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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• classical post-streptococcal glomerulonephritis in child • presents as nephritic syndrome / acute kidney injury • The following features are supportive of diagnosis: haematuria proteinuria oedema hypertension • most common form of renal disease in SLE • In DPGN, more than 50% of the glomeruli (diffuse) show an increase in mesangial, epithelial, endothelial (proliferative), and inflammatory cells (ie, glomerulonephritis). (Increased cellularity) • when < 50% of the glomeruli are involved, the condition is termed focal proliferative glomerulonephritis. However, this entity has the potential to progress to DPGN. Minimal change disease • typically a child with nephrotic syndrome (accounts for 80%) • causes: Hodgkin's, NSAIDs • good response to steroids Focal segmental glomerulosclerosis • may be idiopathic or secondary to HIV, heroin • presentation: proteinuria / nephrotic syndrome / chronic kidney disease Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis • rapid onset, often presenting as acute kidney injury • causes include Goodpasture's, ANCA positive vasculitis Mesangiocapillary glomerulonephritis (membranoproliferative) • type 1: cryoglobulinaemia, hepatitis C associated with low C4 • type 2: partial lipodystrophy associated with low C3 • C3 nephritic factor is an autoantibody specific for alternative pathway C3 convertase (C3NeF), found in mesangiocapillary GN type II and partial lipodystrophy. Diagnosis • Renal biopsy is the best investigation to diagnose Glomerulonephritis • RBC casts in urinary sediment suggest a diagnosis of acute glomerulonephritis (Acute nephritic syndrome) • Immune complex glomerulonephritides can be classified based on normal or decreased C3. Associated with reduced C3 and C4 Cryoglobolinaemia Infective endocarditis lupus nephritis Associated with reduced C3. membranoproliferative GN post-streptococcal GN

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Nephrology

Glomerulonephritis and low complement Disorders associated with glomerulonephritis and low serum complement levels:

1. post-streptococcal glomerulonephritis

2. subacute bacterial endocarditis
3. systemic lupus erythematosus
4. mesangiocapillary glomerulonephritis MRCPUK-part-1-May 2014 exam: A patient of SLE present with pedal oedema , ↑ BP. Dipstick urine shows protein ++, blood+++.What is the renal biopsy most likely to show? Diffuse proliferative glomerulonephritis (Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients.)

Minimal change disease Epidemiology • accounting for 75% of cases in children and 25% in adults. • peak incidence 2-3 years of age Causes • 90% of cases are idiopathic • Other causes (10 – 20%) drugs: NSAIDs, rifampicin gold and lithium Hodgkin's lymphoma, thymoma infectious mononucleosis Pathophysiology • The glomerular basement membrane is normal on electron microscopy • T-cell and cytokine mediated damage to the glomerular basement membrane → polyanion loss • the resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin Features • nephrotic syndrome nearly always presents as nephrotic syndrome • normotension hypertension is rare (only 10%) • highly selective proteinuria* (*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus) A protein selectivity index of less than 10% is highly selective and is a ratio of serum and urine IgG and albumin. High selectivity suggests minimal change disease but is less reliable in adults. • Renal biopsy: light microscopy are normal or small looking glomeruli electron microscopy shows fusion of podocytes

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(Effacement of the epithelial cell foot processes over the outer surface of the GBM) renal biopsy is not indicated unless no response to steroids is seen within one month, there is hypertension, haematuria or renal impairment. renal biopsy is usually only attempted when three or more episodes of oedema have occurred. 0BPodocytes fusion is seen in minimal change glomerulonephritis but may occasionally be a feature of focal segmental glomerulosclerosis as well. Minimal change however is far more common Management • majority of cases (80%) are steroid responsive shows excellent response to steroids since the damage is mediated by T- cell cytokines. • cyclophosphamide is the next step for steroid resistant cases Immunosuppression treatment (cyclophosphamide) should be considered in patients who are frequent relapsers (two or more episodes in six months of the initial response, or four relapses in any one year, children who are steroid dependent or steroid toxic). Prognosis is overall good • Remission: Full renal recovery is the most likely outcome. In Children: 30 – 40% of children achieve spontaneous remission and 90% achieve remission following eight weeks treatment with high dose steroids. In adults only around 50% achieve remission. • Relapse is common. Roughly: 1/3 have just one episode 1/3 have infrequent relapses 1/3 have frequent relapses which stop before adulthood

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Membranous glomerulonephritis • Membranous glomerulonephritis is the commonest type of glomerulonephritis in adults and is the third most common cause of end-stage renal failure (ESRF). • It usually presents with nephrotic syndrome or proteinuria. • It is an antibody mediated disease in which the immune complexes localise to the subepithelial aspect of the capillary loop. That is,

between the outer aspect of the basement membrane and the podocyte (epithelial cell). • Males are twice as commonly affected as females • Typically seen in the over 40 age group (Elderly patients) • Most patients have normal blood pressure at the time of the presentation.

