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Chapter 6

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 6

Nephrology

Type Type 1 Type 2 Type 4 Location Distal tubules Proximal tubules Adrenal Acidosis? Yes (severe) Yes Mild when present Potassium Hypokalemia Hypokalemia Hyperkalemia Pathophysiology H+ secretion Bicarb reabsorption hypoaldosteronism/ pseudohypoaldosteronism January 2010 exam: Which feature is most likely to be seen as a consequence of type 1 renal tubular acidosis? Nephrocalcinosis

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Renal vascular disease (RAS) The presence of difficult to treat hypertension, renal impairment, evidence of other atherosclerotic disease (carotid bruit) and discrepent renal size makes renovascular disease a distinct possibility. • Renovascular disease is due to disease affecting the arterial supply of the kidney(s). • The resulting renal hypoperfusion leads to hyperactivation of the renin-angiotensinaldosterone axis, causing hypertension. • In one third of cases the disease is bilateral; 40% may have peripheral vascular disease and there may be proteinuria. Suspicion for renal artery stenosis: • Current UK guidelines with regard to chronic kidney disease recommend referral for further investigation of atherosclerotic renal artery stenosis when there is: Refractory hypertension (BP >150/90 mmHg despite 3 antihypertensives); Recurrent episodes of pulmonary oedema despite normal left ventricular function; Rise of >20% serum creatinine or fall of GFR >15% over 12 months with high clinical suspicion of widespread atherosclerosis, or during the first 2 months after initiation with an ACE inhibitor or angiotensin receptor blocker. A rise in serum creatinine more than 20% above the baseline after starting an (ACEI) hold the drug, monitor renal function and investigate for renal artery stenosis.

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Causes • Atherosclerosis is most common cause (> 95% of patients). • Arteriosclerosis (renal artery sclerosis) is a more common cause of RAS than fibromuscular dysplasia. 40% may have peripheral vascular disease (PVD) with intermittent claudication there may be proteinuria. • In younger patients however, fibromuscular dysplasia (FMD) needs to be considered. FMD is more common in young women and characteristically has a 'string of beads' appearance on angiography. Patients respond well to balloon angioplasty renal artery narrowing is unlikely to

progress • Takayasu's arteritis • Congenital RAS is extremely rare and may be associated with coarctation of the aorta Associated risk factors • Smoking and hypertension that cause atheroma elsewhere in the body. Presentation It may present as: • Hypertension, which can be resistant to standard treatment. • chronic renal failure • 'flash' pulmonary oedema. • It can also lead to renal impairment when patients are started on ACE inhibitors or angiotensin-II receptor antagonists, hypokalaemia or flash pulmonary oedema. ACE inhibitor reduce vasoconstriction in the efferent arterioles, which in turn reduces glomerular filtration pressure. In patients with RAS this can often prompt a precipitous drop in glomerular filtration rate. A rise in creatinine of 15% from baseline is expected with commencement of an ACEinhibitor. Investigation • MR angiography the investigation of choice and can be performed safely in patients with CKD stage 3 and 4 • CT angiography. Commonly used but can be complicated by radio-contrast nepropathy in patients with CKD. • conventional renal angiography less commonly performed used nowadays, but may still have a role when planning surgery • U/S

Nephrology

 Atherosclerotic renal artery stenosis (RAS) is suggested by the asymmetric reduction in renal size on U/S, with mild proteinuria quite common in the condition. Typical ultrasound changes are asymmetrical kidneys; the affected kidney >2 cm smaller than the unaffected kidney. • ↑↑ Aldosterone • ↑↑ Renin Serum renin can differentiate renal artery stenosis (↑↑ Renin +↑↑ Aldosterone) from primary hyperaldosteronism (↓↓ Renin +↑↑ Aldosterone) ↑↑ Renin work as a mechanism to improve renal perfusion. ↓↓ Renin in primary hyperaldosteronism is due to the resulting hypertension causing excessive renal perfusion, which results in decreased renin production (negative feedback mechanism). Flash pulmonary edema, U&Es worse on ACE inhibitor, asymmetrical kidneys ↓ Renal Artery Stenosis ↓ Do MR angiography Treatment: • Optimize vascular risk factors, • cautious use of ACE inhibitors and angiotensin-II receptor antagonists and avoiding other nephrotoxics. • The current evidence favours medical therapy in these patients, that is, an antiplatelet agent (aspirin), lipid lowering therapy (simvastatin) and tight blood pressure control (amlodipine). • No benefit of vascular intervention such as stenting. The ASTRAL trial showed no significant difference between stenting and medical therapy, it is often decided on an individual level. • Although patients with unilateral renal artery stenosis who have recurrent pulmonary oedema may benefit from stenting, the optimal first step is control of hypertension. Per se, better targeting of blood pressure is likely to reduce the number of episodes of heart failure. • Renal artery stenting to reduce further risk of pulmonary oedema is the next step following medical therapy to control blood pressure. The subsequent reduction in renin production will reduce the incidence of heart failure. • Although surgical renal artery bypass is successful, it is invasive and associated with significant operative morbidity versus percutaneous stent insertion. Indication for stenting in renal artery stenosis:(mrcpass.com) • hemodynamically significant renal artery stenosis Flash pulmonary oedema episodic pulmonary edema, congestive cardiac failure, unstable angina. Prognosis • poor prognosis (80% mortality at five years) is related to concurrent coronary disease.

