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Parasytic: Malaria
Toxoplasmosis
Schistosomiasis
Filariasis

b. Glomerular involvement in multisystem diseases

i. Systemic lupus erythromatosus
ii. Henoch - Schönlein purpura — IgA nephrop
iii. Goodpasture's syndrome — elderly : Anti glomerular basement disease } NB Need urgent Tx } Cl-gos
iv. Systemic necrotizing vasculitis
v. Renal involvement in other multisystem diseases (e.g.. mixed connective tissue disease, rheumatoid arthritis, sjogren's syndrome, sarcoidosis etc.)

c. Dysproteinemias and paraproteinemias

Cryoglobulinemia
Waldenström's macroglobulinemia
Benign monoclonal gammopathy
Multiple myeloma
Light chain nephropathy
Amyloidosis

d. Liver disease

Hepatitis B and C
Chronic active hepatitis
Cirrhosis → NB prone to IgA nephropathy + Bad Prognosis.

e. Neoplasia

Lung
Breast
Stomach
Colon
Ovary etc.

f. Heredofamilial diseases:

Diabetic nephropathy (not glomerulonephritis)
Heriditary nephritis (Alport's syndrome)
Fabry's disease
Nail - patella syndrome
Sickle cell disease
Partial or total lipodystrophy

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g. Medications, Immune-agents and allergens

Gold, heroin, mercurials, anticonvulsants (Mesantoin, Trimethadone) Tolbutamide, Chlorpropamide, Probenecid, Allupurinol, Penicillin, Sulphonamides, Thiazides, Captopril, Non-Steroidal- Anti-inflammatory drugs, milk, pollen, poison ivy, Polio vaccination, Bee stings, Snakebite, Wool, Exposure to insect repellants and Radiological contrast media.

h. Miscellaneous diseases

Massive obesity, Unilateral renal agenesis, Subtotal nephrectomy etc..

Pathogenesis of glomerulonephritis

With few exceptions the underlying mechanism of acute glomerulonephritis is immunologic

a. Immune complex disease

(Antigen - Antibody complexes)

i. In situ formation in glomerulus
ii. Circulating immune complexes deposited in the kidney

b. Anti-basement membrane disease

Antibodies directed against an antigen in the basement membrane of the kidney and/or lung. (goodpasture's syndrome)
All the above immunological mechanism can by means of the coagulation system and complement activation proceed to inflammation with cellular infiltrates and various mediators of glomerular injury, causing glomerular damage.

Diagnostic evaluation

* History and clinical examination-search for evidence of a systemic disease, familial renal disease, exposure to drugs, chemicals and toxins.
* Examination of urinary sediment: - presence of casts, redcells and proteinuria.
* Quantification of proteinuria - more than 3,5 gram\1,73m²/day = Nephrotic syndrome.
* Evaluation of renal function: - Serum creatinine and Creatinine clearance.
* Consideration and exclusion of all secondary or multisystemic diseases, by means of the relevant serological tests e.g. Infection, Vasculitis, Malignancy, Anti-neutrophil cytoplasmic antibodies, Anti-nuclear factor, anti-glomerular basement membrane antibodies, anti-streptolysin antibodies (Post streptococcal

C

GLOMERULONEPHRITIS

CD POTGIETER
RENAL UNIT
PRETORIA ACADEMIES
SOUTH AFRICA

Definition of Glomerulonephritis
Glomerular injury, usually due to a immunological mechanism resulting in:

1. Proliferation of one or all of the glomerular cells e.g. endothelial, mesangial or epithelial.
2. Inflammatory cell infiltration e.g. polymorphs, macrophages, eosinophils, plasmacells and lymphocytes.
3. Glomerular damage - demonstrated by focal or diffuse glomerular sclerosis and or different degrees of mesangial matrix formation.
4. Secondary tubular and Interstitial damage - demonstrated by tubular atrophy, fibrosis and interstitial fibrosis.
5. Damage to the Glomerular basement membrane - demonstrated electronmicroscopically.

Major clinical syndromes of Glomerulonephritis.

1. Acute glomerulonephritis or acute nephritic syndrome is characterized by abrupt of variable degrees of heamaturia, proteinuria, diminshed glomerular filtration rate, sodium and fluid retention (oedema), circulatory congestion, hypertension and occasionally oliguria.

2. Rapidly progressive glomerulonephritis is characterized by a more insidious onset, dominated by a progressive loss of renal function and frequently oliguria with a short course. (crescentic)

3. Chronic glomerulonephritis or chronic nephritic syndrome is a controversial term referring to progressive renal function loss and varying degrees of proteinuria, heamaturia and hypertension. The course is usually protracted over 5 to 10 years.

