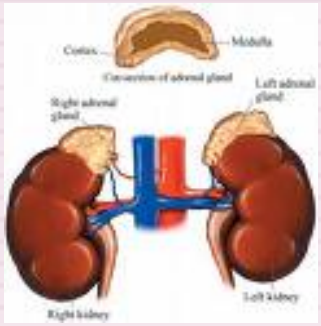
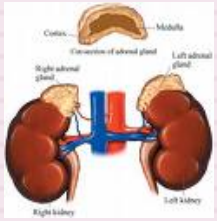


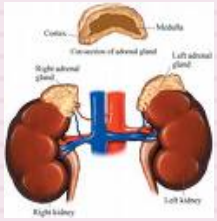
SCLERODERMA RENAL CRISIS

Presented by : Nouf Alanazi



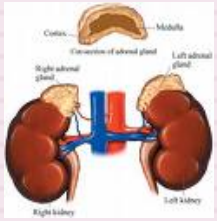
Agenda

- Prevalence
- Risk factors
- Pathology
- Diagnosis
- Prevention & monitoring
- Treatment
- Outcome & mortality.
- Summary & recommendations
- References



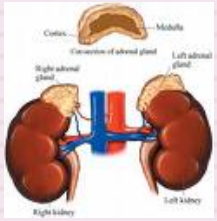
SRC

Abrupt onset of moderate to severe hypertension with Progressive renal failure



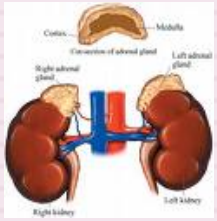
Prevalence

- Autopsy revealed histological evidence of renal involvement in **(60-80)** % of pts with systemic sclerosis .
- **50** % of pts show clinical evidence of renal involvement.
- SRC develops in up to **20 %** **o**f pts with ***diffuse cutaneous SS***, although its incidence appears to be declining.



Risk factors

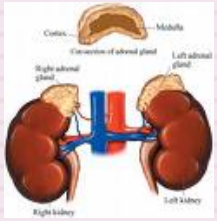
- Diffuse skin involvement
- Advancing skin involvement
- Glucocorticoid use
- Presence OR absence of certain autoantibodies.



Diffuse skin involvement

- The ***most important*** risk factor esp. if rapidly progressive.
- In a series of 110 pts with SS who developed SRC **78 %** had the diffuse cutaneous form of SS.

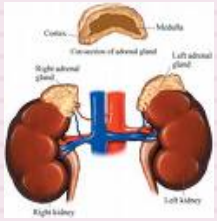
QJM 2007; 100:485.



Glucocorticoid use

- Esp. in ***high doses***.
- **<u>This was best shown in a retrospective case-control study of 110 pts with SRC.</u>**
  - *Moderate to high dose glucocorticoid use* ***(≥15 mg /day prednisone or equivalent)*** *in the preceding 6 M markedly increased the risk .*
  - It was found that around **60 %** of pts with SRC had prior recent exposure to steroids.

<u>Arthritis Rheum 1998; 41:1613</u>.

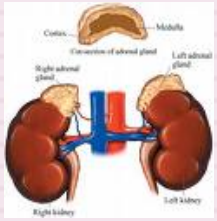


Autoantibodies

- There is an **increased risk** among pts who had ***anti-RNA polymerase Abs.***

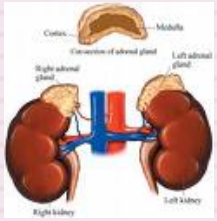
- It was detected in the serum of **12%** of 735 SSc pts who **didn't have SRC**, compared to **59 %** of 96 SSc pts who ***developed SRC.***

QJM 2007; 100:485.



- **(ANA)** : a strong association with ANA speckled pattern , which occurs in **60% of** pts with SRC .

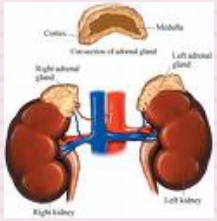
- **By comparison,** the presence of **anti-centromere Ab** was *underrepresented* in pts with SRC **(1.8 vs 28.9 %)** of SSc pts with SRC.



