary history including an estimate of typical daily fluid intake, social history including details regarding occupation and lifestyle, and family history.

The medical history should focus on identifying diseases that increase stone risk including conditions that lead to hypercalciuria, gout, chronic diarrhea and malabsorptive gastrointestinal disorders.

Interpretation of biochemical and urine tests

Urine

The urine sediment should be examined for crystals. A 24-hour urine collection should be performed to measure urine calcium, oxalate, uric acid, pH, volume, creatinine and citrate.

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Some laboratories calculate supersaturation values for calcium oxalate, calcium phosphate and uric acid and these are particularly helpful [12,42,43].

The 24-hour urine collection

The best way to evaluate stone risk is a 24-hour urine collection and analysis [8,12]. Two 24-hour urine collections are recommended for the initial evaluation for an accurate analysis and to determine variability [44]. The 24-hour urine collection should be several weeks after any procedures (i.e. 6-8 weeks after lithotripsy) in order to minimize the risk of result be being influenced by infection or presence of blood due to these causes. Infection can change the pH and citrate levels. It is very important that patients continue with their usual diet and activities during the collection period. The 24-hour urine creatinine excretion can give information about the adequacy of the urine collection. In general, adult males produce 18–24 mg creatinine/kg/d and females 15-20 mg/kg/d [9,12]. 24-hour urine collection is not accurate as the urinary creatinine levels will be higher than normal for over collection and lower than normal for under-collection [44].

Table 2 provides a summary of the normal values for the 24-hour urine collection and likely causes of abnormal values. The 24-hour urine sample should include volume, and the solutes calcium, phosphorus, oxalate, citrate, pH, and uric acid to provide an estimate of supersaturation and the risk of stone formation. Creatinine is tested to ensure full collection and to normalize solute excretion to the more constant amount of creatinine. Dietary factors include sulfates which are mostly from animal protein and sodium since they are related to calcium, potassium, and magnesium excretion. Urea nitrogen is used to estimate protein catabolic rate (PCR). The PCR is usually indicative of dietary protein intake in an individual who is not in a catabolic state. The relationship between urinary nitrogen appearance rate and estimated dietary protein intake is then calculated. The value of the 24-hour urine is to evaluate dietary nutrients and fluid intakes and to provide guidance for the patient's management. For example, normal urinary

Table 2. Normal values of 24-hour urinalysis

	Normal value	Cause of abnormal values
Ca	<250 mg/d for males <200 mg/d for females	↑Idiopathic hypercalciuria, high Na diet (high urine Na), high protein diet ↓with bone disease
Phosphorus	0.6-1.2 g/d	↓with bowel disease, malnutrition, with large amount of food intake
Mg	30–120 mg/d	↓with some laxatives, malnutrition, malabsorption
Oxalate	20-40 mg/d	↑with high oxalate diet, high vitamin C consumption if > 80, intestinal (Inflammatory bowel disease) or oxalosis
Citrate	>450 mg/d for males >550 mg/d for females	↓RTA, hypokalemia, high animal protein diet, acidosis, diarrhea
Uric acid	<0.8 g/d for males <0.75 g/d for females	↑with high animal protein diet (high purine), alcoholic beverages, overproduction
Volume	>2,000 ml/d	↓with low fluid intake
pH	5.8–6.2	↓RTA, urea splitting infection, acidosis, high animal protein intake (high purine content) ↑vegetarian diet, high citrus consumption, soft drink
Na	50-150 mEq/d (1,150–3,450 mg)	↑with high Na diet ↓with low volume
K	20-100 mEq/d	<20 meq Bowel disease, diuretics, laxatives
Cl	70-250 mEq/d	
Urea nitrogen	6-14 g/kg/d	↑with high protein diet
PCR	0.8–1.4 g/d	↑with high protein diet
Sulfate	20-80 mEq/d	↑with high protein diet
Ammonium	15-60 mM/d	↑pH > 7 urea splitting infection ↓pH < 5.5 CRI, UA stones, gout
Cr	18-24 mg/kg for males 15–20 mg/kg for females	↑with more than 24 hour collection ↓with under collection

Range: courtesy from Litolink Corp, Chicago, IL, RTA: renal tubular acidosis, PCR: protein catabolic rate, CRI: chronic renal insufficiency, UA: uric acid, Cr: creatinine.

calcium levels are <250 mg/d for men and <200 mg/d for women. High urinary calcium may be caused by idiopathic hypercalciuria, or diet high in sodium or protein. Low urinary calcium is often due to malabsorption or underlying bone disease. A normal urinary oxalate level is 20-40 mg/d. High levels are due to high oxalate diet, increased endogenous production, high vitamin C consumption and irritable bowel disease. Normal urinary citrate levels are >450 mg/d for men and >550 mg/d for women. High animal protein diets and renal tubular acidosis (RTA) can increase acid production affecting urinary pH so that it declines citrate levels.

Nutrition assessment

The dietitian's role in nephrolithiasis care is very important. The dietitian should assess nutritional risk factors by dietary intake assessments and provide therapeutic recommendations based on dietary risks. Dietary assessment is very important both in treating and preventing stone formation. The dietitian should evaluate dietary intakes of calcium, oxalates, sodium, protein (both animal and plant), dietary supplements and fluid intake since these can either promote or inhibit stone formation, and plan the therapeutic diet based on those information. Fluid intake is particularly important to quantify.

There are several dietary assessment methods: the 24-hour recall, food record diet history and food frequency questionnaire. The dietary intakes should be reflected on the urinalysis and it is good way to evaluate the causes of kidney stones and to prevent recurrence. Food records provide information on intake of foods, beverages, and dietary supplements over specific periods. The most appropriate diet assessment for kidney stones is the food record during a 24-hour urine collection, as well as 1-2 days before the collection. The food record should be analyzed to evaluate intakes of protein, sodium, potassium, calcium, phosphorus, magnesium, uric acid, oxalate and fluid. Based on the food intake and urinalysis, the clinicians can provide the adequate medical and diet treatments.

Risk Factors for Kidney Stones

Major risk factors

Risk factors for stone formation may be hereditary or disease related, such as idiopathic hypercalciuria, hyperoxalosis Dent's disease, medullary kidney disease, polycystic kidney disease, hyperparathyroidism, irritable bowel disease (IBD), renal tubular acidosis or sarcoidosis. Patients with a family history of nephrolithiasis have a 2.5 times greater risk of stone formation [42]. Other risk factors include environment and diet (Table 3).