4. Persistent asymptomatic urinary abnormalities is characterized by mild to moderate proteinuria (usually less than 3 grams/day) with or without haematuria but by few or no clinical abnormalities e.g. hypertension or oedema.

5. Nephrotic syndrome is a term used to characterize the presence of a severe degree of proteinuria, 3,5 grams/ 1,73 m^2/ day, accompanied by oedema, usually hypoalbuminemia, raised cholesterol levels, and lipiduria. Hypertension may be present.

Classification of Glomerulonephritis

Glomerulonephritis can be classified according to division by morphology, etiology, clinical syndrome (above) and pathogenetic mechanism.

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Morphological classification

This classification depends on the morphology as defined by light and electron microscopy. Primary and secondary diseases can both be involved in almost any of the morphological types.
Morphologically the presence or absence of proliferation of cells, subdivides glomerulonephritis into two main groups:

A. Glomerulonephritis without cellular proliferation
i. Minimal change disease
ii. Membranous nephropathy
iii. Focal and segmental glomerulosclerosis. — most common. 1°/2°/Familial (wet syndrome obesity, AG's, edocarditis etc.)

NB →

B. Glomerulonephritis with cellular proliferation
i. Mesangial proliferative glomerulonephritis → assc with
ii. IgA nephropathy
iii. Mesangiocapillary glomerulonephritis
iv. Focal proliferative glomerulonephritis 2° to infex
v. Crescentic glomerulonephritis Rapid progress Cause: vasculitidis

Etiological classification - causes of Glomerulonephritis.
Etiologically glomerulonephritis can be divided into primary glomerulonephritis and secondary glomerulonephritis.

1. Primary glomerulonephritis (the kidney is primary involved)
   a. Post streptococcal glomerulonephritis
   b. Ideopatic glomerulonephritis
2. Secondary glomerulonephritis - secondary or multisystemic disease with secondary involvement of the kidney.
   a. Non -post streptococcal post infectious — Non - Streptococcal.

   Bacterial: Infective endocarditis
   Staphylococcal bacteremia
   Pneumococcal bacteremia
   Syphilis
   Leptospirosis
   Meningococcemia
   Mycoplasma
   Typhoid fever
   Any suppurative infection
   Visceral abscesses

   Viral: Hepatitis B,C
   Influenzae A and B
   Adenovirus
   Infectious mononucleosis
   Cytomegalovirus
   Measles
   HIV — NB collapsing glomerulopathy. Bad Prognosis. Need HAART before Tx
   Mumps

* Angiotensin-converting enzyme inhibitors, when used for the treatment of hypertension should be discontinued in the presence of severe renal failure due to the possible induction of hyperkalaemia.
* Remember, all non-steroidal anti-inflammatory drugs, even in single doses can cause significant renal impairment.
* All secondary causes (etiology) must be seriously considered and ruled out before the diagnosis of primary ideopatic glomerulonephritis is excepted.
* Do not attempt to treat a patient who may need specialised therapy or management.
* The following factors contribute to the progression of renal disease due to glomerulonephritis: high protein diet, high phosphate diet, salt intake, infections and uncontrolled hypertension.
* Remember, renal failure can be subtle and asymptomatic but with grave consequences for the patient.

When to refer

* Whenever there is an indication for a renal biopsy, the case should be referred to a nephrologist.
* Specific therapy for certain glomerulonephritis cases should be administered under specialist supervision.
* Whenever a case of glomerulonephritis presents with renal failure which might need dialysis.
* Refractory or uncontrolled hypertension associated with renal impairment should be referred to a nephrologist.

Further reading

W.N. Suhi, S.G. Massry, Therapy of Renal Diseases. Kluwer Academic Publishers. Boston 1991

glomerulonephritis), serum complement, Hepatitis B Serology, Hepatitis C serology and Cryoglobulins.

* Renal biopsy, when indicated for an rapid diagnosis to consider therapy or prognosis.

Indications for a renal biopsy in glomerulonephritis

* Patients with asymptomatic proteinuria of more than 1 gram/24h, especially if accompanied by red cells in the urine and impaired renal function.
* Recurrent isolated haematuria with normal urography and cystoscopy with/without proteinuria.
* Acute nephritic syndrome with persisting oliguria.
* Nephrotic syndrome in adults, unless the cause is apparent. In children only if haematuria is present or if proteinuria persists after a trial of coricosteroids.

Principles of management

* Prevent renal function deterioration by avoidance of nephrotoxins (drugs etc.)
* Effective control of hypertension by appropriate Anti-Hypertensive therapy.
* Reduction in dietary protein intake to 0,8gram/kg/24h, whenever renal failure is present, or persistant nephrotic syndrome.
* Salt restriction
* Management of oedema
* Specific treatment for certain glomerulonephritides to reverse the immunologically induced glomerular disease or stabilize the process (e.g.: SLE, FSGS etc.).
* Referral for dialysis when severe renal failure is present.
* Monitoring of renal function and patient.
* Remember any form of glomerulonephritis can cause renal failure with many life threatening complications of which Hyperkalaemia is the most dreaded.