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• Most of the patients with membranous glomerulonephritis have antibodies against M-type phospholipase A2 receptor. Causes • idiopathic • infections: hepatitis B, hepatitis C , malaria, syphilis , leprosy, HIV, schistosomiasis, • malignancy: lung cancer, non-Hodgkin's lymphomas lymphoma, leukaemia, colon and gastric cancer (30% of membranous nephropathy cases are secondary, of those around a third (10% of the total cases of membranous nephropathy) are diagnosed with an underlying malignancy) (NOTE: In the case of Hodgkin’s lymphoma, the most common histological type of renal involvement is minimal change glomerulonephritis followed by focal segmental glomerulosclerosis). • drugs: gold, penicillamine, NSAIDs , captopril, and heavy metals: mercury and cadmium • autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid • Sickle cell disease. • Diabetes mellitus. Renal biopsy demonstrates: • light microscopy: diffuse capillary and glomerular basement membrane thickening. • electron microscopy: the basement membrane is thickened with subepithelial electron dense deposits (Thickened capillary loops). This creates a 'spike and dome' appearance • Immune complex deposition with IgG and C3 Complications • Renal vein thrombosis is particularly likely to complicate membranous glomerulonephritis As the left testicular vein drains into the left renal vein, a left-sided varicocele may develop in this condition. Prognosis • Rule of thirds one-third: spontaneous remission one-third: remain proteinuric one-third: develop ESRF • Good prognostic features include: female sex young age at presentation and asymptomatic proteinuria of a modest degree at the time of presentation. Management: • Immunosuppression: corticosteroids alone have not been shown to be effective. • A combination of corticosteroid + another agent such as chlorambucil is often used Cyclophosphamide plus methylprednisolone is the most appropriate management • blood pressure control: ACE inhibitors have been shown to reduce proteinuria

 Ramipril is proven to affect both proteinuria and hypertension in patients with a diagnosis of membranous nephropathy, and is therefore the most likely treatment to affect the patient's prognosis • consider anticoagulation • Approximately 30% of cases are secondary to other conditions, and in those cases treatment of the underlying cause may be curative. MRCPUK-part-1-September 2011 exam: H/O colorectal cancer developed 'frothy' urine. The results suggest nephrotic range proteinuria. Assuming the proteinuria is related to his colorectal cancer what is the renal histology most likely to show? Membranous glomerulonephritis MRCPUK-part-1-May 2012 exam: H/O peripheral oedema with no past medical history of note. His urinary protein is 4.2g/24 hours. BP is 160/92 mmHg. A renal biopsy shows: thickened capillary walls& Subepithelial deposits. Given the likely diagnosis, which one of the following drugs is most likely to be beneficial?

 ACE inhibitor (Δ membranous glomerulonephritis)

IgA nephropathy Basics • also called Berger's disease or mesangioproliferative glomerulonephritis • commonest cause of glomerulonephritis worldwide • thought to be caused by mesangial deposition of IgA immune complexes • there is considerable pathological overlap with Henoch-Schonlein purpura (HSP) • Has a male preponderance • commonly diagnosed in the age range of 20-40. Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis • post-streptococcal glomerulonephritis is associated with low complement levels • main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur) • there is typically an interval between URTI and the onset of renal problems in poststreptococcal glomerulonephritis Presentations • young male, recurrent episodes of macroscopic haematuria • Haematuria occurs within 12-24 hours of pharyngitis,

• typically associated with mucosal infections e.g., URTI , or less commonly infection of other mucous membranes (e.g. GI, bladder, breast). • accompanied also by loin pain, muscle pain and fever. • nephrotic range proteinuria is rare • The majority of patients have normal renal function. • renal failure Associated conditions • Alcoholic cirrhosis (Alcohol excess) (haematuria + alcohol excess IgA nephropathy). • coeliac disease/dermatitis herpetiformis • Henoch-Schonlein purpura Diagnosis • Renal biopsy is the investigation of choice to confirm the diagnosis histology: Mesangial hypercellularity, positive immunofluorescence for IgA & C3 Management • No specific treatment is available. Observation is the most appropriate management • steroids/immunosuppressants not be shown to be useful. Treatment with corticosteroids is usually reserved for those patients with hypertension and a rising creatinine. • When there is nephrotic range proteinuria (>3 g/day) an 8-12 week course of prednisolone should be prescribed. • If the proteinuria is <3 g/day an ACE inhibitor can be used. Prognosis • 30% of children will have a spontaneous remission within 10 years • 25% of patients develop ESRF within 20 years • markers of good prognosis: frank haematuria • markers of poor prognosis: male gender, proteinuria (especially > 2 g/day), hypertension smoking, hyperlipidaemia, ACE genotype DD MRCPUK-part-1-September 2011 exam: A 17-year-old man with several episodes of visible haematuria. occurs within a day or two of URTI . Urine dipstick is normal. What is the most likely diagnosis? IgA nephropathy MRCPUK-part-1-January 2006 exam: A 10-year-old boy with past two days H/O sore throat associated with blood in his urine. glomerulonephritis is suspected. What would a renal biopsy most likely show? Mesangial hypercellularity (Δ IgA nephropathy) MRCPUK-part-1-September 2007 exam: A 12-year-old boy with purpuric rash on the extensor surfaces of his lower legs + abdominal pain and an urticarial rash. Urine dipstick reveals blood ++.What would be the likely finding on renal biopsy?
 Mesangial hypercellularity (Henoch-Schonlein purpura is associated with IgA nephropathy)

MRCPUK-part-1-January 2014 exam: A 19-year-old woman C/O painless visible haematuria, occur within a day or two of developing tonsillitis. BP is 148/90 mmHg. Given the likely diagnosis, which marker indicate poor prognosis? Hypertension (Δ IgA nephropathy) MRCPUK-part-1-September 2007 exam: Which one of the following is associated with a better prognosis in patients with IgA nephropathy? Frank haematuria