Table 4 shows the conditions that favor stone formation. Urinary crystalloids can form nucleus on the existing surface and supersaturate urine. Low urinary magnesium causes decrease complex formation with urinary oxalate allowing free oxalate to be more available in the urine. Low urinary citrate also increases stone formation because citrate forms a complex with calcium so free calcium is more available for stone formation. High concentrations of uric acids in the urine will promote the nuclei to start stone formation. If the patient is dehydrated, he or she will have low urine output and therefore the urine can be supersaturated. Urine pH is very important for the formation of some types of stones. For example, low urine pH is favorable to formation of CaOxand uric acid

Table 3. Risk factors of kidney stone

Hereditary and other disease related		Environment	
Genetic	Idiopathic hypercalciuria Hyperoxalosis Cystinuria: Dent's disease	Climate	Heat Water loss, sweating
Kidney disease related	Medullary sponge kidney PKD (10% develop stones) Horseshoe Metabolic causes: hypercalcemia, hyperparathyroidism, DM and obesity	Dietary	Na Oxalat e Protein (animal) Acid/ alkaline ash diet Fluid Potassium and citrate Fluid Vitamins (C, D) Ca supplement Low Ca diet High protein weight loss diet
Systemic disease	GI, Inflammatory bowel diseases (Oxand UAstones)		
Hyperparathyroidism	CaP stone		
Renal tubular acidosis (RTA)	Hypercalcemic states, Ca phosphate		
Sarcoid	Hypercalciuria, CaOx stone		

PKD: polycystic kidney disease, DM: diabetes mellitus, GI: gastrointestinal, Ox: oxalate, UA: uric acid, CaP: calcium phosphate, CaOx: calcium oxalate

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Table 4. Conditions favoring development of various kidney stones

Factors	Functions
Increased urinary crystalloids	Form nucleus on existing surface Supersaturated urine
Decreased inhibitors	Magnesium (complexes with oxalate) Citrate (complexes with calcium) Nephrocalcin, uropontin Tamm Horsfall
Increased promoters	Uric acid
Dehydration	Low urine volume, supersaturated urine
Urine pH	Alkaline → Ca phosphate Acidic → Uric acid, cysteine
Diet	High protein/sodium/Ca → hypercalciuria, uricosuria, oxaluria High oxalate → oxaluria
Medication	Furosemide: decrease urinary volume Na bicarbonate: increase urinary Ca

stones while a high urine pH promotes CaP stone formation.

Dietary causes may also generate increased risks of various stones. High sodium intake increases urinary calcium excretion. High oxalate diets, large dose of vitamin C supplements (>1,000 mg/d) will increase urinary oxalate level. High protein diets (> 2.0 g/kg/d) can increase urinary calcium, decrease urine pH and also increase urinary uric acid level [14]. Therefore high protein diets can increase CaOx, and uric acid stone risks. Diuretics, such as furosemide can induce dehydration which can increase risk of supersaturation of solutes.

Environmental conditions such as heat may increase non-renal evaporative skin losses and by doing so they reduce urine volume and increase stone risk [24,45-51]. The most challenging aspect of encouraging patients to increase their fluid intakes is that they cannot wait for the normal thirst mechanism to urge them to drink because the hypothalamic- pituitary sensors/ neurons lead to increased antidiuretic hormone levels; therefore, the urine becomes more concentrated before the thirst mechanism is triggered and the urine becomes more dilute. One patient education method used is to remind people to drink fluid after each void.

Urine volume: a critical factor

Urine must be supersaturated with solutes to form a crystal, the first step to form a stone. Low fluid intake will lead to low urine output. When urine volume is low, the urine can theoretically be easily supersaturated with various solutes, such as calcium, oxalate, phosphorus, and uric acid. However, there are several inhibitors normally present in the urine to prevent crystallization of these solutes [52-55]. Only if the supersaturation is very high does the crystallization start. The most direct way for patients to decrease risks of supersaturation is to increase the urine volume with oral fluids to above 2.5 L/d of urine volume [56].

Hypercalciuria

Figure 2 shows a model of how idiopathic hypercalciuria occurs. Normal urine calcium excretion is less than 200–250 mg/d. If urine calcium excretion is higher than this, stone risk increases. To evaluate the stone risk, it is necessary to measure serum calcium, urinary calcium, oxalate, urine urea nitrogen (UUN), citrate, magnesium, creatinine, and volume (Table 5). In idiopathic hypercalciuria, the serum calcium level is normal but urinary calcium is high because of increased absorption of calcium from the gastrointestinal tract. The increased absorption of calcium increases the ionized calcium level, decreases parathyroid hormone (PTH) secretion and decreases renal tubular reabsorption of calcium. The increased intestinal calcium absorption can be treated with 1, 25-dihydroxy vitamin D3. There is also evidence of reduced proximal tubular reabsorption of sodium and calcium in patients with idiopathic hypercalciuria, which leads to a negative calcium balance [57]. The combination of a low sodium diet and thiazide diuretics may lower urinary calcium excretion by increasing reabsorption of calcium.

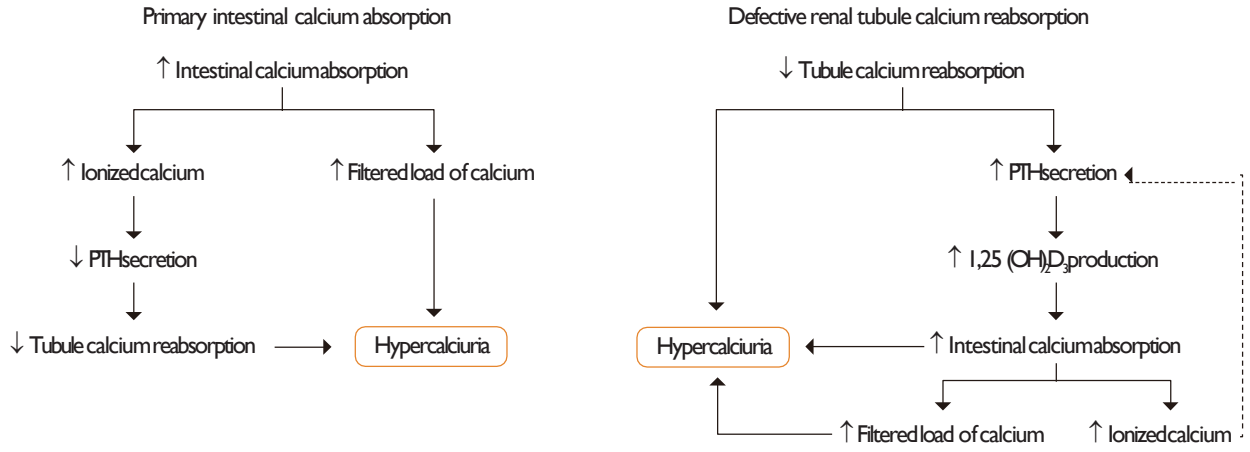

Figure 2. Model of idiopathic hypercalciuria.

