Medicare Evidence Development & Coverage Advisory Committee Meeting
January 19, 2011

Renal Transplantation, Sensitization, and Anemia Management with Erythropoietic Stimulating Agents

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Historical Background:
End Stage Renal Disease Program in Medicare

- Established with Public Law 92-603 Section 2991 on 10/30/1972.
- Included *all ages* with *Stage 5* disease (requiring dialysis) & qualified by work history
- Coverage typically started during 4th month of dialysis
  - →Dialysis services **(out-patient, in-patient)**
  - →Dialysis supplies
  - →Blood transfusions
  - →Drugs associated with dialysis, e.g., heparin & ESAs *(Medicare Part B)*
  - →Transplantation & some transplantation-related costs
- ESA penetration rapid

  Within 1 yr of FDA approval of erythropoietin, it was used by
  - →60% of in-center dialysis patients in Medicare
  - →52% of all dialysis patients in Medicare

Powe 1992

Questions to Consider

What is known about:

- the causes of anemia in patients with renal disease?
- the need to intervene in the setting of anemia?
- the impact of interventions for anemia?
- transfusion reduction by ESAs?
- who receives a renal transplant and why or why not?
- the causes of transplant rejection and how this knowledge has changed
- the causes of sensitization
- how assays for sensitization have changed over time and what they measure
- therapeutic advances to mitigate sensitization

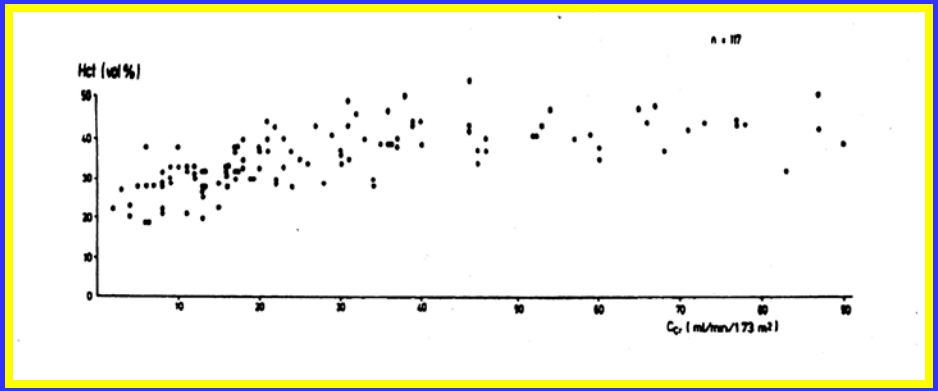
Etiology of Anemia in Renal Disease

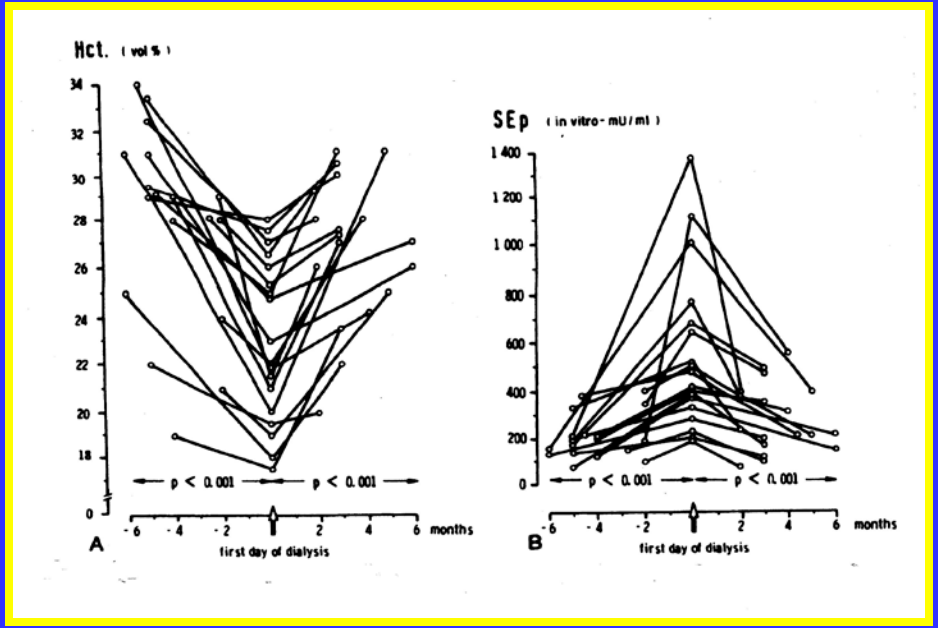
- Uremia → ↓RBC survival
  Marrow suppression
- Hemodialysis procedure & filters → Frank blood loss
  ↓ RBC survival
- Nutrient deficiency, e.g., Fe
- Al toxicity → Direct effects on hematopoiesis
  ↓ Fe metabolism
- Epo Deficiency (related to renal sufficiency level & disease type)
- Epo Resistance (e.g., inflammation)