Lupus nephritis (SLE: renal complications) Epidemiology • Lupus nephritis affects a third of patients early in the disease • it is frequently un-recognised until nephritic and/or nephrotic syndrome with renal failure occur. WHO classification • class I: normal kidney • class II: mesangial glomerulonephritis • class III: focal (and segmental) proliferative glomerulonephritis • class IV: diffuse proliferative glomerulonephritis • class V: diffuse membranous glomerulonephritis • class VI: sclerosing glomerulonephritis end stage renal disease irreversible not respond to any immunosuppression Class IV (diffuse proliferative glomerulonephritis) • the most common type in SLE. • the most severe form, affecting > 50% of glomeruli, carries the worst prognosis for progression to renal failure • Renal biopsy characteristically shows: endothelial and mesangial proliferation, 'wire-loop' appearance the capillary wall may be thickened secondary to immune complex deposition electron microscopy shows subendothelial immune complex deposits granular appearance on immunofluorescence • Treatment high dose steroids and pulses of intravenous cyclophosphamide (initially given monthly for six months and then quarterly). Pulsed intravenous cyclophosphamide appears to be as effective as oral cyclophosphamide but has lower toxicity. Class V (Membranous nephropathy in SLE) • Nephrotic syndrome without haematuria in a patient with (SLE) suggests membranous nephropathy (class V) • The lesion is differentiated from idiopathic (non-lupus) membranous nephropathy by: The presence of tubulo-reticular structures on electron microscopy, immune deposits along the tubular basement membrane (in addition to the glomerular basement membrane) and the presence of concurrent subendothelial and mesangial immune deposits (in addition to the subepithelial deposits typical of membranous) Class V lupus nephritis is the only form of renal disease in SLE where serological and clinical manifestations of the underlying disease may be absent. Complement levels may be normal and dsDNA antibodies may be absent Clinical features • Hypertension is found at presentation in 20-50% • 20-30% present with acute renal failure • Lupus nephritis typically occurs in SLE patients with extrarenal symptoms such as a rash, arthralgia, Raynaud's phenomenon, and pleuro-pericarditis

Nephrology Laboratory features • Proteinuria is found in all patients with lupus nephritis and in 50-60% of cases is heavy enough to lead to a nephrotic syndrome • Microscopic haematuria (80% of patients) • In lupus nephritis a biopsy is indicated in those patients with abnormal urinalysis and/or reduced renal function , for histological classification ,disease activity, chronicity and prognosis. Immunological features • the pathognomonic feature of lupus on renal biopsy is 'full house' immunology on immunostaining, ie mesangial deposition of IgA, IgG, IgM, C3 and C4 This differentiates the necrotising glomerulonephritis with crescent formation seen in lupus from a similar pattern which is seen in systemic vasculitis, as the latter condition is 'pauci immune', ie no immunoglobulin deposition • Lupus nephritis is associated with activation of the classical pathway, and often associated with suppression of both C3 and C4. Prognosis • Features associated with a poorer prognosis, and increased risk of progression to end stage renal failure include: young age (<23) Increased serum creatinine Diffuse proliferative lesions (WHO classification class IV) and

 high chronicity index on renal histologic analysis. Management • treat hypertension • corticosteroids if clinical evidence of disease • immunosuppressants e.g. azathiopine/cyclophosphamide • patients with type IV (and sometimes type III, where < 50% of glomeruli are involved) should be treated with a combination of cyclophosphamide and steroids.

Urinary incontinence (UI) Epidemiology • common problem, affect around 4-5% of the population. • more common in elderly females. Risk factors • advancing age • previous pregnancy and childbirth • high body mass index • hysterectomy • family history Classification • urge incontinence /overactive bladder (OAB): due to detrusor over activity characterized by involuntary loss of urine after sudden desire to urinate. Cystourethroscopy may be performed in patients with urge incontinence to exclude the presence of stones as the primary cause. Urge incontinence may present with frequency, which is defined as urinating more than eight times in the 24 hours. • stress incontinence: leaking small amounts when coughing or laughing coughing, sneezing, and laughing ↑intra-abdominal pressure and overwhelm the strength of bladder sphincter muscles in those with weak pelvic floors.

 Outlet incompetence in stress incontinence is due to: urethral hypermobility or intrinsic sphincteric deficiency. most common in younger women. There is an increased risk of stress incontinence with pregnancy Obesity ↑pressure on pelvic tissues weakening of pelvic structures. • mixed incontinence: both urge and stress • overflow incontinence: causes bladder outlet obstruction, e.g. prostate enlargement Neurogenic bladder (detrusor areflexia) characterized by: absent bladder sensation, decreased tone, increased capacity, hesitancy, and significant residual urine. caused by : diabetes mellitus, multiple sclerosis, cerebrovascular disease (Upper motor neuron lesions) affect descending pathways from the brain delayed bladder sensation urinary retention overflow incontinence. Parkinson's disease, spinal injuries (damage to the conus, cauda equina, and sometimes S2-4 nerve roots) diagnosis Cystometry is the gold standard for the diagnosis increased post-void residual urine on catheterization or ultrasound. Treatment relieve obstruction e.g. catheterization Sacral nerve stimulation can be used for the management of patients with idiopathic detrusor inactivity Investigation • bladder diaries should be completed for a minimum of 3 days • vaginal examination to exclude cystocele • urine dipstick and culture • urodynamic studies Management depends on whether urge or stress UI is the predominant picture. • If urge incontinence is predominant: bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding) bladder stabilising drugs: (antimuscarinic) is first-line modern anticholinergics (Solifenacin) are recommended vs traditional agents, such as oxybutynin: Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative antimuscarinics (e.g. Oxybutynin, Tolterodine) the usual treatment for urge incontinence are contraindicated in patients with a history of urinary retention.

