Approaching glomerular disease

Introduction

Glomerulonephritis (GN) is classified by clinical syndrome/presentation (e.g. nephritic or nephrotic syndrome), histological appearance (e.g. minimal change disease), or by aetiology (e.g. post-streptococcal GN) (see Fig. 7.1).

Clinical syndromes

For further investigation of these clinical syndromes, see 🕮 Chapter 1.

- Asymptomatic urinary abnormalities (🕮 pp. 58 and 66).
- Acute nephritis (🕮 p. 71).
- Nephrotic syndrome (🕮 p. 554).

These may all be accompanied by ↑ BP ± renal impairment.

Dipstick-positive proteinuria (🕮 p. 58)

Common. Usually detected on routine urinalysis. A positive dipstick for haematuria or proteinuria should be repeated (e.g. after 1–2 weeks). Transient proteinuria is not uncommon, esp. in concentrated urine. If persistent, verify with an albumin to creatinine ratio (uACR) or protein creatinine ratio (uPCR) (🕮 p. 21).

Microscopic haematuria (🕮 p. 66)

Dipstick analysis is very sensitive but non-specific. If persistent, ideally arrange urine cytology to confirm haematuria (defined as >2 RBC/hpf), and examine red cell morphology. Dysmorphic red cells, red cell casts, and fragmented red cells (acanthocytes) imply glomerular bleeding (🕮 p. 22).

Urine microscopy will also reveal pyuria and other forms of cast. Urine culture will exclude infection.

Haematuria and proteinuria (🕮 p. 61)

Suggests a glomerular lesion, although independent investigation of the haematuria may be necessary in patients aged >40 (🕮 p. 67).

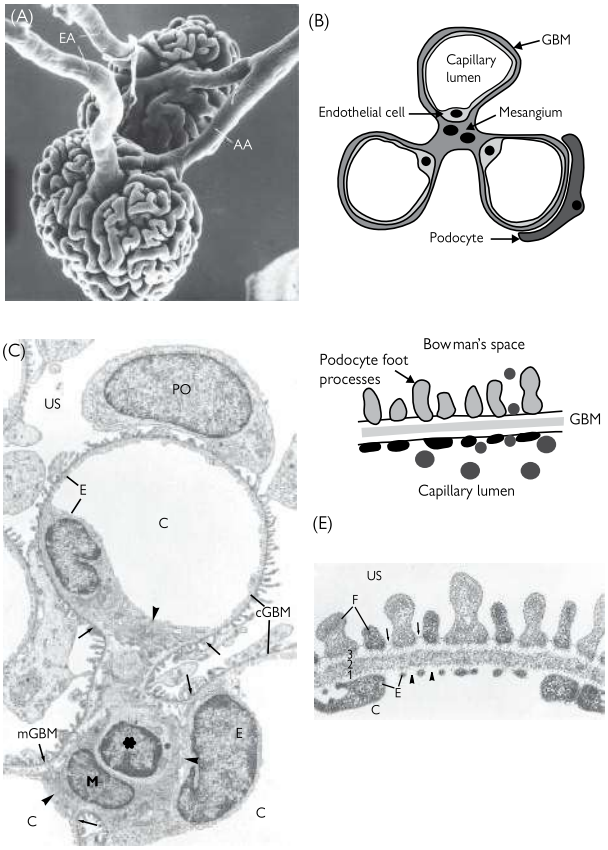

Fig. 7.1 (A) Glomerular vessels: AA, afferent arteriole; EA, efferent arteriole. (B) Cartoon of the glomerular capillaries: GBM, glomerular basement membrane. (C) EM of glomerular capillaries: C, capillary; E, endothelial cell; cGBM, capillary GBM; mGBM, mesangial GBM; PO, podocyte; US, ultrafiltration space. (A–C). (D) Cartoon of glomerular filter. (E) EM of glomerular filter: F, podocyte foot process. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P, *et al.* (2005), *Oxford Textbook of Clinical Nephrology*. Oxford University Press, Oxford.