Cyclosporine

- A renal vasoconstrictor.
- May accelerate renal disease in SS.
- In one report, ARF developed in 3 of 8 pts treated with cyclosporine.
- Cause !!!

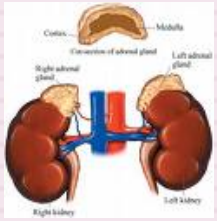
Br J Rheumatol 1994; 33:90.



Other risk factors

- Contractures at the large joints.
- New onset anemia.
- New cardiac events (e.g HF or pericardial effusion).
- <u>Preexisting:</u>
  - HTN
  - high S.Cr
  - abnormal urinalysis
  - Abs against topoisomerase-1

are NOT predictive.

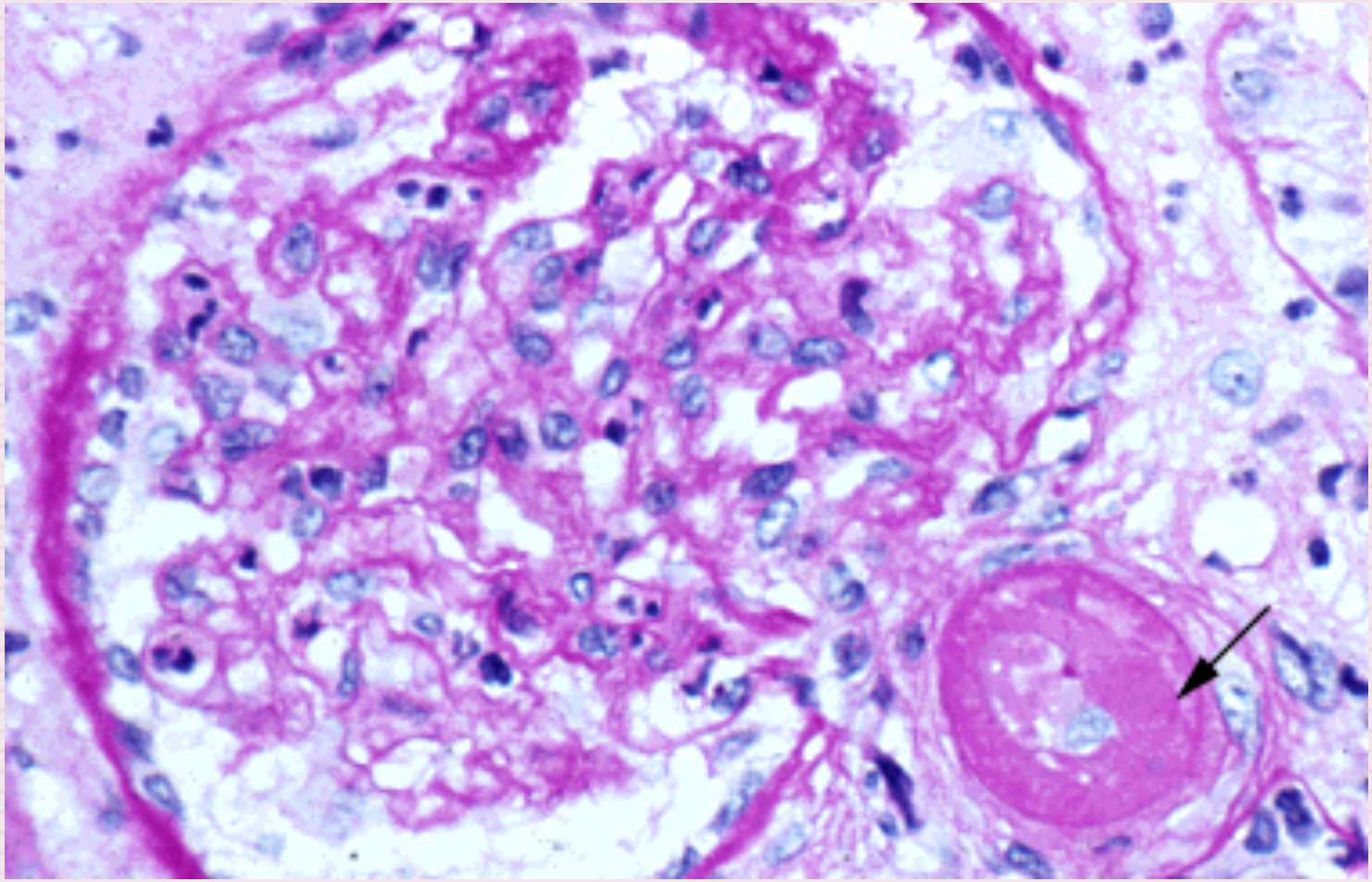


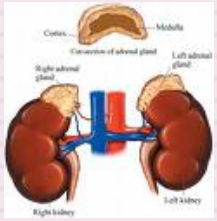
Pathology

- Changes are localized in the small arcuate and interlobular arteries and the glomeruli.

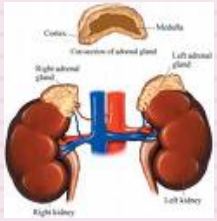
- The CCC finding is ***intimal proliferation and thickening t***hat leads to narrowing and obliteration of the vascular lumen, with concentric **"onion-skin"** hypertrophy.

fibrinoid necrosis in the preglomerular afferent arteriole (arrow) in SRC. The normal muscle layer of the media has been replaced by the fibrinoid material .





- SRC is a ***thrombotic microangiopathy*** , Because of the similar renal histologic findings, **renal biopsy does NOT definitively establish the Dx** of SRC.

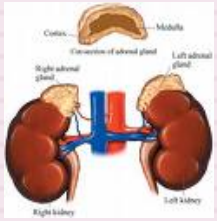


Diagnosis

- **Criteria of diagnosis :**

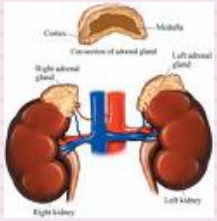
  1. New onset of BP **>150/85** mmHg, measured at *least twice* over the preceding **24 hours**. However, normotensive SRC has been described .

  2. Progressive decline in renal function with rising S.cr.