 because oxybutynin is thought to have particularly negative effects on cognitive function in the elderly. A meta-analysis has shown that the class as a whole may affect the long-term risk of dementia. As such, dose titration to the minimum level required to control symptoms is recommended. Oxybutynin is an effective treatment for detrusor instability and is a parasympathetic muscarinic antagonist. dry mouth is a problem in up to 70% of cases. not recommended for elderly because it is the most negative of the anticholinergic class with respect to its effects on cognitive function. In older men, tolterodine is preferred to oxybutynin as the latter has a greater risk of causing confusion. If anticholinergics fail or are contraindicated, mirabegron may be trialled. Mirabegron activates the β3 adrenergic receptor in the detrusor muscle in the bladder, which leads to muscle relaxation and an increase in bladder capacity surgical management: e.g. sacral nerve stimulation indicated if not respond to pharmacological intervention or unable to tolerate it. • If stress incontinence is predominant: pelvic floor muscle training: NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months surgical procedures: e.g. retropubic mid-urethral tape procedures Which pharmacotherapies represents the most appropriate initial management step for overactive bladder? Tolterodine MRCPUK-part-2-March 2017: A 72-year-old woman with urinary incontinence. Urodynamic studies confirm detrusor overactivity and significant post-voiding residual volume. She is unable to tolerate oxybutynin for bladder control due to postural hypotension and GI symptoms. what is the most appropriate intervention for control of her bladder symptoms? Sacral nerve stimulator MRCPUK-part-2-March 2018: A 74-year-old woman with urge incontinence. Urine dipstick testing and post-void residual bladder volume are normal. Routine urea and electrolytes are also normal. She has attempted bladder training exercises but has not managed to improve her symptoms. What is the most appropriate next step? Solifenacin modern anticholinergics (Solifenacin) are recommended vs traditional agents, such as oxybutynin, because oxybutynin is thought to have particularly negative effects on cognitive function in the elderly.

Urinary retention • Drug causes Amitriptyline has anticholinergic effects being associated with tachycardia, dry mouth and urinary retention. These features are not typical of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or seratonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine with urinary retention and dry mouth rarely reported. Diazepam, a benzodiazepine does not have anticholinergic effects. It has been associated with urinary retention, but this is much less common than with anticholinergics. • Complication of recovery from obstructive uropathy: Amelioration of urinary obstruction and subsequent recovery initially results in a large electrolyte and water loss. And over the next few days as the tubules recover their function his urine will begin to concentrate appropriately. The main approach to management in such patients is to ensure they remain adequately hydrated while their kidneys recover their ability to concentrate urine and manage fluid balance. Supplement oral intake with intravenous fluids The patient should not be fluid restricted as this would lead to severe dehydration. Osmotic cerebral changes precipitated by urinary sodium loss, the major

intravascular cation, is the cause of drowsiness. Hypocalcaemia and hypomagnesaemia may occur as tubular reabsorption is suboptimal in the early stages of recovery but is unlikely to affect conscious level. Acid-base status should improve after relief of the obstruction.

Benign prostatic hypertrophy (BPH) Risk factors • Age: around 50% of 50-year-old men will have evidence of BPH and 30% will have symptoms. Around 80% of 80-year-old men have evidence of BPH • Ethnicity: Black > White > Asian Features BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorized into: • Voiding symptoms (obstructive): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying • Storage symptoms (irritative) urgency, frequency, urgency incontinence and nocturia • Post-micturition: dribbling • Complications: urinary tract infection, retention, obstructive uropathy Investigations • If the suspicion is of prostatic hypertrophy, then post-void residual volume is the best way to estimate the degree of bladder obstruction. Management options • Watchful waiting • Medication:

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 α-blocker (e.g. tamsulosin, alfuzosin) for rapid symptom relief Considered first-line, improve symptoms in around 70% of men α-Blockers relax the smooth muscle of the bladder neck and can improve urinary flow rates ↓ smooth muscle tone (prostate and bladder) Adverse effects: dizziness, postural hypotension, dry mouth, depression 5 α-reductase inhibitors (e.g. finasteride and dutasteride) to reduce prostate volume Block the conversion of testosterone to dihydrotestosterone (DHT), which induces BPH Unlike α-1 antagonists causes a reduction in prostate volume and hence may slow disease progression. This however takes time and symptoms may not improve for 6 months. They may also ↓ PSA concentrations by up to 50% Adverse effects: erectile dysfunction, ↓ libido, ejaculation problems, gynecomastia The use of combination (α-1 antagonists, 5 α-reductase inhibitors) therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial • Surgery: transurethral resection of prostate (TURP)

Prostatic carcinoma A man of advanced age presenting with bony metastases is most likely to have metastatic prostate cancer. Overview • These are adenocarcinomas • hormonal factors are thought to play a part in the aetiology • As a rule, prostate cancer is more aggressive in younger men. • Prostate cancer begins in the outer peripheral zone of the prostate, and grows outward, invading surrounding tissue. BPH begins in an area of the inner prostate called the transition zone, a ring of tissue that makes a natural circle around the urethra. In BPH, the growth is inward toward the prostate’s core. Epidemiology • Prostate cancer is now the most common cancer in adult males in the UK and is the second most common cause of death due to cancer in men after lung cancer. • By 80 years of age some 80% of men appear to have malignant foci within the prostate gland • Prostatic carcinoma is found in 10-30% of patients with BPH.