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Post-streptococcal glomerulonephritis Overview • Also known as acute proliferative glomerulonephritis • typically occurs 7-14 days following a group A beta-haemolytic Streptococcus infection (usually Streptococcus pyogenes). Acute glomerulonephritis can be caused by both pharyngeal and skin infections with group A beta-haemolytic Streptococcus , but only pharyngeal infections typically lead to acute rheumatic fever. • caused by immune complex (IgG, IgM and C3) deposition in the glomeruli. • type III hypersensitivity reaction. Epidemiology • Young children most commonly affected. Features • general: headache, malaise • haematuria Dark-colored urine is often a presenting sign. • nephritic syndrome • hypertension Investigations • BMP (Basic metabolic panel) the most important step in the diagnosis BMP to evaluate serum creatinine kidney function is ideal to determine the level of glomerulonephritis in this patient and guide treatment. • low C3 • normal C4 level or only slightly reduced, indicating activation of the alternate complement pathway • Depressed CH 50 level • Raised ASO titer • Renal biopsy post-streptococcal glomerulonephritis causes acute, diffuse proliferative glomerulonephritis endothelial proliferation with neutrophils electron microscopy: subepithelial 'humps' caused by lumpy immune complex deposits. The hump-like appearance in subepithelial space is characteristic of post-streptococcal glomerulonephritis. 'Lumpy-bumpy' appearance on immunofluorescence is characteristic. immunofluorescence: granular or 'starry sky' appearance There is antibody and compliment deposition on immunostaining.

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 light microscopy 'wire-loop' lesions on light microscopy. Treatment • Patients with acute proliferative glomerulonephritis presenting with hypertension are managed with loop diuretics. Prognosis • Carries a good prognosis • Age is the most important prognostic factor in post-streptococcal glomerulonephritis. 95% of affected children recover completely, compared with 25% of adults over 60 years old.

Membrano-proliferative glomerulonephritis (MPGN). Overview • also known as mesangio-capillary glomerulonephritis(MCGN), • more recently been termed complement mediated glomerulonephritis. Associations • It is associated with SLE, cryoglobulinaemia with or without hepatitis C, chronic infections (SBE) , neoplasms, hepatitis B, schistosomiasis, malaria and leprosy. General features • may present as nephrotic syndrome, haematuria or proteinuria • Circulating immune complexes are seen • Classically associated with decreased serum C3 (and a normal C4, indicating activation of the alternative pathway of complement). • Hypocomplementemia (Low C3 levels) is a characteristic finding with all types of (MPGN). • appears on light microscopy with "tram-track" capillary loops of glomerular basement membranes. Type 1 • Epidemiology

accounts for 90% of cases • histology sub-endothelial immune deposits of electron dense material, Thickening and splitting of the capillary basement membrane (double layer of glomerular basement membrane), resulting in a 'tram-track' appearance • Causes: cryoglobulinaemia (low C3), hepatitis C (hepatitis C is endemic among the iv drug-users). Hepatitis C is now considered the principal cause of 'idiopathic' mesangiocapillary glomerulonephritis (MCGN), Type 2 • Also known as Dense deposit disease • causes: partial lipodystrophy, factor H deficiency, may be idiopathic or

 may occur after measles • Features reduced serum complement C3b nephritic factor (an antibody against C3bBb) found in 70% low C3 • Histology 'dense deposit' characterised by mesangial cell proliferation with electron-dense, linear intramembranous deposits that stain positive for C3 (C3 nephritic factor) Type 3 • Subepithelial and subendothelial deposits • causes: hepatitis B and C Management • steroids may be effective Prognosis • poor prognosis MRCPUK-part-1-September 2009 exam: patient of nephrotic syndrome is noted to have marked loss of subcutaneous tissue from the face. What is the most likely underlying cause of her renal disease? Membranoproliferative glomerulonephritis type II (Δ partial lipodystrophy) MRCPUK-part-1-September 2009 exam: A patient develops membranoproliferative glomerulonephritis secondary to partial lipodystrophy. Which type of complement is likely to be low? C3

Rapidly progressive glomerulonephritis (RPGN) Overview • rapid loss of renal function associated with the formation of epithelial crescents in the majority of glomeruli. • results in a rapid decrease in GFR of at least 50% over a short period (a few days to 3 months). • The most aggressive GN, with potential to cause ESRF over days. Causes • Goodpasture's syndrome • Wegener's granulomatosis Types

1. Type I RPGN (~3%): Serum anti-glomerular basement membrane (Anti-GBM) antibody is positive. Antibody deposits along the glomerular basement membrane in a linear fashion. Example: Goodpasture syndrome.
2. Type II RPGN: Immune complex disease (~45% of cases): (Anti-GBM) antibody is negative, Notes & Notes for MRCP
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• others: SLE, microscopic Polyarthritis • secondary syphilis

