Clinical Considerations for Managing RPGN: Pauci-immune Glomerulonephritis

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Objectives

- Explain the pathophysiology behind RPGN, including pauci-immune glomerulonephritis
- Differentiate between the various types of RPGN
- Recognize the hallmark presentation associated with pauci-immune glomerulonephritis
- Identify the measures used to diagnose pauci-immune glomerulonephritis
- Describe the modalities used for the treatment of pauci-immune glomerulonephritis

RPGN

- **R**apidly **P**rogressive **G**lomerulo**n**ephritis
- Clinical syndrome expressed by
  - Glomerular disease
  - Increase loss of renal function over short time
- Characterized morphologically by crescent formation
  - ≥ 2 layers of proliferating cells in Bowman's space

"Overview of the classification and treatment of rapidly progressive (crescentic) glomerulonephritis". UpToDate. Accessed 5 December 2014.

Pathogenesis of Crescent Formation

- Non-specific response to major injury to glomerular capillary wall
- Rents are induced in glomerular capillary wall, GBM, & Bowman's capsule
- Influx of plasma products, macrophages, & T cells into Bowman's space
- Subsequent fibrin formation & release of pro-inflammatory cytokines

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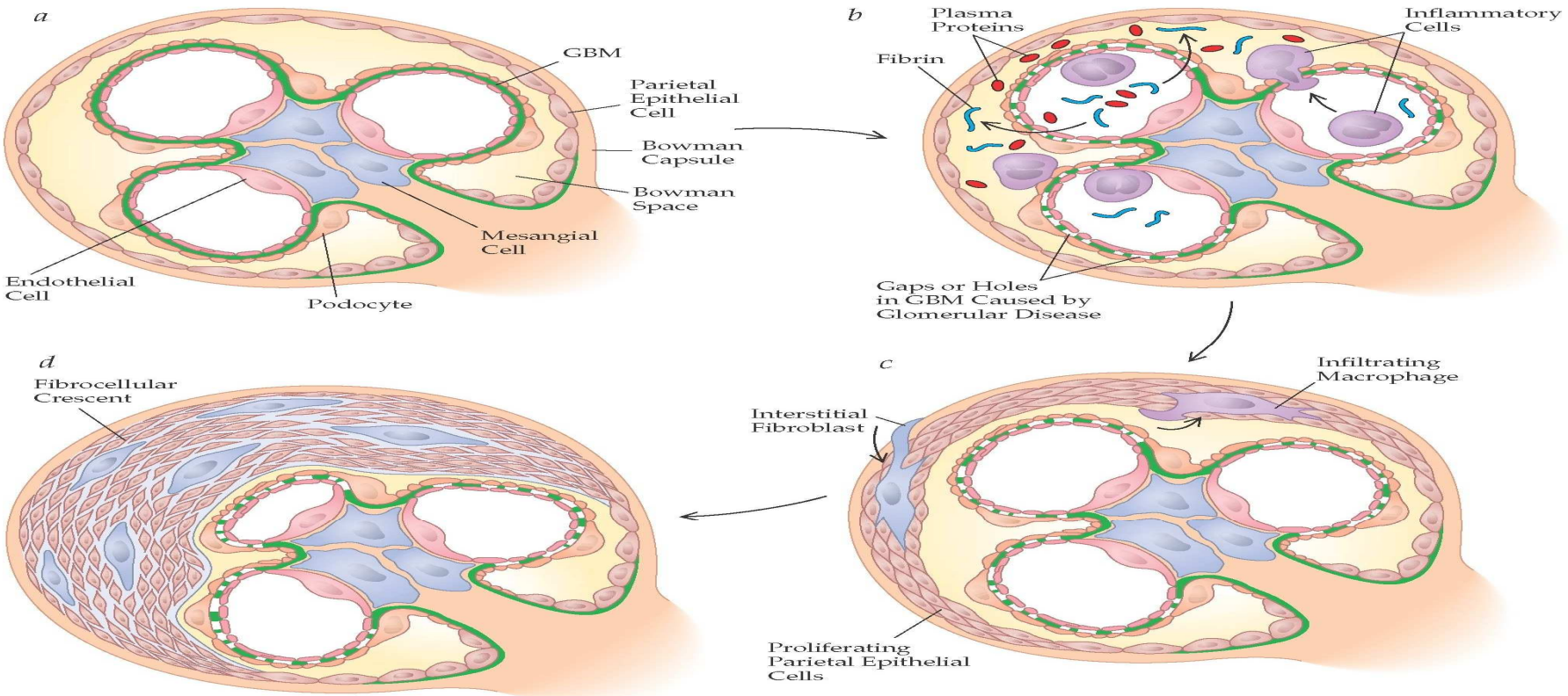
Pathogenesis of Crescent Formation



http://what-when-how.com/acp-medicine/glomerular-diseases-part-3/

RPGN

Mild – Moderate Disease

- Crescent formation in < 50% of glomeruli
- Non-circumferential
- Indolent course
- Remission likely

Advanced Disease

- Crescent formation in > 80% of glomeruli
- Circumferential
- May not respond to tx
- Poor outcome likely

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Anti-GBM Antibody GN

- AKA Goodpasture's disease
- Anti-GBM antibodies attack collagen
  - Lungs = alveolar basement membrane
  - Kidneys = glomerular basement membrane
- Results in pulmonary hemorrhage & glomerulonephritis
- Eight times more common in males
- Presents in early adulthood

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Immune Complex GN

- Immune deposits in glomeruli as result of:
- Mesangial IgA deposits in IgA nephropathy
- Anti-streptococcal antibodies & subepithilial humps in post-infectious GN
- Mesangial + subendothelial deposits in lupus nephritis
- Circulating cryoglobulins & intraluminal thrombi in cryoglobulinemia
- Others

