

# Management of Scleroderma Renal Crisis

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### Diagnosis of Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) usually presents with severe hypertension (often described as accelerated or malignant) and acute kidney injury (AKI). It is one of the most severe complications of Systemic Sclerosis (SSc) disease. SRC occurs in approximately 5-10% of all SSc cases (2% with lcSSc and 12% with dcSSc). It is more common early on in the progressive phase of dcSSc with the majority of cases occurring within two years of disease onset. Penn et al. reported a median duration of SSc at time of SRC of 7.5 months (range 0-200 months) with 66% of patients suffering SRC within one year of diagnosis of SSc (Denton 2009). SRC was the presenting feature of SSc for 22% of patients in Penn's series and this late diagnosis was associated with a poorer outcome.

A diagnosis of SSc should be confirmed with nailfold capillaroscopy and thermography studies. The antibody status of a patient should be established including the presence of RNA polymerase III antibody which is associated with an 11-16 fold increased risk of SRC. Clinically, SRC is characterized by the development of severe hypertension together with acute kidney injury. If a patient with SSc has an elevated blood pressure of >150/85 on two occasions in 24 hours, an ACEi should be introduced and/or an increase in their background anti-hypertensives. The blood pressure should be monitored daily to assess response. If they fail to control their blood pressure or develop grade three or four retinopathy, seizures, altered consciousness or cortical blindness they should be referred urgently to a Nephrologist or Rheumatologist for further assessment. If there is a 30% drop in the estimated GFR or proteinuria (>2+) and/or haematuria (1+) (implying severe cortical ischaemia) present on dip-stick urine analysis they should be referred urgently for further assessment.

Clinically, in addition to the above there may be evidence of microangiopathic haemolytic anaemia (MAHA), oliguria, cardiac failure and tachyarrhythmia's. MAHA or intra-vascular haemolysis is present in approximately 50% of patients and is evidenced by reduced platelet counts, red cell fragments, reduced serum haptoglobin levels, red cell fragments and schistocytes on blood film together with massively elevated lactate dehydrogenase (LDH) levels often greater than 2,000 and importantly normal clotting. There may be evidence of cardiac involvement as the left ventricle (LV) struggles to maintain stroke volume in the face of elevated peripheral resistance. Consequently, impressive tachycardias and tachyarrhythmias develop as physiological responses to maintain cardiac output that may also be impaired by underlying restrictive cardiomyopathy and myocardial ischaemia secondary to cardiac vasculopathy. Pulmonary arterial wedge pressures rise and pulmonary oedema may ensue as the LV fails to cope. If any of the above is present, this should prompt urgent referral to a Nephrologist or Rheumatologist for further assessment.

Renal biopsies are considered to be helpful (to exclude other pathologies and assess prognosis) but the timing of renal biopsy needs to be delayed until the patient's BP is well controlled, the clinical condition of the patient is stable and platelet counts have recovered. The presence of ANCA antibodies may prompt an early renal biopsy.

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### Management of Confirmed Scleroderma Renal Crisis

Acute management of SRC involves general supportive care with thoughtful blood pressure (BP) control. Prompt BP control is essential if hypertensive encephalopathy or cardiac de-compensation dictate it. Otherwise, moderate, steady reduction in BP (10% reduction in systolic BP per day) is likely to optimize chances of renal recovery. The use of an ACEI or ARB in the early stages is now standard and there is evidence that continuation of these agents even if the patient becomes dialysis dependent improves the chances of recovering sufficient renal function and becoming dialysis independent (Zawada 1981, Steen 2007). Intra-venous vasodilators especially prostaglandin inhibitors are effective in the short term and the latter may have the added advantage of discouraging platelet/vascular endothelial activation and are beneficial for digital ischaemia and pulmonary disease. Intra-venous prostaglandin inhibitors, in particular, can be titrated effectively in very sick patients to reduce systemic vascular resistance (SVR), increase stroke volume with consequent slowing of heart rate and improvement of cardiac index and cardiac failure. This type of goal-directed management can be facilitated using Oesophageal Doppler or Swann Ganz monitors in an ITU or high dependency setting. In severely tachycardiac patients  $\beta$ -blockers may be contra-indicated and should be used with extreme caution as the increased heart rate maintains cardiac output in the setting of such high SVR and reduced stroke volume.