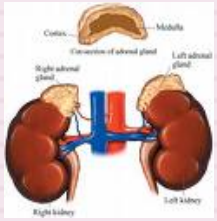


3. ***Additional findings may include the following:***

- MAHA & thrombocytopenia
- Acute retinal changes of malignant hypertension
- New onset proteinuria or hematuria (excluding other causes)
- Flash pulmonary edema
- Progressive oliguria or anuria
- Ccc. changes on kidney Bx

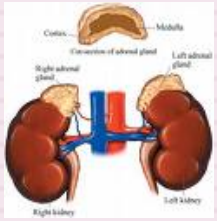


- **Rarely,** severe HTN associated with ARF may occur in individuals who have ***sine scleroderma*** .
- In this setting, signs of SS should be sought& These include:
  - Digital tip pitting and scarring, and nailfold microvascular changes with capillary dilatation & drop-out .
  - Evidence of GI involvement , ILD or PA HTN

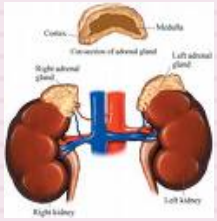


Monitoring

- Close monitoring of pts is **most important** during the *first 4 - 5 years*.
- Rationale !
- No studies.

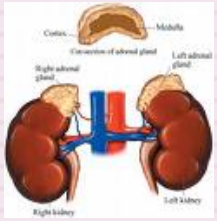


- **<u>It is advised to use the following screening regimen:</u>**
  - BP measurement on a regular basis for all pts.
  - For **high-risk** pts, *daily* home BP measurements & for **others** *twice a week* .
  - In pts with baseline BP of **≤120/70** mmHg, a persistent rise of *20 mmHg in the SBP* or a *10 mmHg rise in the DBP* ,needs further evaluation.

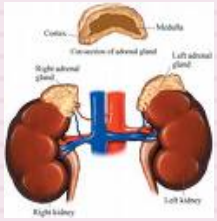


- In pts **taking antihypertensive medications,** sustained HTN > 150/90 mmHg, which is not readily corrected with dose adjustment and modest dietary salt restriction, would trigger further evaluation.

