Post-Transplant Erythrocytosis: How to Treat This Viscous Situation

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SUMS

Post-Transplant Erythrocytosis (PTE)

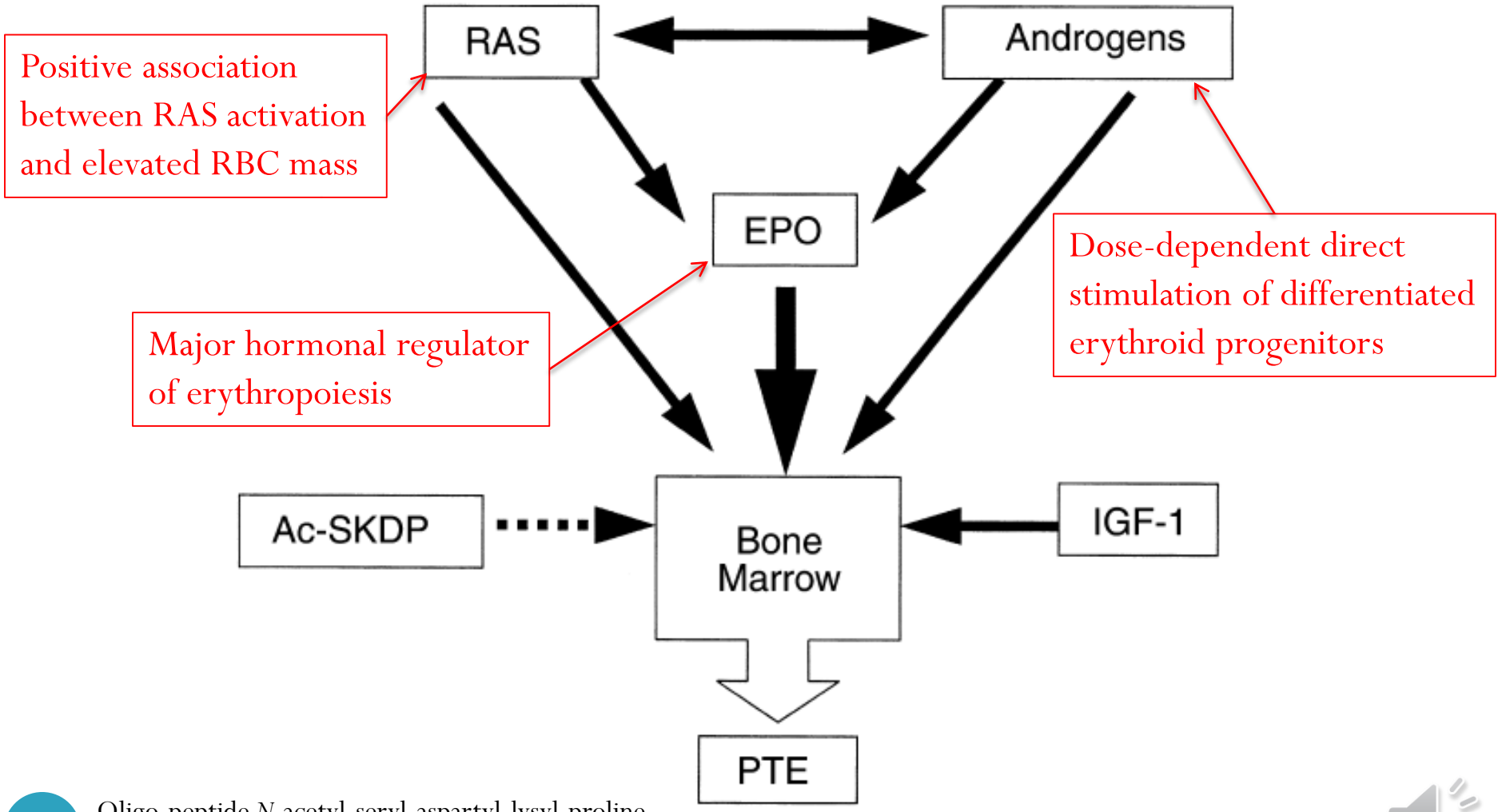
- Reported to occur in 8-15% of renal transplant recipients
- Definition: Hematocrit (Hct) >51% or hemoglobin (Hgb) >17 g/dL for both men and women
  - Persisting longer than 6 months
  - Typical onset: 8 – 24 months after successful transplantation
- Exclude common causes of erythrocytosis including renal artery stenosis, malignancies (renal carcinoma, breast cancer, HCC if positive history of Hepatitis) COPD, Sleep apnea