Histology of glomerular disease

Introduction

Renal tissue is sampled via renal biopsy (📖 p. 80) and prepared for:

- Light microscopy: various histochemical stains (e.g. H+E, periodic acid–Schiff (PAS), Jones (silver) stains). Useful for morphology, chronicity, and diagnosis.
- Immunohistochemistry: usually by immunofluorescence but also immunoperoxidase staining. Localizes immune reactants (particularly immunoglobulins or complement fractions) within glomeruli, using fluorescein-labelled antibodies. The nature and pattern of staining are characteristic for particular glomerular lesions.
- Electron microscopy (EM): useful for examining cell and basement membrane structure and for characterizing glomerular deposits.

The language of glomerular disease

When examining a preparation of renal cortex, several glomeruli (10–30, on average) are sampled. The following descriptive terms (see Fig. 7.2) are then used:

- *Focal or diffuse?*
  - *Focal* lesions affect some (<50%) of sampled glomeruli, but not all.
  - *Diffuse* lesions involve most (>50%) glomeruli, if not all.
- *Segmental or global?*
  - Segmental lesions affect *part* of an affected glomerulus.
  - Global lesions involve *most* of the glomerular tuft.
- *Proliferative or not?*
  - *Proliferative* lesions describe an increase in local cell number; for instance, an increase in mesangial cells ('mesangial proliferative') is a feature of IgA nephropathy.
- *Crescentic or not?*
  - Glomerular parietal epithelial cells (lining Bowman's capsule) proliferate in response to local inflammatory and procoagulant signals, with fibrin deposition and adhesions filling some, or all, of Bowman's space (→'crescent').
- *Matrix or membrane?*
  - Expansion of matrix produced by mesangial cells, as seen in IgA nephropathy, or increase in GBM width (and thus capillary wall thickness) characteristic of immune deposits.
- *Necrosis or sclerosis?*
  - *Necrosis* refers to fresh cell death as a result of ongoing injury.
  - *Sclerosis* reflects a scarred glomerulus or glomerular segment.

Examples

Focal and segmental glomerulosclerosis affects some glomeruli, but not all, and only part of any affected tuft. The disease leads to scarring within glomeruli.

Diffuse proliferative crescentic glomerulonephritis affects most glomeruli, with hypercellularity and the formation of crescents in Bowman's space.

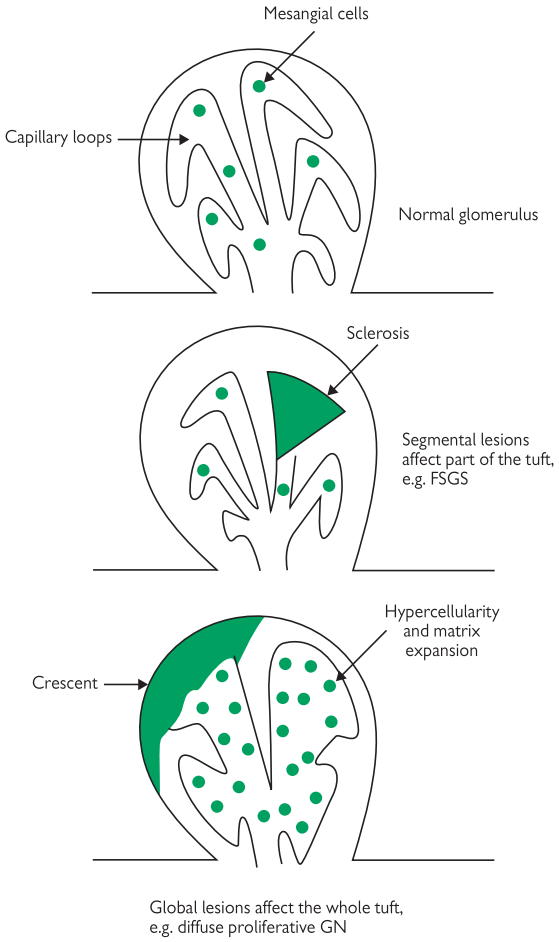

Fig. 7.2 The nomenclature of glomerulonephritis.