QJM 2007; 100:485

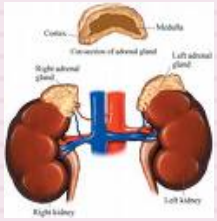


- Measurement of S.Cr & dipstick for protein or calculation of the random Ur (protein:Cr) ratio every 3-6 months.
- An *elevation in the S.Cr* (or fall in Cr cl)or new persistent proteinuria >500 mg/d may be a **warning sign** of impending SRC.



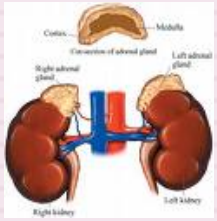
Prevention

- **No prospective studies** demonstrate that the avoidance and/or administration of any agent lowers the incidence or severity of SRC have been performed.



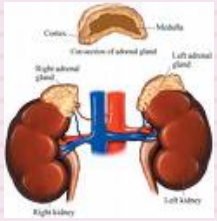
ACE inhibitors

- There is **No clear evidence** of a *preventive effect* of ACE I.
- It should NOT be used solely for the purpose of preventing the occurrence of SRC.
- Studies have largely found **neither benefit nor harm** with ACE I related to the development of SRC.

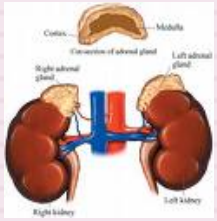


- **A multicenter randomized, double-blind, placebo-controlled study** of **210 pts** evaluated the efficacy of **daily quinapril** (80 mg/d or the maximum tolerated dosage) ***for the prevention of vascular damage in SS.***

Arthritis Rheum 2007; 56:3837.

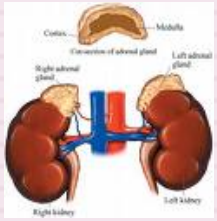


- **At 2-3y :**
  - It didn't affect the occurrence of vascular complications (e.g Raynaud phenomenon or ischemic digital ulcers)
  - Had **No effect** on **renal function.**



Avoidance of glucocorticoids

When glucocorticoid use is unavoidable ,it is recommend to limit the dose of prednisone ***to (< 15 mg/d)*** & to the *shortest possible period*.

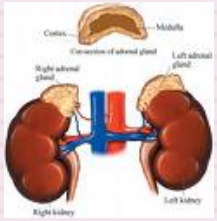


Treatment

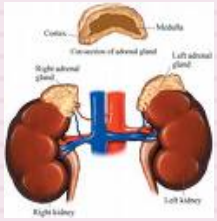
- Left untreated, (SRC) can progress to ESRD over a period 1-2 months & death usually within 1 y .

- The **mainstay of Rx** is:

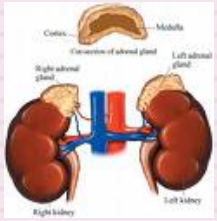
  - ✓ ***effective & prompt BP control***, which improves or stabilizes renal function in up to **70%** of cases & improves **survival** **(80%at 1year).**



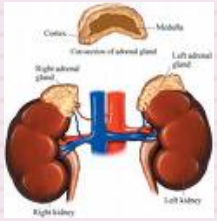
The *success* with antihypertensive Rx depends on its ***early initiation*** before irreversible renal damage has occurred.



- Based upon small no. of pts in observational studies.
- ***NO prospective RCT*** were performed in SRC.



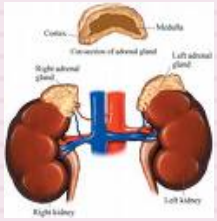
- The optimal class is **(ACE) inhibitors.**
- Most experience has been with captopril. much less data available on other ACEI which may provide comparable benefit.
- **Captopril** is **prefered** due to *(rapid onset & short duration of action)* which permit rapid dose titration.



ACE inhibitor studies

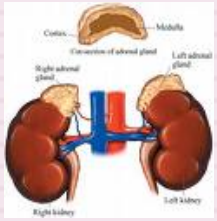
- **A prospective cohort study** of 108 pts with SRC seen b/w (1972 -1987) compared those *treated continuosly with ACEI* **to** *those before availability of ACEI*, It showed the following :

Ann Intern Med 1990; 113:352.