Risk Factors for PTE

- Male gender
- Rejection-free post-transplant course
- HTN
- Diuretic use
- Retention of native kidney
- Longer duration of hemodialysis prior to transplant
- Smoking
- Diabetes mellitus

- The primary cause of ESKD also affects the risk of PTE
  - Polycystic kidney disease
  - Glomerulonephritis
- Transplanted vs native kidney Renal artery stenosis has not been confirmed as a risk factor for PTE
- **SGLT2** inhibitors may increase the risk of PTE by attenuation glucotoxicity to erythropoietin-producing cells in renal tubulointerstitium

Pathogenesis of PTE



Oligo-peptide *N*-acetyl-seryl-aspartyl-lysyl-proline (Ac-SKDP), Insulin-like growth factor-1 (IGF-1)

Malyszko et al. *Transpl Int*. 2012 Oct;25(10):1013-23.

Presentation of PTE

- Often asymptomatic

- General, non-specific symptoms
  - Malaise and fatigue
  - Lethargy
  - Headache
  - Dizziness
  - Plethora

Consequences of PTE

Increased serum viscosity

- Hct > 51%
- Hgb > 17 g/dl

Increased risk for thromboembolic events

- Develop in 10 to 30% of patients

Mortality rate of 1 to 2%

- Arterial thrombosis, stroke, pulmonary embolism

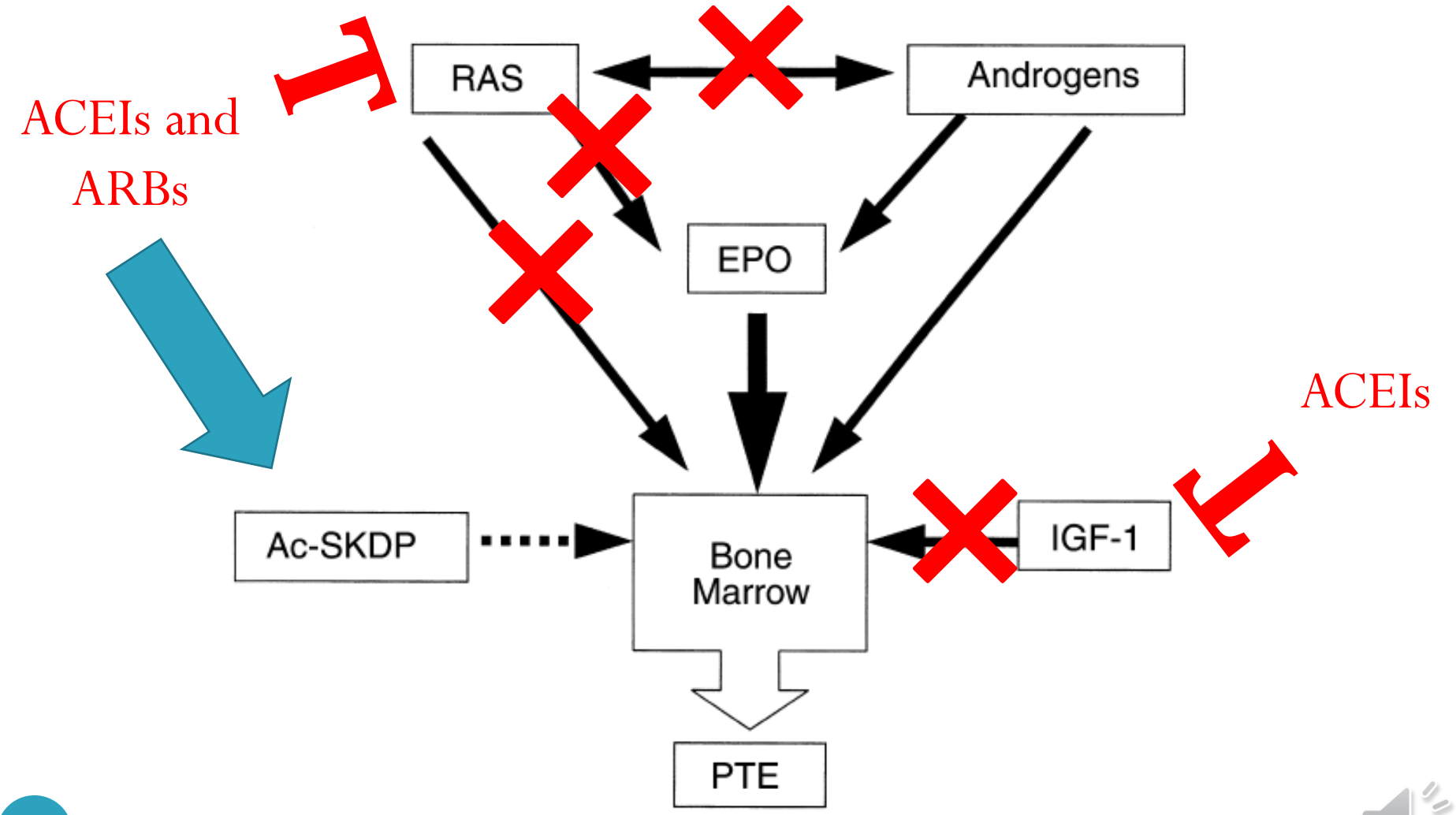
Management and Secondary Prevention

- **Pharmacologic therapy**
  - Angiotensin converting enzyme inhibitors (ACEIs)
  - Angiotensin II receptor antagonists/blockers (ARBs)
  - Theophylline
  - Antiproliferative agents
- **Phlebotomy**
- **Native kidney nephrectomy**

ACEI / ARB Therapy

- ACEIs and ARBs used since 1989 for PTE
  - First line therapy for PTE
  - The choice between ACEI and ARB is dependent upon patient and clinician preference
  - Combination therapy not recommended
- Safety
  - Well tolerated
  - Reversible renal dysfunction may occur
- Efficacy
  - Onset of action within first month in >90% of patients
  - Hct/Hgb nadir within 3 months of therapy