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 but irregular immune complex (antibody-antigen) deposits are found within the glomeruli. Example: lupus nephritis and post-streptococcal glomerulonephritis. 3. Type III RPGN: (Pauci-immune disease (~50% of cases, 80–90% ANCA +ve): Serum anti-neutrophil cytoplasmic (ANCA) antibodies are positive. Negative immunofluorescence. Example: Wegener granulomatosis and microscopic polyangiitis. Features • nephritic syndrome: haematuria with red cell casts, proteinuria, hypertension, oliguria • features specific to underlying cause (e.g. haemoptysis with Goodpasture's, vasculitic rash or sinusitis with Wegener’s Investigations • Immunofluorescence

detects deposits of IgG and C3 in the glomerular BM • The main pathological finding is fibrinoid necrosis ˃ 90% of biopsy specimens with extensive crescent formation in at least 50% of the glomeruli. These crescents are collections of epithelial cells and macrophages proliferation within the Bowman’s space. Treatment • Aggressive immunosuppression with high-dose IV steroids and cyclophosphamide • +/- plasma exchange. Prognosis: • 5-year survival 80%. MRCPUK-part-1-January 2012 exam: H/O chronic sinusitis, haemoptysis and microscopic haematuria. cANCA (PR3)= Positive. Given the likely diagnosis, what findings would be expected on renal biopsy? Crescentic glomerulonephritis

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Focal segmental glomerulosclerosis (FSGS) Overview • cause nephrotic syndrome and chronic kidney disease. • In FSGS, as the name suggests, only some glomeruli are affected (focal) and just some of the affected glomeruli are diseased (segmental). • cholesterol levels rise due to increased cholesterol synthesis in the liver and the loss of lipid-regulating proteins in urine Epidemiology • generally presents in young adults. • the second most common cause of nephrotic syndrome in adults, after membranous glomerulonephritis (GN) • The most common cause of nephrotic syndrome in Hispanic and African-Americans • Incidence: 40% in adults. 20% in children Pathophysiology • Caused by an injury to podocytes in the renal glomeruli. Causes • idiopathic (in 80%) • secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy • HIV 'collapsing glomerulopathy' The most common type of (HIV-associated nephropathy) is a collapsing (FSGS). • intravenous drug use

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• heroin • Alport's syndrome • sickle-cell • associated with severe obesity • medications: Interferon alfa, lithium, sirolimus, and pamidronate. Histology • histology may appear normal and may be confused with minimal change nephropathy • deep glomeruli at the corticomedullary junction are affected first, these may be missed on transcutaneous biopsy, leading to a mistaken diagnosis of a minimal change glomerular lesion • light microscopy Segmental sclerosis and hyalinosis • Immunofluorescence microscopy usually unremarkable. Immunofluorescence is negative because there is no antibody or immune complex deposition. biopsy will show partial scarring of the glomerulus with no immunofluorescence. • Electron microscopy The hallmark pathologic feature is podocyte foot processes fusion. can distinguish primary from secondary FSGS. Foot process fusion is diffuse in primary FSGS but is mostly limited to sclerotic areas in secondary FSGS. • fibrinogen are deposited in juxtamedullary capillaries Treatment • 50% of (FSGS) do not respond to steroid • The first line of management is glucocorticoids. • (ACE) inhibitors are a recognised strategy to slow the progression of renal disease. Prognosis • It leads to chronic renal failure in 50% of cases. • typically progresses to renal failure over a 6–8 year period. • 2% of dialysis patients have FSGS. • have a high recurrence rate in renal transplants FSGS recurs in 40% of renal transplants January 2011 exam: A patient with H/O heroin abuse, his creatinine = 156, urine show = ++ protein. What is the most likely cause of his deteriorating renal function?
 Focal segmental glomerulosclerosis (Heroin is a known cause of focal segmental glomerulosclerosis) Goodpasture's syndrome Goodpasture's syndrome is characterised by pulmonary haemorrhage and crescentic glomerulonephritis.

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Definition • Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis. Epidemiology • more common in men (sex ratio 2:1) • has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket). Genetics • associated with HLA DR2 • p-ANCA positive in 30% and is directed against myeloperoxidase. Pathophysiology • It is a type II cytotoxic reaction caused by anti-glomerular basement membrane (anti-GBM) antibodies against the α 3 chain of type IV collagen (basement membrane of both the kidneys and lungs). • Goodpasture syndrome is due to IgG antibodies produced against the basement membrane causing damage via a type II hypersensitivity reaction. Features • pulmonary haemorrhage respiratory symptoms can vary from minimal hemoptysis to massive alveolar hemorrhage, leading to respiratory failure. In lungs, this is a type 2 hypersensitivity reaction. Hemoptysis is a clinical feature of Goodpasture's syndrome due to cross reaction of anti-glomerular basement membrane antibodies at the lungs. cough Fever • followed by rapidly progressive glomerulonephritis (RPGN) (Renal impairment is caused by a crescentic glomerulonephritis) haematuria proteinuria, and red cell casts. Factors which increase likelihood of pulmonary haemorrhage • normally, the alveolar epithelium prevents contact of antibody with basement membrane collagen, thus any condition that increases permeability of alveoli can cause triggering of this syndrome. Such susceptibility factors include: smoking lower respiratory tract infection pulmonary oedema inhalation of hydrocarbons and toxic gases • young males Investigations • serological testing (for anti-GBM antibodies) • biopsy from kidney rather than lung. Renal biopsy: linear IgG deposits along basement membrane (the most likely finding on renal biopsy Linear immunofluorescence) Lung biopsy linear staining of IgG along the alveolar capillary basement membranes

 disruption of alveolar septa and haemosiderin-laden macrophages because there may be pulmonary haemorrhage associated with the condition. • raised transfer factor secondary to pulmonary haemorrhages. • Serial measurement of carbon monoxide (CO) diffusing capacity or transfer factor (Tlco) can be used to monitor progression, Management • General management ABC If the patient is hypoxic intubate and mechanically ventilate the patient. Patients should not smoke and should avoid hydrocarbon exposure. • The most appropriate initial management IV methylprednisolone and cyclophosphamide • plasma exchange (plasmapheresis) Where there is severe haemoptysis, rapid removal of anti-GBM antibody is indicated, and the best way to do this is by plasmapheresis at a specialist centre. This is usually accompanied by pulsed therapy with IV methylprednisolone and cyclophosphamide. • steroids • cyclophosphamide Response is assessed by monitoring symptoms and anti-GBM antibody titres. Cyclophosphamide and prednisolone continued, typically for 6 - 9 months following remission. In the acute setting, treatment is focused on:

1. managing life threatening complications of renal failure, such as hyperkalaemia haemodialysis.
2. Removing the circulating auto-antibody responsible for disease plasmapharesis (therapeutic plasma exchange), the most important management step in the next few days after haemodialysis
   Prognosis: • Despite treatment, the mortality of Goodpasture's is 11% and it has a high morbidity with 60% of patients becoming dependent on dialysis. • In practice, glomerulonephritis proves to be a much commoner threat to survival than lung haemorrhage, Other causes of raised anti-GBM antibody levels: • Some healthy individuals exposed to inhaled oils,hydrocarbons or solvents can have borderline raised anti-GBM antibody levels. • Anti-GBM antibodies have also been detected in HIV-negative patients with Pneumocystis pneumonia.

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Nephrology Nephrotic syndrome Triad of: •

1. Proteinuria (> 3g/24hr) (The minimum proteinuria which is defined as 'nephrotic' is 300 mg/mmol) causing •
2. Hypoalbuminaemia (< 30g/L) and •
3. Oedema Other features: • Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels predispose to thrombosis. • Loss of thyroxine-binding globulin lowers the total, but not free, thyroxine levels. • Increased serum cholesterol ↑(LDL) LDL and VLDL are removed from serum by lipoprotein signals. If the lipoprotein is lost in the urine with nephrotic syndrome, then the lipid levels in the blood rise. HDL is usually normal • ↓↓Ca & vit D (loss of 25-hydroxyvitamin D3 (25OHD3) in the urine hypocalcaemia) • Serum C3 levels are decreased in immune complex-mediated glomerulonephritis Nephrotic Nephritic Common primary causes Membranous Minimal change FSGS Mesangiocapillary GN IgA nephropathy Mesangiocapillary GN Common secondary causes Diabetes SLE (class V nephritis) Amyloid Hepatitis B/C Post streptococcal Vasculitis SLE (other classes of nephritis) Anti-GBM disease (Figs 1 & 2) Cryoglobulinaemia BP Normal–mild ↑ Moderate–severe ↑ Urine Proteinuria >3.5g/day Haematuria (mild–macro) GFR Normal–mild ↑ Moderate–severe ↓ Causes Nephrotic syndrome - malignancies cause membranous glomerulonephritis • glomerulonephritis accounts for around 80% of cases minimal change glomerulonephritis (causes 80% in children, 30% in adults) membranous glomerulonephritis focal segmental glomerulosclerosis (FSGS). Patients presenting with isolated heavy proteinuria without the other components of nephrotic syndrome is more likely due to (FSGS). membranoproliferative glomerulonephritis • Systemic disease (about 20%) diabetes mellitus (Diabetic nephropathy often presents as nephrotic syndrome but typically develops at least 15 years after onset). systemic lupus erythematosus amyloidosis (in patient with chronic inflammatory state , amyloidosis is the likely cause of NS)

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• Drugs gold (sodium aurothiomalate), penicillamine • Others congenital neoplasia: carcinoma, lymphoma, leukaemia, myeloma Chronic lymphocytic leukemia (CLL) and Non-Hodgkin's lymphoma (NHL) are the most common hematologic malignancies associated with glomerular diseases. Membranoproliferative glomerulonephritis (MPGN) are most common glomerular disease associated with CLL and NHL the most common renal lesion associated with Hodgkin's disease is minimal change disease infection: bacterial endocarditis, hepatitis B, malaria (commonly plasmodium malariae) Investigations • Renal biopsy • Contraindications for renal biopsy: Abnormal clotting Hypertension >160/>90mmHg Single kidney (except for renal transplants) Chronic kidney disease with small kidneys (<9cm) Uncooperative patient Horseshoe kidney Renal neoplasms. Serum electrophoresis in nephrotic syndrome • ↑serum α- and β-globulin fractions. (The increase in globulin fractions is thought to occur due to increased synthesis in patients with urinary protein loss) Increased α1 and α2-globulin fractions, decreased serum albumin • A monoclonal paraprotein band will be present where myeloma is the underlying cause, • there may be associated immune paresis with reduced concentrations of one or more of the immunoglobulins IgG, IgA or IgM Complications • increased risk of infection in particular pneumococcal infections due to urinary immunoglobulin loss and decreased splanchnic blood flow. • Increased risk of thromboembolism related to loss of antithrombin III and plasminogen in the urine , increased fibrinogen and increased factor VIIIc. Renal vein thrombosis occurs in 15-20% of patients with nephrotic syndrome Renal vein thrombosis
 Occurs in 10-20% Feature often clinically silent , (loin pain + haematuria) and acute renal injury Initial investigation US (swollen oedematous kidney) Diagnosis Duplex US renal veins, CT or MRV Treatment long term anticoagulation. • hyperlipidaemia • hypocalcaemia (vitamin D and binding protein lost in urine) • acute renal failure • Intravascular volume depletion :Hypoalbuminaemia results in decreased intravascular oncotic pressure, leading to leakage of extracellular fluid from blood to the interstitium