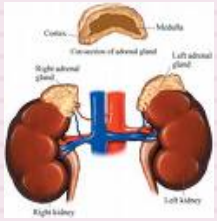


- **> renal functional recovery** (d/c of dialysis) in pts who survived dialysis for >3months **(55 vs 0) %** .
- Continued improvement in renal function for up to 18 months & **higher rate of survival** at 1 year **(76 vs15) %.**

Ann Intern Med 2000; 133:600.

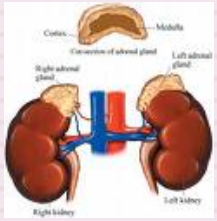


- SRC is a form of BL intrarenal RAS , S.cr may rise initially 2ry to ACE I induced fall in EAR & intraglomerular pressure.
- **Small elevations** in S.cr are usually transient & not progressive & **it is NOT an indication to d/c the ACE I.**



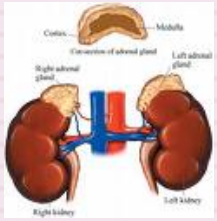
Non-ACE inhibitor therapy

- **<u>It is NOT recommend to use any of these agents:</u>**
  - The efficacy of **ARB** hasn't yet been established.
  - !!! **Prostacyclin** (epoprostenol), has been administered at the onset of crisis based upon anecdotal observations of benefit.
  - !! **Fish oil ,** in view of its theoretical beneficial hemodynamic & antiplatelete properties, its efficacy is unproven .

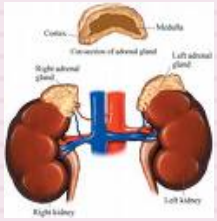


Recommended initial approach

- ***The principal goal of Rx :***
  - To return the BP to the **baseline within 72 h.**
  - Some recommend max. **BP reductions of 20 mmHg/d.**



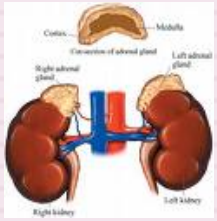
- **W/o evidence of CNS involvement :**
  - **Captopril** should be started at a dose of (6.25 - 12.5 mg).
  - Escalate in 12.5 - 25 mg increments at (4-8) h intervals till the goal BP is reached.
  - The maximum captopril dose is 300 450 mg/ d



- **With evidence of CNS involvement :**

  - It is adviced to administer the same captopril dose escalation regimen & ***add IV nitroprusside***, which has a very short duration of action, for acute BP control.

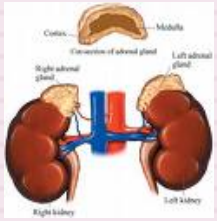
  - The nitroprusside should be d/c ASAP, as captopril in increasing doses lowers the BP .



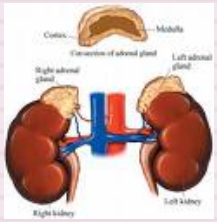
- **Normotensive pts (10%) :**

  - It is adviced to start captopril at a dose of 6.25 mg & if tolerated, increase to 12.5 mg at the 2nd dose.

  - Further dose escalation must be done carefully to prevent the induction of hypotension.

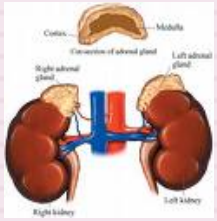


- Some pts have BP within the N range, but still > than the pt's baseline .
- In such pts, the goal is lowering BP to the previous baseline.

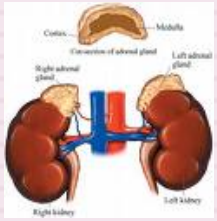


- Over the **long-term,** ACE I (longer acting drugs are usually preferred to captopril) is given to maintain normal BP.

- A **low dose of an ACE I** is ***continued indefinitely***, even if not needed for BP control.

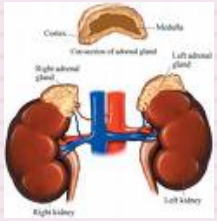


- Some centers in Europe use **parenteral iloprost** infusion in addition to ACE I, but there is ***no clear evidence supporting*** this approach.



Resistant hypertension

- **No studies** that specifically address the role of other antihypertensive agents in pts who are *resistant to initial ACE I*.
- It is prefered to add a **CCB** (eg, amlodipine).
- Minoxidil may be considered if the resistant hypertension persists.
- **BB** are usually **avoided** in pts with scleroderma.