Table 5. Summary of evaluation of stone disease

First stone	Recurrent stone and follow up
Basic medical evaluation Two 24-h urine analysis (no intervention prior to analyze stone risk): Ca, phosphorus, Mg, Oxalate, Citrate, uric acid, volume, creatinine, pH, urea nitrogen, Na, K Blood tests: Serum Na, K, CO_2, BUN, Cr, Ca, phosphorus, uric acid and PTH Usual dietary intake Dietary/ fluid intake history Diet and medical treatment	One 24-hr urine analysis: Ca, Phos, Mg, Oxalate, Citrate, uric acid, volume, creatinine, pH, urea nitrogen, Na, K Blood tests: Serum Na, K, CO_2, BUN, Cr, Ca, phosphorus, uric acid and PTH Dietary and medical treatment ** If patient has recurrent stone after 2 years of last stone formation, two 24-h urinalysis is appropriate.

Adapted from practice guideline at department of nephrology, Harvard Vanguard Medical Associate.

Hyperoxaluria

The most common type of stones are CaOx (75%) and a high urinary excretion of oxalate is a risk factor for them. Dietary sources of oxalate include spinach, rhubarb, beets and some berries. Oxalate is also created from endogenous metabolism of glycine, hydroxyproline and ascorbic acid. A low oxalate diet is recommended for the prevention of CaOx stones; however, a recent study showed that dietary oxalate had little effect on urinary oxalate excretion although vitamin C intake was highly correlated with urinary oxalate excretion [58].

Increased urinary oxalate excretion has also been noted in patients with diabetes [57,59]. Patients with IBD have a high prevalence of CaOx stones with hypocalciuria due probably to their negative calcium balance. Negative calcium balance can also cause secondary hyperparathyroidism to maintain normal calcium levels in blood, and a calcium supplement may be effective for preventing CaOx stone risk by decreasing the hyperparathyroidism. The timing of calcium supplements is important and patients should take supplements at the meal time to bind oxalate from dietary sources. Individuals who have had restrictive bariatric surgery have a high risk of hyperoxaluria due to malabsorption and increased reabsorption of oxalate, which may increase hyperoxaluria [29,60]. Recent studies by Jiang et al. suggest that enteric colonization with Oxalobacter formigenes, which uses oxalate as a main energy source, reduces the risk of CaOx stone recurrence among individuals whose intakes of calcium were low [61]. In contrast, there is insufficient evidence to support the use of probiotics to reduce stone risk at this time [62].

Hypocitraturia

The urine is usually supersaturated with solutes, especially CaOx; however, the level tends to be less than the 10 times the level of concentration to form the CaOx crystals due to the presence of citrate in the urine. Citrate in the urine binds with urinary calcium to form a soluble compound and this

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increases the urine pH. CaOx stone formation is favored by a low urine pH; therefore, citrate can help prevent CaOx stone formation. The most common form of citrate prescribed is potassium citrate. The normal value of urinary citrate for males is >450 mg/d and for females >550 mg/d. Renal tubular acidosis and chronic diarrhea can also cause decreased citrate in the urine. However calcium, oxalate and urine pH should be checked before initiation of citrate treatment [63]. If urine pH increases later with citrate treatment, the risk of CaP stone formation rises. In patients who have IBD with high urinary oxalate, and low urinary sodium levels because of malabsorption and gastrointestinal loss of sodium, sodium citrate is more beneficial than potassium citrate, and it should be used. However, sodium citrate can increase urinary calcium excretion and therefore it may increase the risk of CaOx stones.

pH

Urine pH is an important factor in the formation of kidney stones. A low urine pH can promote CaOx and uric acid stones, and a high urine pH can increase the risk of CaP stones. Urine pH is affected by the acid and alkaline ash from the diet, and before the advent of effective urinary acidifying and alkalinizing agents, it was necessary to rely on diet to alter urinary pH, although this could rarely be accomplished effectively. The practice has been largely outdated by the advent of better acidifying and alkalinizing agents. The mineral salt that predominates in foods determines whether the residue or 'ash' is acidic or alkaline. The minerals producing alkaline ash are sodium, potassium, magnesium, and calcium. Acid-forming minerals are sulfur, chlorine, and phosphorus. High animal protein diets which have high purine content and sulfur containing amino acids can reduce urine pH and will lead to an increased risk of uric acid stones. An alkaline ash diet which is high in citrate, mostly from fruits and vegetables, can increase urine pH and citrate excretion. Today alkali therapy is preferable because an alkaline ash diet is difficult to follow for most patients although an alkaline ash urine is preferable for the certain type of stone risk. However, for other stones, the reverse may be true. A high pH without alkali therapy may increase the risk of struvite stones from a UTI.

Uric acid

The prevalence of uric acid stones is about 5% of total kidney stone disease. The main determinant of uric acid stones is urine pH. A low urine pH has more insoluble uric acids concentration; therefore, the risk of uric acid stone is higher. Measurements of urinary calcium, uric acid, and post-prandial urine pH are used to assess the uric acid stone. The average adult consumes about 2 mg of purine/kg/d, which produces 200-300 mg of uric acid daily. Endogenous production of uric acid is about 300 mg/d. In some studies, uric acid excretion is 5.6 mg/kg/d [32] and total excretion of uric acid is less than 800 mg/d. Dietary consumption of purine varies daily among individuals. Kessler et al. conducted a cross-sessional study by using bicarbonate-rich mineral water and various types of juices on uric acid stone formation and found that black current juice decreased uric acid stone risk the most, by increasing the urine pH [64,65]. Ingestion of alcohol can also affect urinary uric acid excretion, and excesses should be avoided. If patients have gout, allopurinol is usually prescribed along with low purine diet to reduce blood uric acid and uricosuria [32,34].

Dietary risk factors

Several dietary factors can increase risk of the stone formation, including sodium, protein, potassium, calcium, magnesium and other nutrients. These constituents can be modified depending on the types of different stone risks. Foods that produce acid-ash after being metabolized in the body can affect the lowering of urinary pH whereas alkaline-ash foods can increase urinary pH. The specific diets are based on urine pH, urinary uric acid and types of stones (Table 6).

Sodium

Dietary sodium restriction alone decreases urinary calcium excretion [54,67]. Proximal tubular calcium reabsorption is increased on a low sodium diet (2,000-3,000 mg/d) and this in turn decreases the SSCaOx. In addition of thiazide diuretics, calcium reabsorption is enhanced and further decreases hypercalciuria. However, addition of thiazide can lead to volume depletion; although ion exchange and volume status will come to the steady state in a few days. If the patient continues to consume a high sodium diet, sodium will reach the distal nephron and increase the excretion of calcium and potassium along with citrate, resulting in a change in the urinary pH that will eventually increase the risk of stone formation. Therefore, after analyzing the 24-hour urine, stone risk is high, prescribing a low sodium diet will help avoid inappropriate thiazide use for patients with CaOx stones. Patients with IBD usually have low urinary sodium levels and low urinary citrate, and so use of sodium citrate instead of potassium is beneficial to improve fluid status from gastrointestinal losses and increase urine volume.