Mechanism of ACEIs and ARBs



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Literature Review on ACEI/ARB in PTE

Study	Study Population	Intervention(s)	Patient Outcome
Marubayashi et al (1998)	4 patients	Enalapril 2.5 mg/day	Reduction in Hct, Hgb, and RBC
Colak et al (2001)	23 patients	Losartan 50 mg/day	Reduction of Hgb and Hct

Literature Review on ACEI/ARB in PTE

Study	Study Population	Intervention(s)	Patient Outcome
Wang et al (2002)	18 patients (8 with PTE, 10 without PTE)	Enalapril 10mg/day and Losartan 50 mg/day	Similar response rate (>1g/dl decrease in Hb)
Esposito et al (2007)	27 patients	Ramipril 2.5–10 mg/day	Hct normalized

Goals of Therapy

- Treatment goal: Hgb to less than 17g/dL
- Treatment duration:
  - Indefinitely for the duration of the functioning allograft
  - Can reoccur if treatment stopped
- Other treatment modalities may be a consideration in patients who cannot tolerate ACEIs/ARBs or in whom ACEIs/ARBs is ineffective

Phlebotomy

- Standard one unit phlebotomy (500cc) should be performed at intervals appropriate for patient size and tolerability

- Once a Hb level<17 g/dl has been stably maintained, withdraw phlebotomy while continuing treatment with ACEIs/ARBs

- Phlebotomy is quite effective in normalizing HCT and may be used chronically for PTE

Theophylline

- Act as an Adenosine antagonist
- Adenosine facilitate both the release of and the bone marrow response to erythropoietin
- Extended-release oral formulation at a dose of 8mg/kg per day

Antiproliferative agents

- **Sirolimus** may be an effective alternative therapy if other medical therapies are ineffective/contraindicated and the patient doesn't wish to undergo repeated phlebotomy
- We do not alter the immunosuppression regimen (eg, switch to sirolimus) to treat PTE in the absense of other indications