Table 7.1 A glossary of histological terms

Term	Definition
Minimal change	Normal appearance by light microscopy. Note that electron microscopy may show fusion of podocyte foot processes, an association with glomerular proteinuria.
Proliferation	Increase in cell numbers, may be mesangial, endocapillary or extracapillary (which may form crescents). E.g. mesangial proliferation = >4 cells per mesangial area.
Exudation	Infiltrated by neutrophils e.g. acute post-streptococcal nephritis (Fig. 15.10).
Membranous	Specific type of glomerular basement membrane thickening associated with subepithelial immune deposits, e.g. idiopathic membranous nephropathy.
Hyalinosis	Accumulation and condensation of plasma proteins into tissues outside a blood vessel lumen, appears as homogeneous pink staining with H&E (see 'H&E' later in table).
Sclerosis	Scar tissue, a fibrous matrix obliterates normal structure so that capillaries collapse and normal cell nuclei are lost.
Tubular atrophy	Thickening and wrinkling of tubular basement membrane around a shrunken tubule with flattened epithelium; implies irreversible tubular damage.
Crescent	Collection of cells in Bowman's space in response to glomerular damage. Initially only composed of inflammatory and epithelial cells (cellular crescent), later organizes with fibrin and collagen (fibrous crescent).
Diffuse	Applying to all glomeruli in a biopsy.
Focal	Applying to some glomeruli, but not others.
Global	Applying to the whole of a glomerulus.
Segmental	Applying to part of a glomerulus, i.e. part of the glomerular capillary tuft is unaffected.
'Humps'	Deposits of Ig and complement in a sub-epithelial site; typical of acute post-streptococcal nephritis.
'Spikes'	Projections of basement membrane between regular sub-epithelial deposits, typical of membranous nephropathy.
Foam cells	Lipid laden cells, usually histiocytes but also mesangial or tubular cells, seen in nephrotic syndrome and Alport's syndrome.

Table 7.1 (Continued)

Term	Definition
Haematoxylin and eosin (H&E)	Routine histological technique which stains cytoplasm pink and nuclei blue. Allows inspection of all renal structures but is poor at distinguishing deposits or visualizing the basement membrane.
Periodic acid-Schiff (PAS)	Routine histological technique which clearly delineates basement membranes and allows visualization of cellular components.
Silver	Silver stains highlight connective tissue structures such as reticulin, basement membrane, and collagen, which appears black. Very useful for assessment of glomerular capillary basement membrane architecture such as 'spike formation' (see 'Spikes' earlier in table).
Congo red	Stain used for the detection of amyloid, which appears red with 'apple green' birefringence using polarized light examination.
Martius scarlet blue (MSB)	Stain which highlights fibrin deposits as red, collagen in blue, and erythrocytes in yellow.
Toluidine blue	Stain used primarily to visualize 'thin sections' prior to electron microscopic examination.
Glomerulonephritis	Inflammation of the glomerulus.
Tubulointerstitial nephritis	Inflammation of the tubules and interstitium.
Electron dense deposits	Dark lesions identifiable on electron microscopic examination, usually corresponding to sites of immunoglobulin or complement deposition.
Immunohistochemistry (IHC)	Technique for detecting and localizing specific antigens in tissue sections using a detection system visible on routine light microscopy, e.g. immunoperoxidase.
Immunofluorescence (IF)	Technique for detecting and localizing specific antigens in tissue sections using a detection system visible on fluorescence microscopy. Sometimes more sensitive than IHC but requires fresh tissue and is not stable.
Thin basement membrane (thin BM) disease	Age 9–68 years: thin GBM: 262–330nm; normal: 331–547nm.
'Basket weave' GBM	The disordered replication of lamina densa of the GBM in Alport's nephropathy.

Modified from Taylor CM, Chapman S (1989). Renal biopsy. In *Handbook of renal investigations in children*, pp.160–71. Taylor CM, Chapman S (eds). Wright, London.

Acute nephritic syndrome

Introduction

The clinical syndrome associated with underlying glomerulonephritis (📖 p. 71). Presents (often rapidly) as:

- Haematuria and proteinuria.
- Impaired renal function.
- Oliguria with signs of salt and water retention.