Risk factors (BPH is not a risk factor) • ↑age (the strongest risk) • obesity • High intake of animal fats Features • Localised prostate cancer is often asymptomatic. This is partly because cancers

tend to develop in the periphery of the prostate and hence don't cause obstructive symptoms early on. • bladder outlet obstruction: hesitancy, urinary retention • haematuria, haematospermia • pain: back, perineal or testicular • digital rectal examination: asymmetrical, hard, nodular enlargement with loss of median sulcus Investigation (NICE 2015) assess for prostate cancer • lower urinary tract symptoms or • erectile dysfunction or • visible haematuria } (PSA) test and digital rectal examination • Prostate-specific antigen (PSA) (PSA) may be elevated in: Prostatitis Benign prostatic hyperplasia, and Prostate cancer. Some prostatic carcinomas may not be associated with an elevated PSA. False positives PSA associated with: UTI & catheterisation thus should be measured at least two weeks after a treated UTI. prostatic needle biopsy PR examination False negatives PSA: Finasteride is the only factor likely to decrease the level of serum PSA. • Trans-rectal prostatic biopsy The most commonly used pathological grading system is the Gleason score The most well differentiated tumours have a Gleason score of 2, and the most poorly differentiated a Gleason score of 10. • Bone scan, CT abdomen and pelvis also indicated to assess both extent of bony metastases and local spread. (metastases may mimic the appearance of Paget's) Notes & Notes for MRCP
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• low intake of selenium • Afro-Caribbean ethnicity • family history: 5-10% of cases have a strong family history Refer for P. cancer ↑ PSA (within 2 weeks)

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Management: depends on histological grading of the tumour prostate cancer stage Treatment options Localised (T1/T2) T1 - clinically unapparent disease T2 - palpable disease confined to prostate • conservative: active monitoring & watchful waiting • radical prostatectomy • radiotherapy: external beam and brachytherapy Localised advanced (T3/T4) T3 = beyond prostatic capsule T4 = involves bladder neck or rectum Most men will have occult mets hormonal therapy Metastatic binding from intracytoplasmic protein complexes Orchidectomy • Synthetic GnRH agonist (Buserelin, Goserelin, leuprolide) Decreased androgen production gonadotrophin releasing hormone agonist that exerts its actions at the level of the pituitary gland. Initially treatment causes increased gonadotrophin release; however, after a few weeks of continued therapy, gonadotrophin production is inhibited, and testosterone levels fall. The initial increase in testosterone levels may be accompanied by a ‘flare’ in disease symptoms in some patients. • docetaxel-based chemotherapy indicated only for patients with hormone-refractory cancer. • Samarium-153 is a radionuclide useful in treating prostate cancer with painful bone metastases and is not useful when the patient is asymptomatic. What histological grading system is used to grade prostate cancer? Gleason grading Gleason grading takes account of the most prevalent tumour pattern in the pathological system (1-5) and the second most prevalent tumour pattern (1-5). It is presented as, for example, Gleason 3+4 = 7. This is important as a Gleason 4+3 = 7 obviously has a worse prognosis than a Gleason 3+4 = 7 even though they both have the same total score.

Renal cell cancer (RCC) (also known as hypernephroma) Classical triad: haematuria, loin pain, abdominal mass Overview • usually arise from the epithelial cells of the proximal convoluted tubule. • Clear cell RCC is the most common histological variant (~80% of all cases). • Most cases are sporadic, although positive family history increases risk 4-fold. Notes & Notes for MRCP
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• hormonal therapy: see below • radical prostatectomy • radiotherapy: external beam and brachytherapy • Synthetic GnRH agonist e.g. Goserelin (Zoladex) and Leuprolide cover initially with anti-androgen to prevent rise in testosterone • Anti-androgen such as bicalutamide, or flutamide cyproterone acetate prevents DHT

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Epidemiology • Most common malignancy of the renal parenchyma (85% of renal cancers in adults are RCC) • Sex: ♂ > ♀ (~2:1) • Age of onset: 60–80 years Associations • smoking • von Hippel-Lindau syndrome (the most likely inherited condition) is an inherited syndrome in which cysts or tumours in the kidney, pancreas, adrenal gland, epididymis, cerebellum, and spinal cord may form. (30 - 50% develops renal cell tumors) • tuberous sclerosis • incidence of renal cell cancer is only slightly increased in patients with autosomal dominant polycystic kidney disease Features • Often asymptomatic and diagnosed incidentally. • the classical triad of: Haematuria, Loin pain, A palpable mass. only 5–10%of patients present with all three components of the triad Haematuria is the most common presenting symptom (50-60% of cases) • Anaemia (common) Fatigue • Symptoms of local spread left varicocele (due to occlusion of left testicular vein) Budd-Chiari syndrome: (due to hepatic vein obstruction hepatomegaly, ascites, lower limb edema, hepatic dysfunction) • Paraneoplastic syndromes: may secrete renin Hypertension may secrete erythropoietin (polycythaemia) Increased plasma viscosity. may secrete parathyroid hormone (hypercalcaemia), may secrete ACTH Secondary hypercortisolism myopathy • Symptoms of metastatic disease 25% have metastases at presentation Commonest sites of metastases are lung (50-60%) and bone (30-40%) • pyrexia of unknown origin • Urinalysis may show sterile pyuria Investigations • Ultrasound scan of the renal tract the first investigation of choice, as it is able to pick up 95% of renal cell carcinomas greater than 1 cm in diameter. It would also exclude infective or inflammatory collections within the renal tract. • CT abdomen/pelvis (contrast- enhanced CT) Definitive test for diagnosis and staging of RCC. If clinical presentation or ultrasound findings are suspicious for RCC, CT imaging is essential. • MRI abdomen/pelvis Modality of choice for diagnosis and staging in patients where contrast dye is contraindicated (due to renal insufficiency or allergy).