Treatment • In general, steroids are tried first and then second line agents such as cyclosporin and cyclophosphamide are introduced if needed. • Cyclophosphamide is the best treatment for steroid-dependent nephrotic syndrome No more than two courses of cyclophosphamide should be prescribed in children because of the risk of side effects, which include azoospermia An alternative to cyclophosphamide is ciclosporin, which is effective but must be continued long-term to prevent relapse on stopping treatment. Ciclosporin is also potentially nephrotoxic MRCPUK-part-1-January 2006 exam: What changes in patients with nephrotic syndrome predispose to the development of venous thromboembolism? Loss of antithrombin III Which finding would support a diagnosis of a protein losing enteropathy rather than nephrotic syndrome? Low total cholesterol The pathophysiology of protein loss in protein-losing gastroenteropathy is different from that in glomerular diseases. In glomerulopathies, protein loss is determined by molecular weight and charge. By contrast, the leakage of individual serum proteins in patients with proteinlosing gastroenteropathy is independent of molecular weight. For this reason, cholesterol levels are low, in contrast to nephrotic syndrome where cholesterol levels are high (due to the molecular weight of cholesterol).

Analgesic nephropathy • common in women , F : M = 2: 1 , and presents most often in middle age • caused by non-steroidal anti-inflammatory drugs (NSAIDs) for chronic pain or headache, • Characteristically, associated with phenacetin use, particularly in Australia and New Zealand • features may include anaemia, chronic renal failure, symptoms of urinary tract infection, haematuria or hypertension. • Complications Urinary tract malignancy (8-10% of patients with analgesic nephropathy), For example, in women under the age of 50 analgesic abuse is the most common cause of bladder cancer.

Renal stones • The most common stones are calcium oxalate stones followed by calcium phosphate. • Calcium phosphate stones are seen in renal tubular acidosis (RTA). Risk factors • dehydration • hypercalciuria, hyperparathyroidism, hypercalcaemia • cystinuria (AR defect in dibasic amino acid transporter) • high dietary oxalate. hyperoxaluria (for example, XS intake, ileal disease and bypass) • renal tubular acidosis => (Calcium phosphate stones) • medullary sponge kidney, polycystic kidney disease • beryllium or cadmium exposure • Chronic infection with urea splitting organisms: causes stones made of magnesium ammonium phosphate and calcium phosphate (infection stones (5%) • Familial : Idiopathic hypercalciuria inherited as autosomal dominant whereas cystinuria, cystinosis, urate uropathy and hyperoxaluria are autosomal recessive conditions. the most common cause being increased gastrointestinal (GI) absorption of calcium. The most common stones are calcium oxalate stones. • there appears to be a male predominance with a 2:1 ratio. Risk factors for oxalate stones (Calcium oxalate) • foods high in oxalate, (such as spinach, rhubarb and tea) In patients who have oxalate kidney stones, dietary restrictions are necessary. Foods that should be avoided include: spinach, nuts, chocolate, dry beans, rhubarb and strawberries. • calcium-restricted diet • gastrointestinal disease such as Crohn's which increase colonic oxalate absorption in malabsorption, the calcium in the small bowel is bound by the unabsorbed excess fatty acids. Oxalates are left free and are excessively absorbed. Subsequently, they can deposit in the kidney to form stones. • enteric oxaluria may occur in a number of disorders in which malabsorption results in excessive colonic absorption of oxalate. These include: Coeliac disease Crohn's disease Chronic pancreatitis, and

 Short bowel syndrome. Bile salts in the colon increase oxalate absorption. • Excess vitamin C can be converted to oxalic acid in the body. Subsequent hyperoxaluria can lead to the formation of a kidney stone. Primary hyperoxaluria • inherited enzyme deficiency that leads to excessive metabolism of oxalate. • There are three types: types I and III are due to an enzyme defect in the liver glyoxalatepathway Type I is the commonest and results in widespread calcium oxalate deposition throughout the body. in type II there is failure of reduction of glyoxalate to glycolate. • Treatment is aimed at increasing urinary pH to make calcium oxalate more soluble. This is by administering supplemental citrate and magnesium. • Renal insufficiency is common, and patients

require a combined liver and kidney transplant in type I disease. Risk factors for urate stones • gout • ileostomy: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid • high purine intake, • High cell turnover. (for example, haematological malignancy). Primary polycythaemia would predispose to uric acid stone formation, whereas secondary polycythaemia does not. • Dehydration • Thiazide diuretics cause hyperuricaemia and can predispose to hyperuricosuria and uric acid stone formation. Stag-horn calculi (Triple phosphate stones: magnesium ammonium phosphate): • involve the renal pelvis and extend into at least 2 calyces. • They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate). • Urea plasma urea lyticum and Proteus infections predispose to their formation Proteus produces urease, which leads to hydrolysis of urea to produce ammonia, this leads to precipitation of organic and inorganic salts, one of which is known as struvite, or magnesium ammonium phosphate • classically produced by urea splitting organisms such as Klebsiella or Proteus. Drug causes • drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline • topiramate (anti-epileptic) increase the propensity to form calcium phosphate stones. • thiazides can prevent calcium stones (increase distal tubular calcium resorption) Renal conditions associated with recurrent urinary tract infections: • Reflux nephropathy. • Renal stone (but is less likely than reflux nephropathy) Hypercalcuria Thiazide diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation.