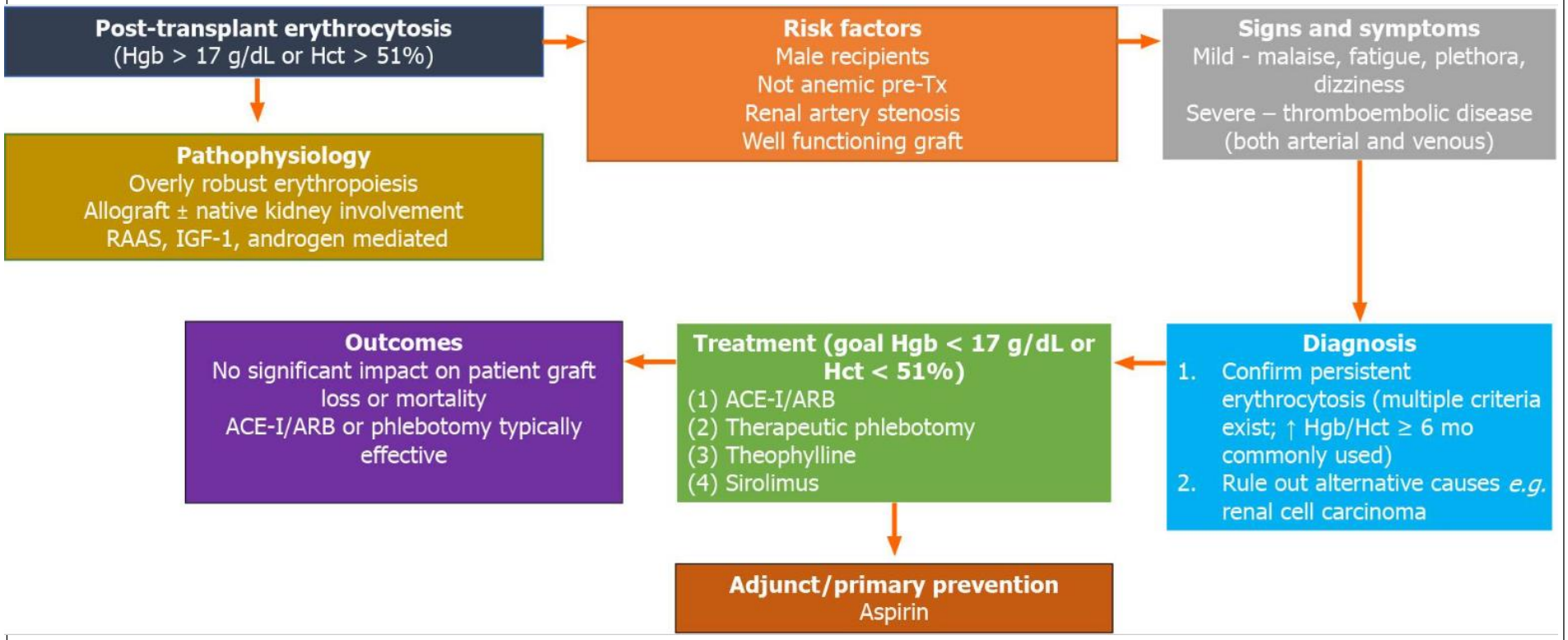
- Management of thromboembolic complications in patients with PTE is similar to other forms of secondary erythrocytosis

- There are no data evaluating the use of Aspirin in patients with PTE, so ASA is often use for primary prevention of cardiovascular events

Remission rates:

- Approximately 25% of patients: spontaneous remission within 2 years

- Remaining 75% of patients: persistent PTE without treatment


Post-transplant erythrocytosis
(Hgb > 17 g/dL or Hct > 51%)
Risk factors
Male recipients
Not anemic pre-Tx
Renal artery stenosis
Well functioning graft
Signs and symptoms
Mild - malaise, fatigue, plethora, dizziness
Severe – thromboembolic disease (both arterial and venous)
Pathophysiology
Overly robust erythropoiesis
Allograft ± native kidney involvement
RAAS, IGF-1, androgen mediated
Diagnosis
1. Confirm persistent erythrocytosis (multiple criteria exist; ↑ Hgb/Hct ≥ 6 mo commonly used)
2. Rule out alternative causes e.g. renal cell carcinoma
Treatment (goal Hgb < 17 g/dL or Hct < 51%)
(1) ACE-I/ARB
(2) Therapeutic phlebotomy
(3) Theophylline
(4) Sirolimus
Outcomes
No significant impact on patient graft loss or mortality
ACE-I/ARB or phlebotomy typically effective
Adjunct/primary prevention
Aspirin

Thank You!