Table 6. Acid-ash and alkaline-ash foods

Acid-ash foods		Alkaline ash foods	
Meat	Meat, fish, fowl, shellfish, egg		
Dairy and other protein	All types of cheese Peanut butter Peanuts	Dairy	Milk and milk products Butter milk
Fat	Bacon, nuts (Brazil, filberts, walnuts)	Fat	Nuts (almonds, chestnuts, coconuts)
Starch	All types esp. whole wheat Crackers, cereal, macaroni, spaghetti, noodle, rice		
Vegetables	Corn, lentils	Vegetables	All types except corn and lentils Beets, beet greens, Swiss chard, dandelion greens, kale, mustard greens, spinach, turnip greens
Fruits	Cranberries, plums, prunes	Fruits	All types except cranberries, plum and prunes
Desserts	Plain cakes, cookies	Sweets	Molasses

Modified from reference [66].

Potassium

Potassium is abundant in most fruits and vegetables. However, if the patient has low urinary citrate and low urine pH, potassium citrate is commonly used along with such a diet to further improve hypocitruria. Monitoring 24-hour urinary excretion of potassium is important to evaluate compliance to diet and medications. Taylor et al. analyzed the 24-hour urine with the Diet Approaches to Stop Hypertension (DASH) diet and found that diets conforming more closely to DASH had decreased risk of stone formation [68,69]. Because high DASH score foods are high in potassium, magnesium, and phosphorus, these may increase urine pH, resulting in a decrease in SSCaOx and uric acid in the urine as well as increased urine volume and citrate [68,69]. If patients have chronic kidney disease and take angiotensin converting enzyme inhibitors (ACEI) as antihypertensive medications, serum potassium level should be monitored closely.

Protein

There are few markers of 24-hour urine to evaluate dietary protein intake, production and excretion. Urea nitrogen appearance (UNA) and PCR are measurements of daily protein intake that are calculated per kg body weight. In normal healthy steady state, intake of protein can be equivalent to protein catabolism; therefore, PCR determines the nitrogen balance from 24-hour urine urea concentration:

PCR=[6.25({24-h urea N} +{0.031x weight})]/ weight

Patients who have acute, or chronic infection are usually malnourished and experience catabolism, and have more nitrogen in the urine. Therefore, this formula should not be used to evaluate protein intake. For patients without active stress of illness, the PCR can guide protein recommendations for patients to prevent further stone risks.

The ammonium (NH_4) level should be low in patients who are prescribed alkali therapy or who present with RTA. Monitoring citrate, an indicator of urine acidity, can identify these problems. Patients who take alkali therapy especially with low citrate levels have low urinary ammonium levels with higher pHs and therefore the risk of uric acids or CaOx can be substantially decreased.

High ammonium and sulfate are indicators of a high protein diet, especially one which is high in animal protein [30,70]. A high protein diet (>2.0 g/kg/d) can reduce urine pH; therefore, a moderate to low protein diet should be advised (0.8-1.4 g/kg/d). Currently most common and popular weight loss diets promote consumption of large amounts of protein but such a reducing diet is not recommended for the patients who have a history of kidney stones. This high protein diet regimen increases hypercalciuria, lowers pH of urine and increases uric acid levels, which increase kidney stone risk [14]. Massey et al. conducted a study to monitor the effect of stone risk in beef vs. plant protein and concluded that a moderate amount of protein intake of either type had the same effects in reducing CaOx stone risk [71]. The amount of protein seemed to be a more important factor in that study. Recently, an epidemiological study showed that animal protein intake was not independently associated with the incidence of nephrolithiasis among a large cohort of postmenopausal women [72]. However, the evaluation of stone risk varies by individuals and is complicated. Therefore, the recommendation of a usual pro-

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tein intake remains until the scientific evidence to change this recommendation is provided.

Calcium

Approximately 20% of dietary calcium is absorbed under normal conditions. There is substantial evidence that a higher calcium diet is associated with lower kidney stone formation, because the higher calcium intake will bind oxalate in the gut if it is consumed with meals thereby reducing oxalate absorption. Patients who consumed a diet with a normal calcium intake (i.e., 1,200 mg/d) plus a low animal protein intake had a 51% lower incidence of recurrent stones than patients who consumed low (400 mg/d) calcium diets [20]. Although data to date on taking calcium supplements does not show that they are theoretically effective in reducing stone risk, taking a calcium supplement with meals is beneficial because calcium can bind with the dietary oxalate and thus it is not absorbed.

Magnesium

Magnesium forms a complex with oxalate and decreases SSCaOx in the urine, which can reduce the risk of stone formation [68,69]. The DASH diet, which is high in magnesium, showed a decrease in stone risk by increasing pH and lowering SSCaOx [13,68,69,73]. Magnesium can also bind with oxalate in the gastrointestinal tract to reduce oxalate absorption; however, a magnesium supplement is not recommended especially patients with chronic kidney disease because magnesium is accumulated in the blood in advanced kidney disease. Decreased urinary magnesium may be a sign of malabsorption, malnutrition, small bowel disease or laxative abuse. Hypomagnesemia is not a risk factor for stone formation.

Vitamin C

Vitamin C is metabolized to dehydroascorbic acid and then converted to oxalate which is then excreted in the urine; therefore, a high vitamin C intake can be a risk for stone formation by increasing endogenous oxalate. A recent observational study showed that consumption of more than 1,000 mg/d vitamin C was associated with a 40% higher risk of stone formation in men than in those who consumed the Dietary Reference Intake (DRI) for vitamin C [74].

Other dietary factors

Citrate consumption can increase urine pH, and also increases citrate concentration in the urine. Citrate also decreases SSCaOx due to its capacity to form a complex with calcium ions and inhibit crystallization of CaOx [63]. However, citrate may increase the risk of CaP stones. A clinical trial conducted by Koff et al. used potassium citrate and lemonade for 21 stone patients, and showed that potassium citrate increased urine pH with increased urinary citrate level but lemonade did not have an effect on urinary pH or citrate levels except for increasing urine volume [75].

Phytates are present in whole grains and legumes and they can inhibit CaOx stone formation. Some studies have shown an inverse correlation with phytate intake and the risk of kidney stone formation in women [74,76-78].

Treatment of Kidney Stones

Management in the acute setting

Urgent surgical intervention is indicated in a patient with an obstructed, infected urinary tract, worsening renal function, intractable pain or vomiting or obstruction of a solitary or transplanted kidney. Analgesia is essential and parenteral Non-Steroid Anti-Inflammatory Drugs (NSAIDs: Ketorolac) are as effective as narcotics. NSAIDS are less likely to cause nausea, but should be avoided if the patient has impaired renal function. Pain is due to renal capsule dilatation, and so intractable pain may require decompression of the obstruction. Volume expansion with intravenous fluids is important in correcting the volume depletion that may have occurred from decreased intake and/ or vomiting and it may also increase the likelihood of stone passage by increasing urine production.

If urgent intervention is not required, the treating physician needs to decide if the stone can be passed spontaneously. The likelihood of spontaneous passage decreases as the size of the stone increases and stones >5-6 mm are not likely to pass spontaneously.