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Idiopathic GN

- An immune complex disease that does not fall in other categories
- Includes pauci-immune disease that is ANCA- negative
- Accounts for < 5% of cases of crescentic GN

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Pauci-immune GN

- Necrotizing GN with little to no immune deposits
- Most cases of renal-limited vasculitis are ANCA- positive
- **A**nti**n**eutrophil **C**ytoplasmic **A**ntibody
  - Attack inside of neutrophils
  - WBC's attack walls of small vessels of various organs
- For kidney: causes hematuria/proteinuria with renal failure
- 75-80% are MPO-ANCA positive
  - Systemic symptoms
- Drug-induced: PTU, hydralazine, allopurinol, penicillamine, minocycline

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Clinical Presentation

Common Sx

- Fatigue & edema with insidious onset
- Renal insufficiency (SCr >3 mg/dl)*
- Systemic manifestations
  - Pulmonary, musculoskeletal, skin, nervous system
  - Granulomatosis with polyangitis or MPA
- U/A reveals proteinuria, hematuria with dysmorphic RBCs & casts

Less Common Sx

- Acute onset of gross hematuria & ↓ U/O
- Nephrotic syndrome

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Diagnosis

- If pt presents with clinical symptoms suggestive of RPGN
- URGENT appropriate serologic tests needed
  - ANCA
  - Anti-GBM antibodies
  - Complement component assays
  - Antinuclear antibodies
- Renal biopsy (if needed)

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Treatment

- Induction of remission (3 – 6 mo.)
- Cyclophosphamide IV 0.75 g/m^2 Q 3-4 weeks
  - Less leucopenia & fewer infections
- Cyclophosphamide PO 1.5-2 mg/kg/d
  - Less risk of remission or need for RRT
- Methylprednisolone IV 500 mg daily x 3 days
- Prednisone PO 1 mg/kg/d x 4 weeks (max dose: 60 mg)
- Rituximab 375 mg/m^2 weekly x 4
- Plasmapheresis 60 ml/kg volume replacement
  - Diffuse alveolar hemorrhage or SCr > 5.66 mg/dl
- IVIG 2 g/kg x 1 for resistant cases

Ch. 13: Pauci-immune focal and segmental necrotizing glomerulonephritis. Kidney International Supplements (2012) 2, 233–239; doi:10.1038/kisup.2012.26

Treatment

- Prevention of relapse aka maintenance tx (6-18 mo.)
- Risk factors for relapse:
  - Persistence of PR3-ANCA, h/o of URT dx or LRT dx
- Azathioprine PO 1-2 mg/kg/d first line
- MMF PO up to 1 GM BID second line
- Methotrexate PO initially 0.3 mg/kg/wk (max: 25mg/wk) third line
- Bactrim as adjunctive tx for pts with URT dx

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Treatment

- Severe relapses from remission:
- Same tx as initial therapy for induction
- Rituximab > cyclophosphamide
  - Cumulative dosage of cyclophosphamide approaching 36 GM

- Other relapses from remission:
- Restart IMS
- Corticosteroids > cyclophosphamide

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Highlights from Guidelines

- Rituximab is recommended first line for induction tx for severe cases
- Cyclophosphamide no longer used after 3 mo. induction tx in HD pts with no extra-renal sx
- No maintenance tx for HD pts with no extra-renal sx
- Plasmapheresis for ANCA-vasculitis + anti-GBM antibody dx
- Avoid using ANCA titer alone to change IMS tx

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Take Home Points

- RPGN is a serious disease that can lead to irreversible renal damage
- Current therapies are potentially lengthy & associated with significant risks
- Treatments are often individualized pending pt preference & tolerance
- Pharmacists can play an integral role in helping pts choose appropriate therapy
  - Decrease adverse effects
  - Increase compliance
  - Save health care costs

Patient Case

- JM is a 54 YO male admitted to Hixson Campus with CC of left sided paresthesia
- PMH significant for: HA, blindness in L eye, deafness in L ear, COPD, chronic back pain s/p spine fx, depression/anxiety, wt loss of 40 lbs, anemia, Hepatitis C, & substance abuse
- Within 10 days of admission, SCr increases from 0.9 – 2.0
- Lab work reveals MPO-ANCA +
- Pt sent to Glenwood for renal biopsy & possible HD

Patient Case

- JM receives Solu-medrol 1000 mg daily x 3 days initially while awaiting biopsy results
  - Was this appropriate?
- Biopsy confirms pauci-immune GN with ATN
- JM receives Cytoxan 2 GM IV x 1 with plasmapheresis, & PO steroids
  - Was this appropriate? (Hint: his BSA: 1.74)
  - Should pt have received Mesna?
- Despite all these therapies, JM must go on chronic HD
  - If JM does not have extra-renal manifestations, how long do we continue Cytoxan tx while he's on HD?

Patient Case- Answers

- According to guidelines: NO. 500 mg IV daily is recommended as 1000 mg doses have not shown to be superior & are associated with more AE's.
- According to KDOQI guidelines-no. Cytoxan is dosed 0.75 g/m^2 (1.74) = 1.3 GM. Pt received significantly higher dosage. However, in practice it can be given as high as 1 g/m^2 (1.74) = 1.74 GM, so pt still got higher dosage than typically used.
- NO. Mesna is really reserved for pts receiving high doses of Cytoxan (such as 1.5 – 2 g/m^2).
- After 3 months, it is recommended to D/C Cytoxan for pts on HD with no extra-renal manifestations due to lack of any clear benefit in this pt population

Questions

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