It is a spectrum of disease with a variety of aetiologies but with a common site of primary injury: the glomerulus. Onset may be insidious, with urinary abnormalities alone, or fulminant, with a rapidly progressive crescentic GN, AKI, and other organ involvement or failure (📖 p. 71).

Causes

- IgA nephropathy and Henoch–Schönlein purpura.
- Lupus nephritis.
- Post-infectious GN.
- Anti-GBM disease.
- ANCA-associated vasculitis.
- Mesangiocapillary GN (MCGN).

Mechanisms of glomerular injury

The injury leading to most GN is immunologically mediated, with loss of tolerance to autoantigens, provoking both the cellular and humoral arms of the immune system. These antigens may be native to the glomerulus itself (occurring normally within the tuft, e.g. the GBM in anti-GBM disease) or circulating antigens/antigen-antibody complexes that become trapped in glomerular structures.

Antibody to antigen binding may then fix and activate complement (forming immune complexes, ICs) or recruit inflammatory cells (see Fig. 7.3). The nature of the injury will depend on the site of the IC (e.g. IgA-containing mesangial complexes activate mesangial cells to cause IgA nephropathy). Local complement activation and cell recruitment (neutrophils, macrophages) generate oxidant species, proteases, inflammatory cytokines, growth factors, vasoactive factors, and procoagulants.

Damage to, and activation of, surrounding cells and matrix then lead to the changes evident on histological examination and the clinical syndrome of haematuria, proteinuria, and impairment of glomerular filtration. The number of ICs formed and the host response to them will determine the extent of the injury.

Cellular immunity may also contribute to structural glomerular damage—this is especially true of pauci-immune GN (e.g. the GN associated with ANCA-positive vasculitis) where ICs play no pathological role.

Resolution of inflammation might return an inflamed glomerulus to normal or, if the healing phase is poorly regulated, may result in cellular dropout, scarring, glomerulosclerosis, and CKD.

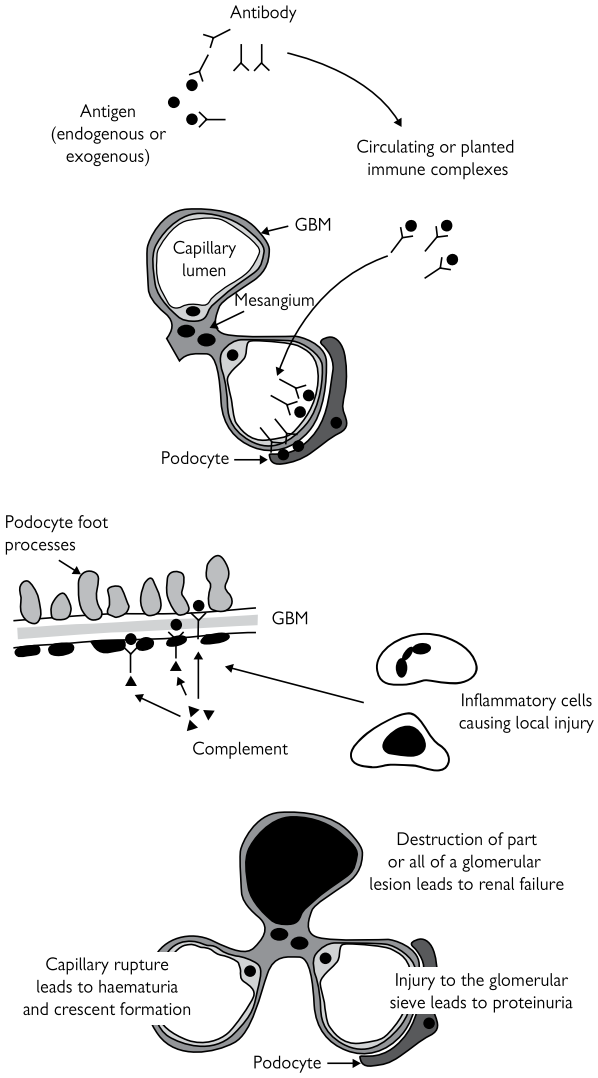

Fig. 7.3 An example of an immune complex-mediated GN.