Patients who are having repeated stone attacks should be instructed to strain their urine and to submit the stone for composition analysis. Repeated imaging (plain abdominal radiography (KUB) for radiopaque stones and CT for radiolucent stones) is warranted to confirm stone passage. If follow-up imaging reveals no movement after a month, urologic intervention is generally warranted [79].

Surgical treatment

Larger and more proximal ureteral stones are less likely to pass spontaneously and usually require urologic evaluation. If the stone does not pass rapidly, the patient can be sent home with oral analgesia and instructions to return for fever

or uncontrollable pain. Most urologists wait a few days before intervening unless there is a possible infection, low likelihood of spontaneous passage or unrelenting pain. Infection in the setting of obstruction is a surgical emergency and mandates emergency drainage.

Extracorporeal shock wave lithotripsy (ESWL) is a non-surgical procedure using shock waves to fragment stones into small pieces which pass spontaneously several days or weeks later. Obese patients may not be effectively treated with ESWL. Cystine stones are very hard and are often not effectively treated with ESWL (Figure 3).

Flexible ureteroscopic stone removal, although invasive, is associated with a better chance of becoming stone free with a single procedure. It does have higher complication rates of ureteral injury or structure, though has become increasingly popular, because of the variety of devices that are available for stone removal including small diameter flexible ureteroscopes, ureteral access sheaths, holmium laser lithotripsy and stone baskets.

Percutaneous nephrostolithotomy is more invasive, but may be necessary for large stones or stones that cannot be removed cystoscopically. It is rare that a patient requires open ureterolithotomy or nephrolithotomy.

Medical and dietary treatment – preventive therapy

A recurrent stone former should undergo an evaluation for a treatable metabolic cause of kidney stones. This is guided by the results of the 24-hour urine collection.

Table 7 summarizes the dietary managements of kidney stones. Fluid intake is an essential component of treatment and should be adjusted so that urine output is greater than 2.5 L/day. Low urine citrate can be corrected using potassium citrate. Table 8 provides some general guidelines for treatment.

Treating calcium stones

Dietary sodium restriction is important as it is associated with a reduction in urine calcium excretion. Thiazide diuretics lead to increased serum calcium levels and reduced urine calcium levels and are therefore used in therapy for patients with hypercalciuria. Oxalate reabsorption in the colon is reduced by the formation of insoluble calcium oxalate. This is very important in therapy because restricting dietary calcium results in less calcium being available in the intestinal lumen to bind oxalate. This leads to increased oxalate absorption and therefore increased urinary oxalate excretion [25]. Table 9 shows the list of high oxalate foods.

The high oxalate foods are considered to be healthy, with high fiber and nutrient dense in vitamins and minerals. Patients who have diabetes, hypertension and high blood cholesterol are often instructed to consume high oxalate foods such as fruits and vegetables. When patients develop kidney stones, they are instructed to change the diet to lower oxalate contents and therefore most patients are confused. The clinical dietitian should be able to advise the patients individualized diet to prevent kidney stone but to keep healthy diet.

Treating uric acid stones

As uric acid is more soluble in an alkaline urine, urine alkalinization is an important part of the treatment of uric acid stones. Patients should decrease their intake of animal proteins which helps decrease uric acid generation. Allopurinol, a xanthine oxidase inhibitor, is used to decrease the formation

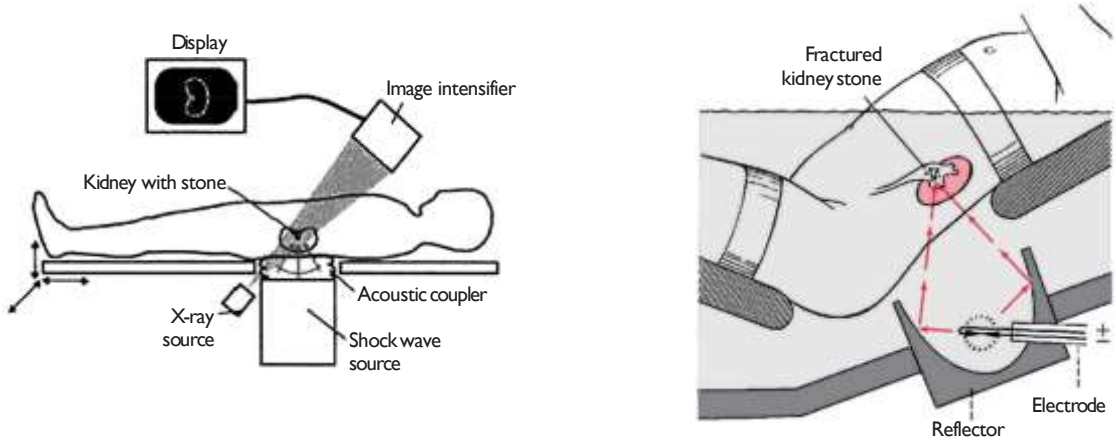

Figure 3. Extracorporeal shock wave lithotripsy (ESWL).

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Table 7. Management of all types of kidney stones

Abnormality	Evaluate	Management
Hypercalciuria	Urine Na and urea nitrogen	Na, protein restriction, Thiazide, not low Ca diet
Hypercalcemia	PTH, ionized Ca, vitamin D, malignancy, thyroid, bone disease etc	Parathyroidectomy, treat underlying disorder
Hyperoxaluria	Dietary oxalate, low dietary Ca, vitamin D, sweeteners, ileal disease, gastric bypass, ethylene glycol, enzyme deficiencies	Restrict oxalate, supplement magnesium, Ca, pyridoxine, cholestyramine
Hypocitraturia	Urinary citrate, serum potassium (K), creatinine, malabsorption, RTA, acetazolamide	Alkali (potassium citrate), sodium citrate if volume deplete
Hyperuricosuria	Dietary purines	Purine restriction, allopurinol, alkali
Acid urine (pH)	Exclude chronic diarrhea, gout, ileostomy	Alkali (Potassium citrate)
Low urine volume	24 hr urine volume	At least 2.5 liters fluid intake

PTH: parathyroid hormone, RTA: renal tubular acidosis.

Table 8. Dietary recommendation to prevent kidney stones

Nutrients	Recommendation
Ca	800–1,200 mg/d
Oxalate	40-50 mg/d
Na	2,000–3,000 mg/d
Protein	0.8–1.4 g/kg/d
Fluid	>2.5 L/d
Vitamin D	Low dose if vitamin D insufficiency or deficiency (1,000 IU/d)
Vitamin C	Dietary Reference Intake

Adapted from reference [55].
National Kidney Foundation: Diet Guidelines for Kidney stone. Litolink Corp, Chicago, IL.

of uric acid.

Low purine diet is recommended if patient has elevated blood uric acid level [32,34]. A high protein diet (>2.0 g/kg) can cause a decrease in urine pH which can increase risk of uric acid stone therefore moderate amount of protein (0.8-1.4 g/kg/day) is recommended.