Pharmacological interventions

The following is used, when indicated, for the treatment of some forms glomerulonephritis:

* Corticosteroids
* Cyclophosphamide
* Azathioprine
* Anticoagulants
* Anti-hypertensive drugs
* Loop diuretics
* Plasmaphoresis

* The potential side effects of the drugs or treatment must always be considered.

Tx: Penicillin
Antibiotics
Steroids
Plasmapheresis → sterility
Cyclophosphamide
Cyclosporine
Tacrolimus
Sirolimus
Ruthixinab (Anti CD20)
ACEI / ARBs

Treatment of specific forms of glomerulonephritis

Post streptococcal glomerulonephritis

Penicillin might be indicated initially when there is still evidence of a throat infection but long term prophytactic antibiotics is unnecessary

Non - post streptococcal infections glomerulonephritis

This is best treated with the appropriate antibiotic or drug for which the particular organism is sensitive.

Multisystemic disease glomerulonephritis

* The connective tissue diseases causing glomerulonephritis is usually treated by means of steroids and/or immunisupressants.
* Systemic lupus with glomerulonephritis is currently being treated with oral steroids (1mg/kg/day) and intravenous cyclophosphamide (0,50mg/m^2) on a monthly basis for the response of the disease.
* Systemic vasculitis responds to oral steroids and intravenous cyclophosphamide.

Anti-glomerular basement membrane disease

Plasmaphoresis is an excepted form of therapy early in the course of the disease and usually has a positive effect on the lung haemorrhage seen with this disease. The glomerulonephritis doesn't respond as well to plasmaphoresis. Both intravenous cyclophosphamide and oral steroids must be used in conjunction with plasmaphoresis.

Idiopathic / Primary glomerulonephritis

Minimal change disease

Steroids (60mg/m^2) will induce remission in most patients in 6 to 12 weeks. In adults steroid resistance might occur and oral cyclophosphamide or chlorambucil will have to be considered. Frequent relapses will also benefit from oral cyclophosphamide therapy. Adults normally take longer to respond. The administration of prednisone at 1mg/kg/day (usually 60 - 80mg/day) will induce remission in 95% of patients within 12 weeks, 85% of patients will be in remission within 4 weeks of therapy. Prednisone can also be given in a dose of 120mg/1,73m on alternative days in adults. 80% of patients usually relapse, the majority within the first year. Some patients are steroid resistant or late non responders Cyclophosphamide therapy. Side effects of Cyclophosphamide include leukopenia, bonemarrow suppression, infection, alopecia, vomiting, possible tumour induction, sterility and cystitis.

Focal segmental glomerulonepohritis

Steroids and immunosuppressants has not clearly been shown to provide any benefits in all patients

Membranous nephropathy

For stage I and II membranous nephropathy some units will use steroids, but most patients will not respond. A high incidence of renal vein thrombosis is seen with this entity and anti-coagulation is indicated whenever Hypoalbuminemia is severe.

Crescentic glomerulonephritis

High dose steroid therapy, combined with Cyclophosphamide and plasma-exchange is indicated. The response to therapy varies and is often not very favourable. Once severe renal failure is present the prognosis despite therapy is grave.

Mesangial proliferative glomerulonephritis

* The first drug of choice is prednisone, either daily or alternative days. Treatment should be continued until remission, or up to 8 weeks in patients with a nephrotic syndrome.
* 50% of patients with the nephrotic syndrome can be expected to respond, but the majority will be steroid dependent.
* Cyclophosphamide in a dose of 2mg/kg/day can be administered for 8 weeks.
* The presence of IgM on immunofluorescence is a hallmark of a less favourable response and prognosis.

Mesangiocapillary glomerulonephritis

* No clear response with any form of therapy has been demonstrated.
* Antiplatelet agents, dipyridamol/aspirin have occasionally had a stabilizing effect on the progression of the disease.
* The prognosis is poor with frequent progression to renal failure.

Avoiding treatment errors

* Steroids and immunosupressants drugs have serious and potentially life threatening side effects which should always be considered. The potential benefits of therapy will have to be weighed against the potential side effects in each individual case. Be careful of overzealous use of potent diuretics which can often precipitate pre-renal failure, in patients with hypoalbuminemia.
* Potassium sparing diuretics e.g. Spironolactone and amyloride shouldn't be used in severe renal failure of glomerulonephritis due to the danger of hyperkalaemia.