Nephritis: management overview

Investigations

- Dipstick urine for haematuria, proteinuria.
- Urine microscopy for red morphology ± casts (📖 p. 22).
- Amount of proteinuria variable (often <1g/day, i.e. uACR <70mg/mmol and uPCR <100mg/mmol, but may be nephrotic range).
- SCr, eGFR, U&E, FBC, bone profile, LFT.
- Acute phase markers (CRP, ESR).
- Immunological and serological ('nephritic') screen (📖 p. 40).
- USS kidneys.
- Renal biopsy (📖 p. 80).

Salt and water restriction

► It is vital to correctly assess volume status.

- Fluid overload ± pulmonary oedema often complicates oliguric GN. If present:
  - Limit salt intake <80mmol/day (<5g/day).
  - Set oral intake at 500–1,000mL/day (adjusted according to volume status and UO).
- Diuretics may promote a natriuresis and provide symptomatic relief: use loop diuretic, e.g. furosemide 40–160mg/day PO or IV, titrated against response and renal function.
- Less commonly, dehydration may be present, in which case increased oral intake or rehydration with IVI 0.9% NaCl may be needed.
- Review volume status and monitor weight daily, and chart input and output to plan following day's fluid balance. Indwelling catheter only rarely required.

Control BP

- ↑ BP is usually volume-related and may be significant. Aim for target BP of ≤130/80mmHg.
- Suggested treatment:
  - Diuretic (as described in salt and water restriction).
  - Stepwise add-on therapy, using β-blockers ± calcium channel blockers.
  - ACE-I or ARB: titrate up from low dose with daily increments. ACE-I or ARB offer theoretical advantages in the control of ↑ BP secondary to renal disease due to their antifibrotic and anti-proteinuric effects. However, their use in GN-associated with AKI may precipitate a further decline in renal function. ⚠ Careful monitoring is essential.

Other supportive measures

- ► Prompt treatment of infection.
- Adequate nutrition.
- Management of the complications that may be associated with a systemic disease causing GN (e.g. lupus, vasculitis).
- Renal replacement therapy, according to standard indications (📖 p. 172).

Specific therapies: immunosuppression

Almost always tailored to a histological diagnosis (so a renal biopsy is often indicated as soon as is possible). See Nephritis: overview of immune suppression (📖 p. 540) and under each particular diagnosis.

KDIGO clinical practice for glomerulonephritis

This important guideline, first published in 2011, aims to help clinicians caring for patients with GN understand the evidence (or lack of) that underpins current clinical practice in this area. The recommendations contained within it are based on a comprehensive review of relevant literature across many kidney diseases. The strength of all the evidence presented is graded, current shortcomings are acknowledged and proposals for future research are offered.

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. KI, Suppl. 2012; **2**: 139–274.

Available online at 🖱 http://www.kdigo.org

Nephritis: overview of immune suppression

Introduction

⚠ Treatment of glomerulonephritis often involves toxic therapies in the short term to improve long-term renal and patient outcomes. The initial goal is to *achieve remission* before altering therapy to *maintain remission*.

When considering and commencing therapy, the dictum of 'first do no harm' always applies. These are potentially dangerous drugs—does the risk:benefit assessment justify their use?

Preventing drug toxicity

Corticosteroids

- Issue patients with a steroid card, and counsel regarding the risks of abrupt steroid withdrawal as well as the potential need to increase dose with stressors (such as intercurrent illness or anaesthesia). Check blood glucose at start of therapy.
- ⚠ Warn diabetic patients and those with impaired glucose tolerance to monitor blood sugars closely whilst on corticosteroid therapy and to inform their diabetic team.
- Prophylaxis against gastric irritation: proton pump inhibitor or H_2 receptor antagonist by convention (◆ although evidence poor).
- Steroid-induced bone demineralization is an early event (within first few months of treatment).
  - Consider bisphosphonate (e.g. risedronate 35mg weekly or alendronic acid 70mg weekly) in those at risk (or if >5mg prednisolone/day for >3 months). ⚠ Many bisphosphonates require a dose reduction in renal impairment.
  - Calcium (1,500mg/day) and vitamin D_3 (800 IU/day) preparations are a less effective alternative.
  - Consider baseline and interval DEXA if long-term steroids.
- Treat steroid-exacerbated hyperlipidaemia with a statin.