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Management • for confined disease: partial or total nephrectomy depending on the tumour size no role for adjuvant therapy after surgery • for metastatic disease: Targeted molecular therapy receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) first line therapy have been

shown to have superior efficacy compared to interferonalpha recommended by NICE as a treatment for advanced renal cell carcinoma. Sunitinib is superior to interferon alfa in improving progression-free survival. Also, interferon alfa has significant toxicity. Prognosis • Prognosis is related to tumour staging: the 5-year survival rate is around 80-100% in those with TNM stage-1 lesions, but this falls to 5-10% in those with stage-4 lesions • Risk of distant relapse remains 30% for curatively resected renal cell carcinoma. Wilms' tumour • Wilms' nephroblastoma is one of the most common childhood malignancies. • typically presents in children under 5 years of age, with a median age of 3 years old. • primarily composed of blastema, which is primitive kidney mesenchyme. Features • abdominal mass (most common presenting feature) • painless haematuria • flank pain • hypertension • other features: anorexia, fever • unilateral in 95% of cases • metastases are found in 20% of patients (most commonly lung) • Histologic examination is characterized by blastemal, stromal, and epithelial cells (triphasic tumor). Associations • Beckwith-Wiedemann syndrome • as part of WAGR syndrome with Aniridia, Genitourinary malformations, mental Retardation • hemihypertrophy • around one-third of cases are associated with a mutation in the WT1 gene on short arm of chromosome 11 Management • nephrectomy • chemotherapy • radiotherapy if advanced disease prognosis: • good, 80% cure rate

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Angiomyolipoma Overview • the most common benign tumour of the kidney • is a benign hamartomatous tumor composed of blood vessels, smooth muscle cells and fat cells. • caused by mutations in either the TSC1 or TSC2 genes, which govern cell growth and proliferation. Association • commonly seen among patients with tuberous sclerosis. • also commonly found in women with the rare lung disease lymphangioleiomyomatosis. Presentation: • retroperitoneal hemorrhage (most frequent) • unilateral flank mass. Diagnosis • There are three methods of scanning that detect angiomyolipoma: ultrasound, CT and MRI. • Ultrasound is standard and is particularly sensitive to the fat in angiomyolipoma but less so to the solid components. However it is hard to make accurate measurements with ultrasound. • CT is very detailed and fast and allows accurate measurement. However, it exposes the patient to radiation and the dangers that a contrast dye used to aid the scanning may itself harm the kidneys. • MRI is safer than CT but many patients (particularly those with the learning difficulties or behavioural problems found in tuberous sclerosis) require sedation or general anaesthesia and the scan cannot be performed quickly. • Biopsy Some other kidney tumours contain fat, so the presence of fat isn't diagnostic. It can be difficult to distinguish a fat-poor angiomyolipoma from a renal cell carcinoma and a lesion growing at greater than 5 mm per year may warrant a biopsy in order to distinguish it from this form of cancer. Treatment • Large angiomyolipoma can be treated with embolisation. • do not normally require surgery unless there is life-threatening bleeding

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Bladder cancer Epidemiology • In the Western world transitional-cell (TCC) 93% of bladder cancers squamous-cell carcinomas (SCCs) 6% adenocarcinomas less than 1% • male: female ratio 3:1 • women generally have a worse prognosis than men. Use of cyclophosphamide in granulomatosis with polyangiitis is associated with increased risk of bladder cancer (transitional cell carcinoma)

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• At the time of diagnosis around 70% of carcinomas are still localised to the bladder, 20% extend to involve regional lymph nodes and 3% present with distant metastases Risk factors • Risk factors for transitional cell carcinoma of the bladder include: Smoking Exposure to aniline dyes in the printing and textile industry Rubber manufacture (exposure to nitrosamines (used in the manufacture of some cosmetics, pesticides, and in most rubber products)) Cyclophosphamide • Risk factors for squamous cell carcinoma of the bladder include: Schistosomiasis Calmette-Gurin (BCG) treatment Smoking Diagnosis • Cystoscopy is the gold standard for diagnosing bladder cancer. Treatment • Treatment of choice for localised tumours is transurethral tumour resection, with the use of intravesical chemotherapy. • Intra-vesical instilling of BCG has virtually replaced cystectomy in the treatment of bladder carcinoma in situ. Orthotopic bladder reconstruction for carcinoma of the bladder: • Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons. Associated electrolyte abnormalities may include hypokalemia, hypocalcaemia, and hypomagnesaemia. it's usually improves with time and is mild. treat metabolic acidosis with intravenous fluids and bicarbonate. Intravenous infusion of 1.26% sodium bicarbonate and potassium replacement Metabolic acidosis associated with bladder reconstruction (e.g: for carcinoma of the bladder). • Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild. • Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient. • Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and treat metabolic acidosis with intravenous fluids and bicarbonate.

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Rhabdomyolysis Overview • Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission Pathophysiology • muscle trauma or necrosis myoglobin (a muscle protein), which may cause tubular damage or blockage, intense renovascular constriction, and local inflammation Acute renal failure • Rhabdomyolysis is strongly suggested by the fact that urinalysis is strongly positive for blood, whereas urine microscopy is negative for red blood cells. The positive urinalysis is caused by myoglobin, a muscle protein released during muscle damage; this appears in the urine and can cause acute renal failure. Causes • seizure • collapse/coma (e.g. elderly patients collapses at home, found 8 hours later) • ecstasy • Crush injury: electrical injury, compartment syndrome, prolonged limb or tourniquet anaesthesia, extensive surgical dissection and infectious or inflammatory myopathies. • McArdle's syndrome • Metabolic myopathy should be suspected when myoglobinuria is recurrent, associated with exercise or fasting and occurring with muscle