Treating cystine stones

There are no specific diet recommendations for cysteine stones except increasing fluid intake. Cystine solubility can be increased by alkalinization of the urine, although solubility only increases when the pH reaches 7-7.5. Thiol containing drugs like Penicillamine and Tiopronin may be given to patients who are unable to comply with increased fluid intake and urinary alkalinization or fail despite it. These drugs increase the solubility of cystine. Tiopronin is better tolerated than penicillamine which is associated with multiple side effects including rash, fever, serum sickness, epidermolysis and membranous nephropathy. Captopril is used because of its sulfhydryl group forms a thiol-cysteine disulfide bond that is more soluble than cysteine. However its efficacy is unclear. Low animal protein diet can lower the stone risk by lowering methionine which is precursor of cystine [84].

Treating Struvite stones

The preferred treatment of struvite stones is surgical removal because they are large. Antibiotic therapy is important and may slow stone growth. It is important to culture stone material to help direct antibiotic therapy. However low sodium diet can help prevention of struvite stone [84].

Conclusion

Kidney stones are common and recur frequently. Calcium oxalate stones are the most common. Urine supersaturation is increased with low urine volume and with increased urinary excretion of calcium, oxalate, phosphate, cysteine or uric acid. Citrate is the most common inhibitor of crystal formation

Table 9. Oxalate content of foods

Foods (3.5 oz or 100 g)	Oxalate (mg)	Foods (3.5 oz or 100 g)	Oxalate (mg)	Foods (3.5 oz or 100 g)	Oxalate (mg)
Flours & Mills		Seed containing vegetables		Leafy vegetables	
Barley flour	56	Cucumber, raw	20	Amaranth leaves, raw	1,090
Buckwheat flour	269	Eggplant, raw	190	Beet leaves, raw	610
Corn meal	54	Eggplant, green, long, raw	55	Brussels sprouts, raw	360
Rice flour, brown	37	Okra, raw	50	Cabbage, green raw	100
Rye flour, dark	51	Pepper, raw	40	Chicory, raw	210
Semolina flour	48	Snap beans, raw	360	Chinese cabbage, raw	6
Soy flour	183	Squash, raw	20	Chinese, kale, raw	23
Wheat flour, white unbleached	40	Tomato, raw	50	Chives, raw	1,480
Wheat flour, whole	67	Yard long beans, green, raw	38	Collards, raw	450
Wheat Germ	269			Coriander, raw	10
				Endive, raw	110
				Kale, raw	20
Fruits		Legumes (Beans & Peas)		Leek	89
Bitter melon, raw	71	Anasazi beans, boiled	80	Lettuce, raw	330
Papaya raw	5	Azuki beans, boiled	25	Parsley, raw	1,700
Green goose berries	88	Black beans, boiled	72	Purslane, raw	1,310
Black berries	19	Cowpeas (blackeye peas), boiled	4	Spinach, raw	970
Blueberries, strawberries, red raspberries	15	Gabanzo beans, boiled	9	Turnip greens, raw	50
		Great northern beans, boiled	75	Watercress, raw	310
Black raspberries	55	Kidney beans, red cooked	16	Tuber & Root vegetables	
Concord grapes	25	Lentils, boiled	8	Beetroot, boiled	675
Currents	19	Lima beans, large, boiled	8	Carrot, raw	500
Lemon peel	83	Navy beans, boiled	57	Cassava root, raw	1,260
Lime peel	110	Peas, green, split, boiled	6	Parsnip, raw	40
Rhubarb	800	Peas, raw	50	Potato, raw	50
		Peas, yellow, split, boiled	5	Radish, raw	480
		Pink beans, boiled	75	Rutabaga, raw	30
		Pinto beans, boiled	27	Sweet potato, raw	240
		Red beans, boiled	35	Turnip, raw	210
		Soybeans, boiled	56		
Nuts		White beans, small boiled	78	Other vegetables	
Almonds, roasted	469			Corn, sweet, raw	10
Cashews, roasted	262			Garlic, raw	360
Hazelnuts, raw	222			Onion, raw	50
Macadamia nuts, raw	42				
Peanuts, raw	142			Miscellaneous foods	
Pecans, raw	64			Black pepper	419
Pine nuts, raw	198			Chocolate	117
Pine nuts, roasted	140	Stem & Stalk vegetables		Cocoa powder	623
Pistachio nuts, roasted	49	Asparagus, raw	130	Indian tea (1 C)	72
Soy nuts (1 oz)	392	Broccoli, raw	190	Soy protein	496
Walnuts, raw	74	Cauliflower, raw	150	Soy yogurt	113
		Celery, raw	190	Soybean cracker	207
				Tofu	275

Sources: references [80-83].

and urinary pH is very important for preventing or treating different types of stones. There are many stone risk factors among which diet is very important one. Urgent stone removal and treatments are done by urology using surgery or ESWL. Medical and dietary treatments are most important ways to prevent recurrence of stone. Consumption of ample fluids is essential, and dietetic advice is helpful.

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ABC of burns

Pathophysiology and types of burns

This is the second in a series of 12 articles

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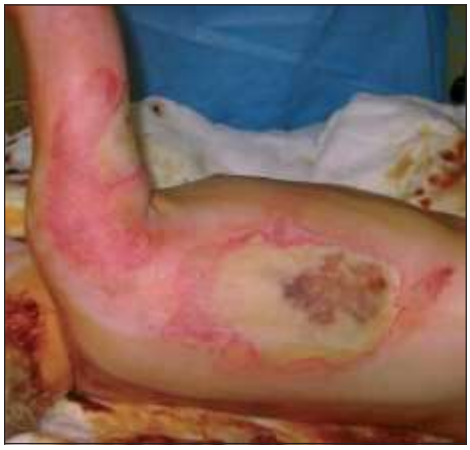
Understanding the pathophysiology of a burn injury is important for effective management. In addition, different causes lead to different injury patterns, which require different management. It is therefore important to understand how a burn was caused and what kind of physiological response it will induce.



Clinical image of burn zones. There is central necrosis, surrounded by the zones of stasis and of hyperaemia

The body's response to a burn

Burn injuries result in both local and systemic responses.

Local response

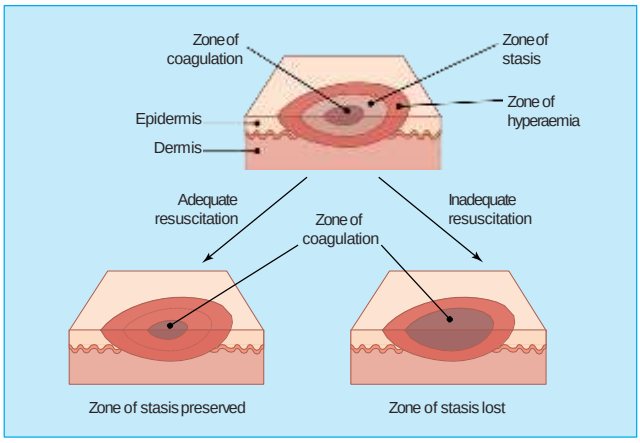
The three zones of a burn were described by Jackson in 1947.