Tapering steroids

Prednisolone is the most widely used oral corticosteroid. Its use in renal disease is usually for >3 weeks and it will therefore often require slow tapering to allow recovery of a suppressed hypothalamic–pituitary axis.

A potential regimen from 20mg/daily prednisolone might be:

- Reduce by 5mg every fortnight until on 5mg/day.
- Reduce to 5mg, alternating with 2.5mg daily for 2 weeks.
- Reduce to 2.5mg daily for 2 weeks.
- Reduce to 2.5mg alternate days for 2 weeks.
- Stop.

Advise re potential Addisonian symptoms, and warn to seek medical help if unwell.

Others, e.g. alkylating agents (cyclophosphamide, chlorambucil)

- ⚠ Monitor toxicity: FBC, U&E, and LFT weekly to fortnightly at induction of therapy (see 📖 p. 542).
- Offer prophylaxis against PCP for duration of cyclophosphamide therapy (e.g. co-trimoxazole 480mg bd PO or nebulized pentamidine if allergic).
- In those at high risk for tuberculosis (e.g. previous TB, recent exposure, patients from endemic areas), consider primary prophylaxis with isoniazid + pyridoxine (🔥 evidence poor).
- Recommend influenza and pneumococcal vaccines. Live vaccines should be avoided for the duration of treatment.

Commonly used drugs

- Induction (I) brings about disease remission.
- Maintenance (M) maintains remission.

Prednisolone (I, M)

- To induce remission, either as high dose PO (1mg/kg/day) or as 'pulsed' IV (0.5–1g/day for 3 days).
- Corticosteroids are also used at lower dose for maintenance.
- Potent anti-inflammatory action, modulating both B and T cell-mediated immunity. Also inhibit the effector function of both monocytes and neutrophils through regulation of cytokine-driven responses.
- SE: insomnia, weight gain, ↑ BP, impaired glucose tolerance, dyslipidaemia, mood disturbance, poor wound healing, osteoporosis.

Cyclophosphamide (I)

- Either orally (e.g. 1.5mg/kg) or as periodic (monthly) IV pulses.
- A cytotoxic alkylating agent that binds to purine bases and impairs cellular DNA replication (→↓ cell turnover and cell death), with consequent restriction of lymphocyte proliferation.
- SE:
  - Leucopenia (see 📖 p. 542) and ↑ risk of infection, esp. *Herpes zoster*.
  - Gonadal toxicity. Discuss loss of fertility prior to starting treatment—in ♀, measure LH/FSH before therapy. Limit cumulative exposure as much as possible (>15–20g causes infertility in ~50% of those aged >30. The risk is lower in younger patients). Consider GnRH analogues in ♀ (see 📖 p. 542). Egg preservation may be possible, but the pace of disease (and ∴ need for swift intervention) often renders this impractical. Discuss sperm banking in ♂.
  - Haemorrhagic cystitis → longer-term risk of bladder cancer. ⚠ Use mesna if giving IVI (see 📖 Using IVI cyclophosphamide (CYC), p. 542); low threshold for investigating haematuria in those previously exposed (mesna binds to the cyclophosphamide metabolite acrolein that is the cause of urothelial toxicity).
  - 🔥 Oral cyclophosphamide (CYC) is potentially more toxic to ovaries and bladder than IVI because cumulative doses are usually higher.
  - Nausea and vomiting, esp. if given IVI.
  - Teratogenic; contraindicated in pregnancy (although not associated with birth defects in ♀ who receive it prior to pregnancy).
  - SIADH.