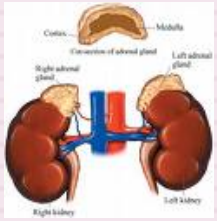


RENAL OUTCOMES

- Despite treatment with ACE I, **(20 - 50 %) of pts progress to ESRD.**

- Pts who require dialysis during the acute episode, an appreciable proportion recover sufficient renal function to d/c dialysis.

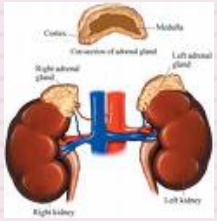
Ann Intern Med 2000; 133:600.



- **In a study145 pts with SRC who were continuously treated with ACE I ,The following findings were noted :**

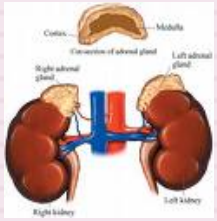
  - 28 pts **(19 %)** died at a mean of 3 m , 18 of whom required dialysis.
  - 55 pts **(38 %)** didn't require dialysis.
  - These pts had a mean peak S. cr of (336 µmol/L) that fell to (159 µmol/L) at 7.1 years.
  - **Only two** had slow deterioration of renal function, requiring dialysis at 4 & 6 y.
  - 28 pts **(19 %)** required permanent dialysis.

Ann Intern Med 2000; 133:600.

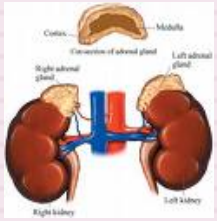


- **In a retrospective single center study of 110 pts (MBP of 193/114 mmHg), 108 were treated with ACE I. It was titrated to reduce the SBP by 20 mmHg /d :**
  - Dialysis was required in 72 pts **(64 %)**, 24 of whom **(33 %)** recovered sufficient renal function to d/c dialysis.
  - Approximately 40 % of pts required permanent dialysis.
  - Overall survival at (1 & 5) y was 82 & 59 %, respectively.
  - The poorest survival seen in those requiring dialysis.

QJM 2007; 100:485

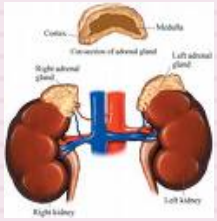


- Despite the improvement with long-term ACE I the outcome of SRC remains **suboptimal.**
- Recurrent SRC occurs in 5% of pts who receive a renal transplant.
- The Rx of recurrent SRC in such pts is the same as that for initial renal crisis.



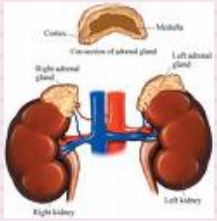
Dialysis

- If indicated, either HD or continuous PD is effective
- **Survival** of dialysis pts with SS is **worse** than in other forms of ESRD .
- In a study of 820 scleroderma pts on dialysis, the 2-y survival was 49 %, compared to 64 % in all other pts .
- vascular access !

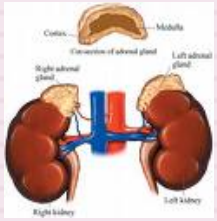


- In the dialysis pt, captopril may only be tolerated *on non-dialysis days.*

- Since the improvement in renal function can continue for up to 18 ms, decisions regarding *renal transplantation shouldn't be made during or immediately following an episode of SRC*.



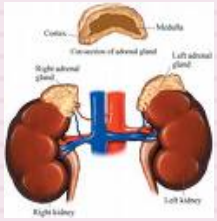
- It is recommended not to perform **renal transplantation** for ***at least one year*** after the initiation of dialysis.



Renal transplantation

- limited experience
- The **UNOS database** *(United Network for Organ Sharing)* included 260 transplants performed b/w 1987 & 2004 for the renal Dx of SS.
- Renal allograft survival in such pts is reduced compared to transplant recipients with other disorders, but outcomes appear to be better than in pts treated with dialysis .
- Reported graft survival rates from the UNOS registry have been (68 – 79) % at 1y, (60 - 70)% at 3 y, and 57 % at 5 y.

Am J Kidney Dis 2001; 37:1152.