If AKI is refractory or worsening, consider peritoneal or haemodialysis. Small intravascular changes in the early stages of SRC can alter a patient's clinical situation quickly and dramatically, therefore continuous treatment or PD is preferred if available. In PD, a tenckhoff catheter can be used immediately. An individual patient's hands (contractures) or occasionally severely thickened abdominal skin may preclude this choice.

For dialysis dependent patients renal transplantation is an option but careful consideration needs to be given to the timing of transplantation as renal recovery can occur up to two years following a SRC. Similarly, a suitable immuno-suppressive agent needs to be selected bearing in mind that cyclosporine is known to precipitate SRC. Furthermore, co-existing cardiac and pulmonary disease may dictate suitability for listing. Although in general renal transplantation offers superior survival in SRC patients, graft survival is reduced compared to the general renal transplant population and recurrence of scleroderma may play a role in this poor post-renal transplant outcome.

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### Renal Surveillance in Systemic Sclerosis

SRC occurs in 12% of dcSSc and 2% of lcSSc patients (men and women) and carries a high morbidity and mortality although careful supportive care and BP (blood pressure) management using angiotensin converting enzyme inhibitors (ACEI) or angiotensin-II receptor blockers (ARBs) have improved short-term outcomes. The presence of RNA-polymerase III auto-antibodies (ARA) and recent initiation or intensification of steroid therapy (> 15 mg per day) together with rapidly progressing skin scores are recognized as risk factors. Anaemia, thrombocytopenia and new cardiac events may arise as early consequences of the SRC rather than representing true risk factors yet they serve as useful alerts to the possibility of SRC. The prevalence of ARA in patients whose disease is progressing to renal crisis is at least five times as high as the prevalence in patients who do not develop SRC. Conversely, anti-Scl-70 antibodies though present in 70% of SSc patients are under represented in the SRC population occurring in only 30%. These findings have facilitated targeted vigilance and early anti-hypertensive therapy in those most at risk.

Any patient with SSc who is ARA positive and within three years of diagnosis should have an eGFR and dip-stick urine analysis every six months. A 30% drop in eGFR or dip-stick urine analysis positive for 2+ protein and/or 1+ blood should prompt urgent assessment by a Rheumatologist or Nephrologist. Patients should be encouraged to monitor their BP at home every week and every three months with their GP or hospital consultant. The target BP is less than 140/85.

Clinically, SRC should be suspected when AKI develops in SSc patients. Nevertheless, AKI occurring in SSc patients is not always due to SRC. Asymptomatic renal injury affects 10-55% of patients with SSc and proteinuria is reported in up to 25% of SSc patients. ANCA associated glomerulonephritis has been reported in SSc. Patients typically present with progressive renal failure, mild hypertension, proteinuria and MPO antigen. Renal biopsy is required to exclude SRC and demonstrate crescentic glomerulonephritis.

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**Appendix**

ACEi	Angiotensin converting enzyme inhibitor
AKI	Acute kidney injury
ANCA	Anti-Neutrophilic cytoplasmic antibodies
ARA	RNA polymerase III antibody
ARB	Angiotensin receptor blocker
BP	Blood Pressure
CI	Cardiac index
c/i	Contra-indication
CK	Creatine kinase
Cr	Creatinine
CTDs	Connective Tissue Diseases
CVVHD	Continuous veno-venous haemodialysis
CVVHF	Continuous veno-venous haemofiltration
DBP	Diastolic blood pressure
DcSSc	Diffuse cutaneous systemic sclerosis
EF	Ejection fraction
eGFR	estimated Glomerular filtration rate
GI	Gastrointestinal
HD	Haemodialysis
HDU	High dependency unit
HR	Heart rate
ITU	Intensive therapy unit
LcSSc	Limited cutaneous systemic sclerosis
LDH	Lactate dehydrogenase
MAHA	Microangiopathic haemolytic anaemia
MAP	Mean arterial pressure
PD	Peritoneal dialysis
Pro-BNP	Pro-Brain Natriuretic peptide
SBP	Systolic blood pressure
SRC	Scleroderma renal crisis
SSc	Systemic Sclerosis
SV	Stroke volume
SVR	Systolic vascular resistance

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