Zone of coagulation – This occurs at the point of maximum damage. In this zone there is irreversible tissue loss due to coagulation of the constituent proteins.

Zone of stasis – The surrounding zone of stasis is characterised by decreased tissue perfusion. The tissue in this zone is potentially salvageable. The main aim of burns resuscitation is to increase tissue perfusion here and prevent any damage becoming irreversible. Additional insults—such as prolonged hypotension, infection, or oedema—can convert this zone into an area of complete tissue loss.

Zone of hyperaemia – In this outermost zone tissue perfusion is increased. The tissue here will invariably recover unless there is severe sepsis or prolonged hypoperfusion.

These three zones of a burn are three dimensional, and loss of tissue in the zone of stasis will lead to the wound deepening as well as widening.



Jackson's burns zones and the effects of adequate and inadequate resuscitation

Systemic response

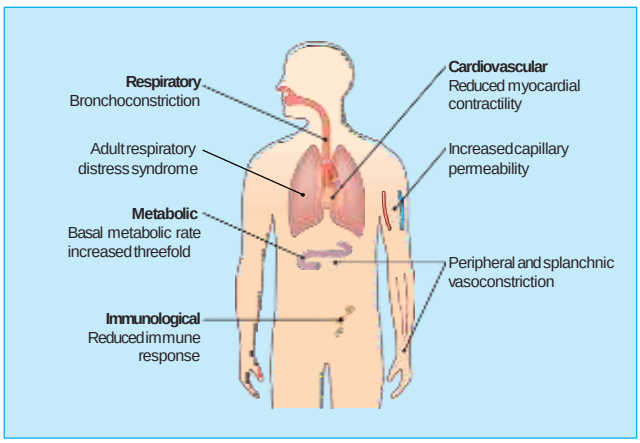
The release of cytokines and other inflammatory mediators at the site of injury has a systemic effect once the burn reaches 30% of total body surface area.

Cardiovascular changes – Capillary permeability is increased, leading to loss of intravascular proteins and fluids into the interstitial compartment. Peripheral and splanchnic vasoconstriction occurs. Myocardial contractility is decreased, possibly due to release of tumour necrosis factor a. These changes, coupled with fluid loss from the burn wound, result in systemic hypotension and end organ hypoperfusion.

Respiratory changes – Inflammatory mediators cause bronchoconstriction, and in severe burns adult respiratory distress syndrome can occur.

Metabolic changes – The basal metabolic rate increases up to three times its original rate. This, coupled with splanchnic hypoperfusion, necessitates early and aggressive enteral feeding to decrease catabolism and maintain gut integrity.

Immunological changes – Non-specific down regulation of the immune response occurs, affecting both cell mediated and humoral pathways.



Systemic changes that occur after a burn injury

Mechanisms of injury

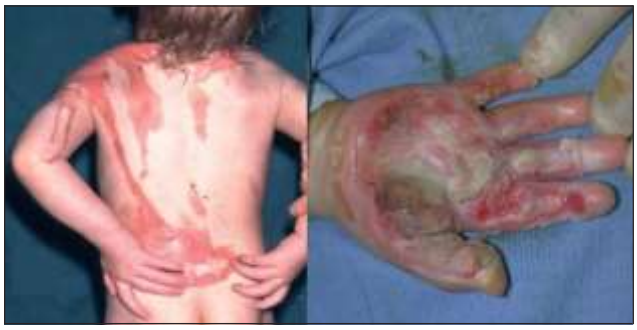
Thermal injuries

Scalds – About 70% of burns in children are caused by scalds. They also often occur in elderly people. The common mechanisms are spilling hot drinks or liquids or being exposed

to hot bathing water. Scalds tend to cause superficial to superficial dermal burns (see later for burn depth).

Flame—Flame burns comprise 50% of adult burns. They are often associated with inhalational injury and other concomitant trauma. Flame burns tend to be deep dermal or full thickness.

Contact—In order to get a burn from direct contact, the object touched must either have been extremely hot or the contact was abnormally long. The latter is a more common reason, and these types of burns are commonly seen in people with epilepsy or those who misuse alcohol or drugs. They are also seen in elderly people after a loss of consciousness; such a presentation requires a full investigation as to the cause of the blackout. Burns from brief contact with very hot substances are usually due to industrial accidents. Contact burns tend to be deep dermal or full thickness.



Examples of a scald burn (left) and a contact burn from a hot iron (right) in young children

Electrical injuries

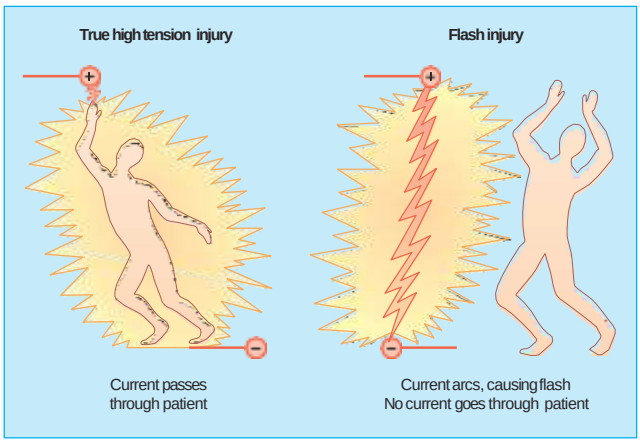
Some 3-4% of burn unit admissions are caused by electrocution injuries. An electric current will travel through the body from one point to another, creating "entry" and "exit" points. The tissue between these two points can be damaged by the current. The amount of heat generated, and hence the level of tissue damage, is equal to $0.24\times(\text{voltage})^2\times\text{resistance}$. The voltage is therefore the main determinant of the degree of tissue damage, and it is logical to divide electrocution injuries into those caused by low voltage, domestic current and those due to high voltage currents. High voltage injuries can be further divided into "true" high tension injuries, caused by high voltage current passing through the body, and "flash" injuries, caused by tangential exposure to a high voltage current arc where no current actually flows through the body.

Domestic electricity—Low voltages tend to cause small, deep contact burns at the exit and entry sites. The alternating nature of domestic current can interfere with the cardiac cycle, giving rise to arrhythmias.