Using IVI cyclophosphamide (CYC)

- Body surface area is calculated as $\sqrt{}$ (height (cm) × wt (kg)/3,600).
- Counsel re side effects and potential risks.
- Protect the bladder from haemorrhagic cystitis: vigorous oral fluids, with 1L 0.9% NaCl over 4h post-therapy. Oral mesna at –2, +2, and +6h as (0.2 × cyclophosphamide dose in mg) per dose.
- Antiemetics, e.g. granisetron 1mg (can repeat at +12h) + dexamethasone 10mg PO at –2h.

Monitoring for CYC-induced neutropenia

- Check WCC weekly for the first month, every 2 weeks for the second and third, and monthly thereafter.
- If WCC $<4 \times 10^9$/L, then discontinue temporarily. Restart with a 25% dose reduction when WCC has recovered, and resume weekly monitoring.
- If the WCC is falling rapidly, e.g. by $>2 \times 10^9$/L between tests, reduce the dose by 25% pre-emptively.
- If WCC $<1 \times 10^9$/L or WCC $<4 \times 10^9$/L persists for >2 weeks, then restart at low dose (e.g. 25–50mg/day) only after WCC recovers.
- For IV CYC, check WCC the day of the proposed pulse. If $<4 \times 10^9$/L, postpone until $>4 \times 10^9$/L, and reduce dose by 25%.
- Check WCC 14 days after each pulse; if WCC nadir:
  - $2–3 \times 10^9$/L, reduce the dose of the next pulse by 20%.
  - $1–2 \times 10^9$/L, reduce by 40%.

Protecting against gonadal cyclophosphamide toxicity

Glomerular disease, particularly SLE, often affects ♀ of childbearing age. Cyclophosphamide (CYC) treatment is associated with a significant risk of premature ovarian failure (POF). This may play an important role in the choice of induction therapy but must be balanced against the risks of potential undertreatment.

When given continuously, GnRH analogues induce reduced ovarian blood flow and limit ovarian exposure to CYC. In small observational studies, the administration of GnRH analogues during treatment with CYC for lupus nephritis demonstrably preserves ovarian function. An example regimen is depot leuprolide acetate, ideally administered at least 10 days prior to the commencement of CYC.

Calcineurin inhibitors (I, M)

- Ciclosporin and tacrolimus (📖 p. 386).
- Limit IL-2-driven nuclear transduction, and thus T cell activation.
- ⚠ Nephrotoxic: monitor GFR throughout use.
- Given orally (although IVI available).
- SE (ciclosporin (C) and tacrolimus (T)):
  - Infection (T + C), ↑ BP (C), tremor, hirsutism (C), gum hypertrophy, dyslipidaemia, impaired glucose tolerance (T > C), gout (C), nephrotoxicity (T + C), microangiopathy (T + C), amongst others.

Azathioprine (M)

- Antiproliferative pro-drug metabolized to 6-mercaptopurine.
- Restricts lymphocyte proliferation through the inhibition of folate-dependent DNA synthesis.
- ⚠ Interaction with allopurinol may precipitate profound leucopenia.
- Given orally, usually as a single daily dose.
- SE: infection, myelosuppression, hepatotoxicity (check WCC, LFT 14–21d after starting). Long-term risk of skin cancers.

Mycophenolate mofetil (I, M)

- Antiproliferative agent that inhibits lymphocyte expansion and antibody production. It can also promote T cell apoptosis and affect cell:cell interactions.
- Given orally in divided doses (IVI available).
- SE: infection, myelosuppression, GI toxicity (diarrhoea is not uncommon—divide dose qds, rather than bd, or reduce dose). Teratogenic.

Rituximab (I, possibly M)

- A chimeric anti-CD20 monoclonal antibody against B cell surface marker that induces B cell lysis. Given IVI. Results in widespread B cell and antibody depletion over time.
- SE: cytokine release type syndrome during infusion, infection—particularly serious viral infections, including CMV and JC virus (the latter the cause of progressive multifocal leucoencephalopathy). Others: fever, headache, nausea, abdominal pain, hepatitis, bronchospasm, hypogammaglobulinaemia. Serious neutropenia is uncommon.
- Circulating B cell counts may be helpful to guide dosing.