• high urine calcium that is not due to hypercalcemia (idiopathic hypercalciuria) • Idiopathic hypercalciuria is often familial, the most common cause being increased gastrointestinal absorption of calcium. • predisposes to stone formation. • The 24-hour urine is an essential component of the initial evaluation and guides recommendations for prevention • Treatment including dietary calcium restriction and pharmacological management. • Both thiazide diuretics and potassium citrate can be used to reduce urinary excretion of calcium. Potassium citrate is generally preferred as it has fewer side effects, and is therefore better tolerated. • Thiazide diuretics are the drug treatment of choice as they act directly on the renal tubule to reduce urinary calcium excretion (there is a disagreement between onexamination and pastest in which drug is better for hypercalcuria? But after thorough review of sources and uptodate, thiazide is a better choice than potassium citrate) • Dietary calcium restriction alone has minimal effect on calciuria, given the large amount of calcium that can be mobilised from bone.. • Loop diuretics increase urinary excretion of calcium, and therefore would exacerbate calcium renal stone formation. • Pencillamine is used in the management of hypercalcuria associated with Wilson's disease • Idiopathic hypercalciuria has a familial or sporadic pattern. In the familial pattern an autosomal dominant inheritance is present. The type of the disease is identical in affected members of the same family and the typical presentation is of recurrent urinary calculi. Imaging The table below summarises the appearance of different types of renal stone on x-ray Type Frequency Radiograph appearance Calcium oxalate (the most common) Mixed calcium oxalate/phosphate stones Triple phosphate stones 10% Opaque Calcium phosphate 10% Opaque Urate stones 5-10% Radio-lucent Cystine stones 1% Semi-opaque, 'ground-glass' appearance Xanthine stones <1% Radio-lucent • patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones) • the imaging of choice is a non-contrast CT (NCCT). 99% of stones are identifiable on NCCT. Notes & Notes for MRCP
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40% Opaque 25% Opaque

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Imaging (European Association of Urology guidelines 2016) • Ultrasound (US) should be used as the primary diagnostic imaging tool. US is safe (no risk of radiation), reproducible and inexpensive. US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones. the preferred method of imaging in pregnant women. • KUB (kidney-ureter-bladder radiography) x-ray The sensitivity: 44-77% and specificity: 80-87%. should not be performed if NCCT is considered. KUB is helpful in differentiating between radiolucent and radiopaque stones and be used for comparison during follow-up. • Non-contrast CT (NCCT) (Non-contrast helical CT kidneys, ureters and bladder (CT KUB)) The imaging of choice is a non-contrast CT (NCCT). become the standard for diagnosing acute flank pain 99% of stones are identifiable on NCCT. Following initial ultrasound assessment, use non-contrast-CT to confirm stone more accurate than intravenous urography (IVU), so has replaced it. • Imaging in pregnant women first-line ultrasound as the preferred method of imaging second-line magnetic resonance imaging (MRI) last-line option low-dose computed tomography (CT) Management Acute management of renal colic Medication • the British Association of Urological Surgeons (BAUS) recommend diclofenac (intramuscular/oral) as the analgesia of choice for renal colic* *Diclofenac use is now less common following the MHRA warnings about cardiovascular risk. It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen • BAUS also endorse the widespread use of alpha-adrenergic blockers to aid ureteric stone passage • Stones < 5 mm will usually pass spontaneously. • Lithotripsy and nephrolithotomy may be for severe cases. Prevention of renal stones Calcium stones may be due to hypercalciuria, which is found in up to 5-10% of the general population. • high fluid intake the main initial treatment should aim for a daily urinary output in excess of 2000 ml. • low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet) • thiazides diuretics (increase distal tubular calcium resorption) and hence lower calcium concentration in the urine. Oxalate stones • cholestyramine reduces urinary oxalate secretion • pyridoxine reduces urinary oxalate secretion • High fluid intake and calcium carbonate are mainstay of prevention.

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• Avoid foods high in oxalate such as chocolate, rhubarb and nuts . • Increasing dietary calcium intake decreases urinary oxalate excretion by reducing absorption (as free oxalate is bound). • Other treatments which can help enteric hyperoxaluria include: Calcium, cholestyramine and magnesium - bind strongly to free intestinal oxalate, preventing absorption. Iron and aluminium - act as intestinal oxalate binding agents. Potassium citrate - alkalinises the urine, which reduces urinary oxalate excretion. propensity to form stones is reduced when citrate intake is increased. Uric acid stones • allopurinol • urinary alkalinization e.g. oral bicarbonate • Reducing intake of offal is most helpful at reducing urate excretion Contraindications to lithotripsy • absolute

contraindication uncorrected bleeding disorder • relative contraindications Ureteric stricture, UTI and cardiac pacemaker MRCPUK-part-1-September 2008 exam: What is the most likely composition of a staghorn calculus? Struvite MRCPUK-part-1-September 2012 exam: What are staghorn calculi normally composed of? Magnesium ammonium phosphate

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Cystinuria • The commonest inborn error of amino acid transport. • Amino acids excreted in urine are cystine, ornithine, arginine and lysine (mnemonic - COAL). • The glomerulus is unable to resorb these amino acids, and they are therefore excreted into the urine. Genetics • autosomal recessive condition. • The rBAT gene is responsible, • There are two genes identified: SLC3A1 (Chromosome 2)and SLC7A9(Chromosome 19) Features: • Cystinuria usually presents with recurrent nephrolithiasis in the form of cystine stones (which are often bilateral, multiple, and can form staghorns). • The renal stones are semi radio-opaque due to the presence of sulphur. (Semi-opaque, 'ground-glass' appearance) On plain film, which is not used as much in the UK any more, they are radio-lucent. On CT, as with almost all stones, cysteine stones are radio-opaque.