cramps or weakness Carnitine palmitoyltransferase (CPT) deficiency is the commonest cause of inherited metabolic myopathy resulting in recurrent myoglobinuria The enzyme defect is diagnosed using ischaemic forearm testing and muscle biopsy, which demonstrates abnormal lipid or glycogen deposits • Drugs: statins (should be stopped in any patient presenting with the syndrome.) Statins are metabolised via the CYP3A4 pathway. Drugs that inhibit its action and lead to excess statin toxicity include macrolide antibiotics such as clarithromycin. It is important to note that atorvastatin (as a more hydrophilic agent) is less metabolised by CYP3A4 and hence the side effects of this combination are less profound. Features The biochemical features of rhabdomyolysis are raised creatine kinase, hypocalcaemia (especially early after injury), hyperkalaemia and acute kidney injury. • acute renal failure with disproportionately raised creatinine • elevated CK , detectable a few hours after injury and peaks at the 48-h stage • myoglobinuria, on urine dipstick (shows as haematuria), Urine is dark due to myoglobin. Rhabdomyolysis can result from co-prescription of clarithromycin and statins

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 Dipstick will be positive for blood (a false positive). On microscopy no red cells are seen although there may be pigmented granular casts. Dipstick is the most quickly test for diagnosis • hypocalcaemia (myoglobin binds calcium) • elevated phosphate (released from myocytes) • hyperuricaemia • hyperkalaemia • metabolic acidosis in severe cases secondary to raised serum lactic acid levels from the ischaemic muscle fibres. The serum lactate is raised which would suggest an acidotic picture over a normal blood gas picture Management • IV fluids to maintain good urine output • urinary alkalinization is sometimes used

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Loin pain-haematuria syndrome • characterised by severe, unrelenting loin or flank pain and haematuria with dysmorphic features suggesting a glomerular origin • A recent report suggested an important psychological component (unexplained somatic symptoms, an adverse psychological event preceding the onset of pain and a history of greater analgesic ingestion) • One possible explanation for the haematuria in some patients is coexistent thin basement membrane disease. • It was proposed that bleeding into and obstruction of the renal tubules was responsible for the loin pain • Management difficult to treat Dependency on narcotic analgesia is common Some patients undergo autotransplantation of the affected kidney in an attempt to relieve the pain

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Renal tuberculosis • accounts for 15-20% of extra-pulmonary tuberculosis • The combination of sterile pyuria, haematuria, dysuria and renal tract calcification is highly suggestive of renal tuberculosis • Many patients have refractory hypertension, which is renin-mediated and presumably due to segmental renal ischaemia • Excretion urography is the most helpful diagnostic investigation, may show cavitating lesions in the renal papillary areas, commonly with calcification. There may also be evidence of ureteral obstruction with hydronephrosis

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Xantho-granulomatous pyelonephritis (XGP) Pathogenesis • It develops as an abnormal macrophage response to infection, particularly in the presence of urinary tract obstruction, and is pathologically related to malacoplakia Clinical features • A flank mass is usually palpable, thereby distinguishing it from simple acute pyelonephritis or renal abscess, and occasionally mimicking renal cancer • The disease is almost invariably unilateral • Patients with XGP often appear chronically ill

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• Symptoms include anorexia, fevers, weight loss and flank pain Diagnosis • The relatively rapid history, leukocytosis, renal impairment and positive urine culture make XPN much more probable than cancer • Computed tomography is the investigation of choice to confirm the diagnosis, and it will show the replacement of renal parenchyma by rounded, low-density areas surrounded by a ring of enhancement; it will also establish the extent of the lesion (which may involve surrounding structures) Prognosis and complications • The course may extending over months or years • AA amyloid may develop, resulting in the onset of nephrotic syndrome

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Vesico-ureteric reflux Vesico-ureteric reflux management: • in childhood: surgical intervention would be beneficial. • When picked up in adulthood, the mainstay of management would be blood pressure control Strict glycaemic control (reduce the frequency of recurrent infections and reduce the risk of progression to diabetic nephropathy.) prompt treatment of UTI and careful surveillance during pregnancy. • Vesicoureteric reflux refers to the retrograde flow of urine from the bladder to the upper urinary tract • It is the most common cause of recurrent urinary tract infections in children. It is identified in approximately 40% of patients. • This may occur due to incompetence of the valve at the vesicoureteric junction • It is most commonly detected the earliest in newborn girls • Present with recurrent UTI • Micturating cystourethrography is the most useful investigation to check for vesicoureteric reflux during voiding in children. It is identified in approximately 40% of patients. (not useful in adult women because by this time the reflux tends to disappear) • the single most appropriate management for grade-V vesicoureteric reflux in child less than 1 year Antibiotic prophylaxis grade Age(year) scaring Initial treatment Follow up V < 1 No Antibiotic prophylaxis Surgery V 1-5 No If unilateral: antibiotic prophylaxis Surgery V 1-5 No If bilateral: surgery V 1-5 Yes Surgery V

> 5 Surgery Grading of vesicoureteric reflux grade Description I Reflux into a non-dilated ureter II Reflux into the upper collecting system without dilatation III Reflux into a dilated ureter and/or blunting of calyceal fornices IV Reflux into a grossly dilated ureter V Gross dilatation of the ureter, renal pelvis and calyces; calyces show loss of papillary impression