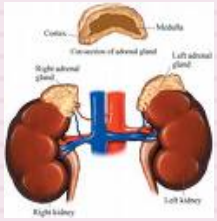


- Despite these relatively lower allograft survival rates, but survival after renal transplantation is superior to that in dialysis pts .

- **This was shown in a study of 258 pts with SS who were listed for renal transplantation b/w the years 1985 - 2002 :**

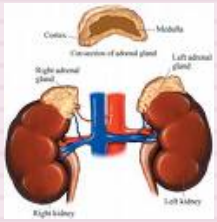
  - The 1 & 3 y pt survival with transplantation was 90 & 80 % , respectively, compared to 81 & 55 % in those who remained on the wait list.

Am J Transplant 2004; 4:2027.



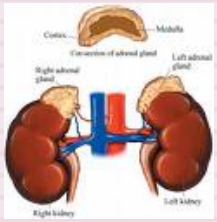
- To help **reduce the risk of recurrent** disease among pts who undergo kidney transplantation, it is adviced to *avoid calcineurin inhibitors & high-dose steroids.*

- Instead, the maintenance immunosuppressive regimen includes ***low-dose steroids, mycophenolate mofetil & sirolimus.***



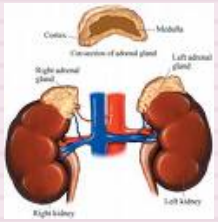
- ***ACE I should be continued indefinitely.***
- Prior to the use of ACE I the recurrence rate of renal damage in the kidney allograft was as high as 20%.
- IN UNOS database the recurrent disease developed in (1.5)% .
- Most recurrences occur within the 1st (1-2) y after transplantation, with many occurring within a few months.

Am J Kidney Dis 2001; 37:1152.



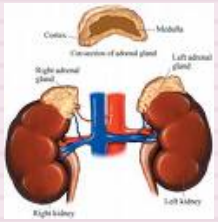
MORTALITY

- A potentially ***life-threatening complication*** .
- Prior to the widespread use of ACE I, almost all pts with significant renal involvement died within 1 y .



- **In a review of 110 pts :**
  - 1-y pt survival was **76 %** in pts treated with ACE I compared to **15 %** treated with other drugs .

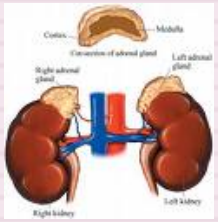
Arthritis Rheum 1998; 41:1613.



Recommendations

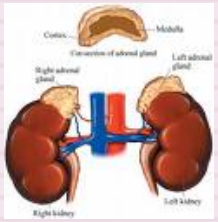
- When glucocorticoid use is unavoidable in pts with SS, we recommend limiting the dose of prednisone to < 15 mg/d & limiting use to the shortest possible period **(Grade 1B).**

- We do NOT use ACE I for the purpose of preventing the occurrence of SRC.



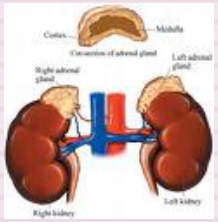
- The therapeutic approach to the pt with SRC varies with the patient's BP & whether the pt has CNS manifestations or not **(Grade 2C)**.

- The principal goal of initial captopril therapy is to return the pt to his or her previous baseline BP within 72 hours.



- We recommend the administration of ACE I rather than other antihypertensive agents **(Grade 1A).**

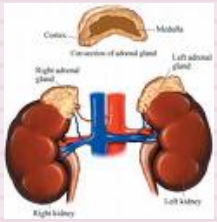
- We suggest initial use of captopril rather than other ACE I b/c of extensive clinical experience & its short onset & duration of action, which permit rapid dose escalation **(Grade 2B).**



- Based principally upon survival benefits with kidney transplantation among all pts with (ESRD), we recommend transplantation rather than HD or PD among pts with SRC who require RRT **(Grade 1B).**

- Renal transplantation shouldn't be performed for at ***least 1 y*** after the initiation of dialysis given **the chance of recovery of renal function.**

- **ACE I** should be continued **indefinitely** in all pts with ESRD, if tolerated.



References

- Uptodate
- Medscape
- Emedicine

THANK YOU