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Nephrology

Diagnosis • Diagnosis of cystinuria can be made by stone analysis; such stones are pale yellow, and analysis reveals high cystine levels. It can then be confirmed by an amino acid chromatogram and quantification of cystine excretion. • cystine may precipitate out as pathognomonic hexagonally-shaped crystals Management includes: • conservative high fluid intake (>4 L/day); alkalinisation Urine pH should be regularly monitored (aiming for 7.5-8), with sodium bicarbonate being used if necessary (not in hypertensive patients or those with renal failure). The aim of such treatment is to reduce the urinary cystine concentration to below 300 mg/L. • If this fails, d-penicillamine, alpha-mercaptopropionylglycine or captopril can be used. • Cystine stones are not easily broken by lithotripsy, and therefore percutaneous removal is most often used.

Cystinosis • autosomal recessive • caused by mutations in the CTNS gene, which encodes a lysosomal transporter of the amino acid cystine. Without this transporter, cystine accumulates in the lysosomes of proximal tubule cells, eventually leading to cell toxicity. • the most common form of Fanconi syndrome in children. • occurs almost exclusively in whites. Feature • presents in the first year of life with: failure to thrive, and rickets progressive renal damage (Renal failure develops before the age of 10 years) polyuria, polydipsia Visual impairment (occurs as a result of cystine deposits in the retina and cornea) hypothyroidism

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Renal tubular acidosis (RTA) • All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap) Type 1 RTA (distal) (acid retention) • Inability to generate acid urine (secrete H+) by a failure of the alpha intercalated cells of the distal

tubule to excrete hydrogen ions. • Causes Idiopathic, gene defects, Autoimmune diseases such as primary biliary cirrhosis, thyroiditis RA, SLE, Sjogren's, Drugs: amphotericin B toxicity, analgesic nephropathy , hypergammaglobulinaemic states, • Features hypokalaemia, (as K+ reabsorption is linked to H+ excretion). acidosis low urinary ammonium production inability to lower the urinary pH below 5.3 after ammonium chloride administration despite systemic acidosis low urinary citrate Hypercalciuria: These predispose to renal stones, rickets or osteomalacia and nephrocalcinosis • Complications nephrocalcinosis and renal stones (Alkaline urine increases the risk of calcium deposition) Osteomalacia develops because of calcium loss and buffering of retained H+ in bone • Management Bicarbonate and potassium supplements should be given to maintain adequate plasma levels. Recurrent kidney stones, hypokalaemia, acidosis and a normal anion gap is a typical presentation for RTA type 1. RTA type 2 present with similar biochemical features but is more unlikely to have a history of kidney stones. Treatment of RTA involves correction of the acidaemia with oral sodium bicarbonate, sodium citrate or potassium citrate

Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA Type 2 RTA (proximal) (bicarbonate loss) Fanconi syndrome (RTA type 2) is associated with Wilson's disease • decreased HCO3- reabsorption in proximal tubule • very rare in adult practice • As the distal tubule functions normally, the acidosis is less severe than type 1 RTA, and they urine has a pH of less than 5.3. • Causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, lead poisoning myeloma outdated tetracyclines carbonic anhydrase inhibitors • Features acidosis, hypokalaemia hypophosphataemia increased risk for hypophosphatemic rickets. • Complications • osteomalacia (Phosphate wasting results in marked bone demineralisation) Type 4 RTA (hyperkalaemic)(hypoaldosteronism) • the most common renal tubular disorders • Causes include: Aldosterone deficiency (hypoaldosteronism): decreased aldosterone production, secondary to: adrenal insufficiency diabetes

 Diabetic nephropathy decreased renin production Hyporeninaemic hypoaldosteronism low sodium and raised potassium Patients with diabetes may have impaired extrarenal potassium homeostasis, caused by a lack of insulin, and autonomic neuropathy with resulting impaired beta2 - mediated influx of potassium into cells. chronic reflux nephropathy Aldosterone resistance → 1.Drugs: Non-steroidal anti-inflammatories, angiotensin converting enzyme inhibitors, angiotensin 2 receptor blockers, eplerenone, spironolactone, trimethoprim, pentamidine heparin, cyclosporine → 2.Pseudohypoaldosteronism • Features: hyperkalaemia usually mild but may be exacerbated by drugs such as beta-blockers and ACE inhibitors. low sodium metabolic acidosis Urinary pH is commonly normal reduction in renin and aldosterone leads in turn to a reduction in proximal tubular ammonium excretion • Treatment: Treatment is usually successful with conservative measures such as: stopping provocatory agents, low potassium diet. Small doses of fludrocortisone could be considered for refractory cases. Type 3 RTA

(Juvenile RTA) is combined proximal & distal RTA. • autosomal recessive • Results from inherited carbonic anhydrase II deficiency. • 70% of the reported cases are from the Magreb region of North Africa • rarely discussed • described as a failure to generate NH3 in the setting of a decreased glomerular filtration rate, • Features: normokalaemic hyperchloraemic metabolic acidosis. A syndrome of osteopetrosis Renal tubular acidosis Cerebral calcification Mental retardation.

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