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Chronic reflux nephropathy (Chronic pyelonephritis) • Chronic pyelonephritis is also known as 'reflux nephropathy': • starts in infancy or early childhood, • predisposes to recurrent infections and progressive renal fibrosis and loss of function • the kidneys are small, shrunken and scarred Renal scarring • is a serious complication of chronic pyelonephritis that occurs due to vesicoureteric reflux. • It is mediated by cytokines, chemokines and their receptors, complement, adhesion molecules and extracellular matrix proteins. • The cytokines which seem to play the largest role are: interleukin (IL)-1beta, IL-3 Transforming growth factor (TGF)-beta. TGF-beta in particular seems to be pro-fibrotic by recruiting fibroblasts, In a genotype where its production is limited has been shown to be less likely to develop renal scarring. • Chronic reflux nephropathy should be suspected in the presence of multiple urinary tract infections, including during childhood • may present with difficult-to-treat hypertension in young age • The investigation of choice is excretion urography (Micturating cystourethrogram), which may show : an irregular renal outline, calyceal clubbing and cortical scarring on the affected side • The best course of action is to recognise this condition in childhood and consider surgical management where demonstrable ureteric reflux exists, or early intervention with antibiotics where repeat infection exists • Chronic reflux nephropathy is a relatively common cause of end-stage renal failure in late childhood or early adult life if it goes unrecognized Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis • Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis. • Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis. • Perform ultrasound of the upper urinary tract to exclude obstructive pyelonephritis. • Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis. (European association of urology)

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Phimosis • Phimosis is common in 2-year olds • Prognosis and management Most will slowly dilate, thus Wait and watch is the most appropriate treatment In those who have persistent problems into teenage years, around 85% will respond to topical steroids, reducing the need for circumcision Where there is obvious infection, a dorsal slit may be considered

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Urethral syndrome • The condition is common in elderly postmenopausal women due to dryness and atrophy of the urethral tissue • Presented with dysuria , increased frequency of micturition and sterile urine. • Treatment: Topical oestrogen cream often results in a dramatic response

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Urinary tract infection (UTI) in adults Classification of UTI (European association of urology guidelines) Uncomplicated UTIs Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.

Complicated UTIs All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes. Recurrent UTIs Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Catheterassociated UTIs UTIs in a person currently catheterised or has been catheterised within the past 48 hours. Urosepsis A systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia. Features • classic symptoms of (UTI):dysuria, frequency of urination, suprapubic tenderness, urgency, polyuria, haematuria • upper urinary tract infection (UUTI): evidence of UTI with symptoms suggestive of pyelonephritis (loin pain, flank tenderness, fever, rigors or other manifestations of systemic inflammatory response). • lower urinary tract infection (LUTI): evidence of UTI with symptoms suggestive of cystitis (dysuria or frequency without fever, chills or back pain). Causes of UTI: • Escherichia coli is the first most common • Staphylococcus saprophyticus is the second most common cause of UTI in sexually active women

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Nephrology Diagnosis • Diagnosis of UTI is primarily based on symptoms and signs. Bacteriuria or pyuria do not establish the diagnosis of UTI. • The gold standard test for diagnosis of bacteriuria is culture of bladder urine obtained by needle aspiration of the bladder as it minimises the risk of contamination of the urine specimen. All other techniques (urethral catheter and midstream specimens of urine) carry a higher risk of contamination and therefore produce some false positive results • Nitrite test: Gram negative organisms test positive on the nitrite test as they convert nitrates to nitrites for energy. Gram positive organisms are unable to reduce nitrate to nitrite and therefore, test negative. • UTI is usually diagnosed by a bacterial count of >100 000/ml at mid-stream urine (MSU) • Presentation with a first urinary tract infection associated with haematuria in elderly patient Re-testing of urine with cytological examination after antibiotics • Sterile pyuria and negative urine cultures suggest urinary tract infection by the bacteria Neisseria gonorrhoeae or Chlamydia trachomatis. • Persistent haematuria should be investigated with excretion urography and cystoscopy If the mid-stream urine (MSU) reveals bacteriuria, in asymptomatic pregnant lady. what is the most appropriate intervention? Repeat sample NICE guidelines recommend a second confirmatory sample to be sent before initiating treatment. Recommendations for the diagnostic evaluation of uncomplicated cystitis (European association of urology) Diagnose uncomplicated cystitis based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated urinary tract infections. Use urine dipstick testing, as an alternative to culture for diagnosis of acute uncomplicated cystitis. Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within two-four weeks after the completion of treatment; • women who present with atypical symptoms; • pregnant women. Management (Sign.uk recommendations for UTI 2012) • Men urine sample should be taken for culture. empirical antibiotics with a quinolone in men with symptoms suggestive of prostatitis. • Non-pregnant women LUTI Symptomatic bacteriuria

 three-day course of trimethoprim or nitrofurantoin.

 Amoxicillin, ampicillin, nitrofurantoin and oral cephalosporins may be considered as alternatives Routine urine culture is not required to manage If not respond to trimethoprim or nitrofurantoin urine for culture to guide change of antibiotic asymptomatic bacteriuria Do not treat with an antibiotic. Recurrent UTI consider using cranberry products to reduce the frequency of recurrence. UUTI ciprofloxacin (7 days) or co-amoxiclav (14 days). Acute pyelonephritis hospital admission should be considered the BNF currently recommends a broad-spectrum cephalosporin or a quinolone (for non-pregnant women) for 10-14 days • Pregnant women: Treat symptomatic and asymptomatic UTI Urine culture before starting empiric antibiotic and 7 days after completion empiric antibiotic treatment. First line agent Nitrofurantoin A dose of 50 mg QDS or 100 mg BD of modified release for 7 days is recommended. Care for nitrofurantoin elderly patients may be at increased risk of toxicity. contraindicated in significant renal impairment. The BNF advises against its use in patients with GFR<60. Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate). Second line Trimethoprim contra indicated in established folate deficiency, low dietary folate intake, or women taking other folate antagonists. Third line cephalosporins There is 20% cross-over with respect to allergy to penicillin and cephalosporins. Complications asymptomatic bacteriuria is associated with premature delivery and low birthweight. routine screening for asymptomatic bacteriuria at antenatal appointments is therefore recommended. Infections in pregnancy should be treated, as 25% of patients will develop acute pyelonephritis