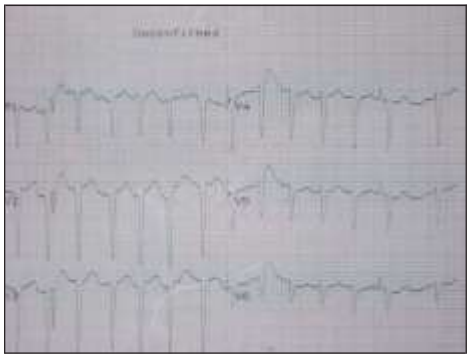
"True" high tension injuries occur when the voltage is 1000 V or greater. There is extensive tissue damage and often limb loss. There is usually a large amount of soft and bony tissue necrosis. Muscle damage gives rise to rhabdomyolysis, and renal failure may occur with these injuries. This injury pattern needs more aggressive resuscitation and debridement than other burns. Contact with voltage greater than 70 000 V is invariably fatal.

"Flash" injury can occur when there has been an arc of current from a high tension voltage source. The heat from this arc can cause superficial flash burns to exposed body parts, typically the face and hands. However, clothing can also be set alight, giving rise to deeper burns. No current actually passes through the victim's body.

A particular concern after an electrical injury is the need for cardiac monitoring. There is good evidence that if the patient's electrocardiogram on admission is normal and there is no history of loss of consciousness, then cardiac monitoring is not required. If there are electrocardiographic abnormalities or a loss of consciousness, 24 hours of monitoring is advised.



Differences between true high tension burn and flash burn

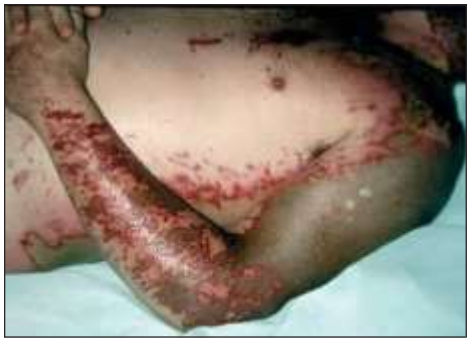


Electrocardiogram after electrocution showing atrial fibrillation

Chemical injuries

Chemical injuries are usually as a result of industrial accidents but may occur with household chemical products. These burns tend to be deep, as the corrosive agent continues to cause coagulative necrosis until completely removed. Alkalis tend to penetrate deeper and cause worse burns than acids. Cement is a common cause of alkali burns.

Certain industrial agents may require specific treatments in addition to standard first aid. Hydrofluoric acid, widely used for glass etching and in the manufacture of circuit boards, is one of the more common culprits. It causes a continuing, penetrating



Chemical burn due to spillage of sulphuric acid

injury and must be neutralised with calcium gluconate, either applied topically in a gel or injected into the affected tissues.

The initial management of all chemical burns is the same irrespective of the agent. All contaminated clothing must be removed, and the area thoroughly irrigated. This is often best achieved by showering the patient. This has been shown to limit the depth of the burn. Litmus paper can be used to confirm removal of alkali or acid. Eye injuries should be irrigated copiously and referred to an ophthalmologist.

Non{accidental injury

An estimated 3-10% of paediatric burns are due to non{accidental injury. Detecting these injuries is important as up to 30% of children who are repeatedly abused die. Usually young children (< 3 years old) are affected. As with other non{accidental injuries, the history and the pattern of injury may arouse suspicion. A social history is also important. Abuse is more common in poor households with single or young parents. Such abuse is not limited to children: elderly and other dependent adults are also at risk. A similar assessment can be made in these scenarios.

It is natural for non{accidental injury to trigger anger among healthcare workers. However, it is important that all members of the team remain non-confrontational and try to establish a relationship with the perpetrators. The time around the burn injury is an excellent opportunity to try to break the cycle of abuse. In addition, it is likely that the patient will eventually be discharged back into the care of the individuals who caused the injury. As well as treating the physical injury, the burn team must try to prevent further abuse by changing the relationship dynamics between victim and abuser(s).

Any suspicion of non{accidental injury should lead to immediate admission of the child to hospital, irrespective of how trivial the burn is, and the notification of social services. The team should carry out the following:

- Examine for other signs of abuse
- Photograph all injuries
- Obtain a team opinion about parent-child interaction
- Obtain other medical information (from general practitioner, health visitor, referring hospital)
- Interview family members separately about the incident (check for inconsistencies) and together (observe interaction).

It should be remembered that the injury does not have to be caused deliberately for social services to intervene; inadequate supervision of children mandates their involvement.

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The ABC of burns is edited by Shehan Hettiaratchy; Remo Papini, consultant and clinical lead in burns, West Midlands Regional Burn Unit, Selly Oak University Hospital, Birmingham; and Peter Dziewulski. The series will be published as a book in the autumn.

Competing interests: See first article for series editors' details.

Further reading

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Specific chemical burns and treatments

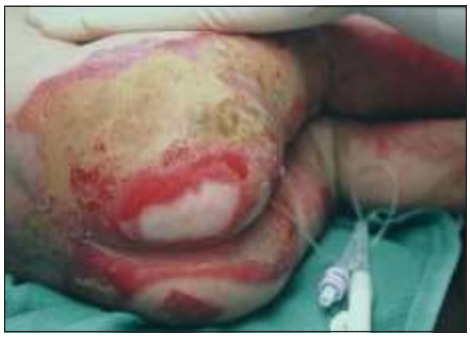
Chromic acid – Rinse with dilute sodium hyposulphite
Dichromate salts – Rinse with dilute sodium hyposulphite
Hydrofluoric acid – 10% calcium gluconate applied topically as a gel or injected

Injury pattern of non{accidental burns

- Obvious pattern from cigarettes, lighters, irons
- Burns to soles, palms, genitalia, buttocks, perineum
- Symmetrical burns of uniform depth
- No splash marks in a scald injury. A child falling into a bath will splash; one that is placed into it may not
- Restraint injuries on upper limbs
- Is there sparing of flexion creases—that is, was child in fetal position (position of protection) when burnt? Does this correlate to a "tide line" of scald—that is, if child is put into a fetal position, do the burns line up?
- "Doughnut sign," an area of spared skin surrounded by scald. If a child is forcibly held down in a bath of hot water, the part in contact with the bottom of the bath will not burn, but the tissue around will
- Other signs of physical abuse—bruises of varied age, poorly kempt, lack of compliance with health care (such as no immunisations)

History of non-accidental burns

- Evasive or changing history
- Delayed presentation
- No explanation or an implausible mechanism given for the burn
- Inconsistency between age of the burn and age given by the history
- Inadequate supervision, such as child left in the care of inappropriate person (older sibling)
- Lack of guilt about the incident
- Lack of concern about treatment or prognosis



"Doughnut sign" in a child with immersion scalds. An area of spared skin is surrounded by burnt tissue. The tissue has been spared as it was in direct contact with the bath and protected from the water. This burn pattern suggests non{accidental injury

Key points

- A burn results in three distinct zones—coagulation, stasis, and hyperaemia
- The aim of burns resuscitation is to maintain perfusion of the zone of stasis
- Systemic response occurs once a burn is greater than 30% of total body surface area
- Different burn mechanisms lead to different injury patterns
- Identification of non{accidental burn injury is important

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