Nephrology

UTI in diabetes Data from the American Diabetes Association have shown that 9.4% of people diagnosed with type 2 diabetes had a UTI compared to only 5.7% of those without. The most common pathogens isolated from the urine of diabetic patients with UTI were E. coli and other Enterobacteriaceae such as Klebsiella spp., Proteus spp., Enterobacter spp. and Enterococci. Infection with Extended spectrum beta-lactamase-producing coli (ESBLproducing E. coli) is an increasingly recognised cause of infection in diabetes patients and is associated with poor outcomes. Carbapenems are generally considered the drug of choice for the treatment of ESBL/E. coli (ESBL–EC) infections With a half-life of 4 h, ertapenem is commonly used as it is administered only once daily. Fosfomycin is an oral antibiotic agent that has broad activity against multidrug-resistant pathogen, including ESBL–EC. Another oral antimicrobial agent that can be considered for the treatment of ESBL-EC cystitis is nitrofurantoin. Extended spectrum beta lactamase (ESBL) urine infection Intravenous meropenem What is the next step in management of first episode of UTI in elderly after treatment with antibiotics? Re-testing of urine with cytological examination after antibiotics UTI may develop in patients with an underlying urothelial tumour. Persistent haematuria should be investigated with excretion urography and

cystoscopy. Bladder tumours are around 50 times more common than tumours of the ureter or renal pelvis. Antibiotic guidelines for urinary tract: The following is based on current BNF guidelines: Condition Recommended treatment Lower urinary tract infection Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin Acute pyelonephritis Broad-spectrum cephalosporin or quinolone Acute prostatitis Quinolone or trimethoprim

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Asymtomatic bacteriuria (ABU) Risk factors for asymptomatic bacteriuria • Female sex • Sexual activity • Comorbid diabetes • Age • Institutionalisation • Presence of catheter

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Recommendations for the management of ABU (European association of urology) • Do not screen or treat asymtomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with catheters in the urinary tract; • patients with renal transplants; • patients prior to arthoplasty surgeries; • patients with recurrent urinary tract infections. • Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa. • Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment. • Take a urine culture following treatment of asymptomatic bacteriuria to secure treatment effect.

UTI in childhood • In up to 75% cases of single infection, no abnormality can be found • Escherichia coli is the most common organism isolated (> 70% of cases) • Chronic diarrhoea or even acute diarrhoea can be a presenting feature of childhood urinary tract infection • Trimethoprim is often the best initial antibiotic of choice • In children (particularly neonates and infants), UTI can be haematogenous and may be part of a septicaemic process, therefore, blood cultures and iv antibiotics are necessary

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Recurrent urinary tract infection (rUTI) Definition • two episodes of infection in six months, or three episodes in one year Recurrent bacteriuria: • Relapse diagnosed by the recurrence of bacteriuria with the same organism within 7 days of completing antibacterial treatment and implies failure to eradicate infection. usually occurs in conditions in which it is difficult to eradicate the bacteria, such as: renal stones, scarred kidneys, polycystic disease or bacterial prostatitis. • Reinfection occurs when bacteriuria is absent after treatment for at least 14 days, usually longer, followed by recurrence of infection with the same or a different organism. Incidence • annual incidence of a single UTI is 30 per 1000 women, with 44% experiencing recurrence within 12 months Risk factor Age-related risk factors for rUTI in women

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Young and pre-menopausal women Post-menopausal and elderly women • Sexual intercourse • Use of spermicide • A new sexual partner • A mother with a history of UTI • History of UTI during childhood • Blood group antigen secretory status • History of UTI before menopause • Urinary incontinence • Atrophic vaginitis due to oestrogen deficiency • Cystocoele • Increased post-void urine volume • Blood group antigen secretory status • Urine catheterisation and functional status deterioration in elderly institutionalised women • Sexual activity in young females Recurrent cystitis may often accompany the onset of sexual activity in young females The appropriate first-line management is to advise strict attention to personal hygiene, and an increase in fluid intake and subsequent urine flow around times of sexual activity • Vesicoureteric reflux • Chronic reflux nephropathy: the best diagnostic investigation is Micturating cystourethrogram • Posterior urethral valves the chief complaint of children with this disorder is a poor urinary stream • Urinary tract obstruction in BPH: post-void residual volume is the best way to estimate the degree of bladder obstruction Diagnosis of rUTI • should be confirmed by urine culture. • Do not perform an extensive routine workup in women with recurrent UTI without risk factors. (European association of urology) Treatment • After treating the acute infection, low dose antibiotics for 6-12 months are the most evidence based preventive measure for recurrent (UTI) in women and are recommended by Scottish Intercollegiate Guidelines Network and the European Association of Urology guidelines as the standard of care. Prevention (European association of urology) • Non-antimicrobial interventions behavioural modifications vaginal oestrogen replacement in post-menopausal women Immunoactive Prophylaxis (in all age groups) bacterial extracts to stimulate the host’s immune system to produce antibodies e.g. Oral immunostimulant OM-89 • Antimicrobial prophylaxis (continuous or post-coital) When non-antimicrobial interventions have failed, continuous or post-coital antimicrobial prophylaxis should be used. For patients with good compliance, self-administrated short-term antimicrobial therapy should be considered.