- Co-morbid Condition: Anemia of Chronic Disease → Cytokines that :
  ↓ Nutrient utilization
  ↓ Epo production
  ↓ Epo effect

Anemia: Longitudinal Data

- Hct & CrCl related if CrCl <30 or 40 ml/min/173 m^2 (r=0.69)
- Hct levels ↓ in the 6 mo prior to dialysis & ↑ with dialysis (no ESA)
- Endogenous* Epo levels ↑ in the 6 mo prior to dialysis & ↓ with dialysis & the related improvement in anemia
- Endogenous Epo more preserved in polycystic kidney disease





Radtke 1979

*Endogenous=made by the body vs Exogenous=produced outside the body

European Blood Alliance *Manual of Optimal Blood Use:*

Co-funded by the European Commission & Scottish National Blood Transfusion Service.

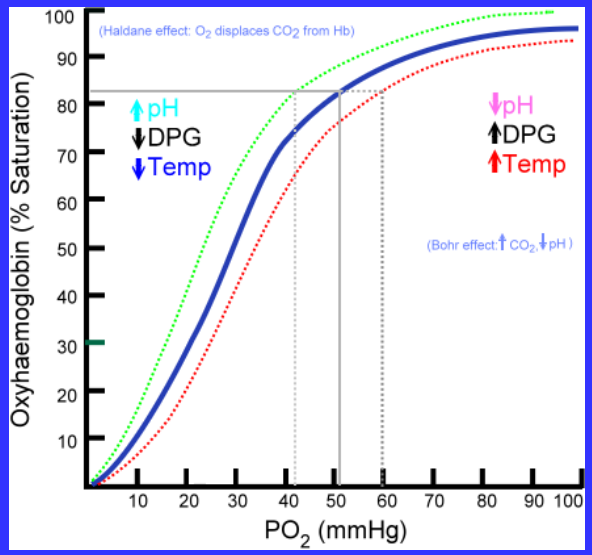
Based on German Medical Association Analysis

Hemoglobin (g/dl)	Compensatory Capacity Risk Factor(s)	RBC Transfusion	Evidence Rating
≤6 g/dl	-----	Yes	1C+ No randomized, controlled studies, but unambiguous data available
>6-8 g/dl	Symptomic Decompensation (ECG ischemia, hypotension, lactic acidosis, tachycardia)	Yes	1C+ No randomized, controlled studies, but unambiguous data available
	Limited Compensation Risk factors such as cardio-vascular disease & cardiac insufficiency	Yes	1C+ No randomized, controlled studies, but unambiguous data available
	Adequate Compensation No risk factors	No	1C+ No randomized, controlled studies, but unambiguous data available
>8-10 g/dl	Symptomic Decompensation (ECG ischemia, hypotension, lactic acidosis, tachycardia)	Yes	2C **Very Weak recommendation,** depending on the individual case, a different course of action may be indicated
>10 g/dl	-----	No	1A **Strong recommendation.** Valid for most patients.

College of American Pathologists (CAP) no longer issues guidelines

Chronic Anemia

- Most data derived from acute care settings
- May not be completely generalizable
- Other compensatory mechanisms
  - ↑ levels of 2,3 DPG (diphosphoglycerate) →
    ↑ release of oxygen to the tissue



Reasons for Transfusions

- Anemia management
  - Epo mediated
  - Non-epo mediated
- Blood loss from hemodialysis
- Surgical Procedures
  - Vascular access
- Bleeding diathesis (↑ *with uremia*)
  - Often GI

Co-morbid disease (↑ *with age*)

- Other causes of anemia
- Other procedures

Transfusion Use

- EASTR survey (UK) (Wells et al. 2009)
  - Most transfusions performed for GI procedures/disease (19%), orthopedic-rheumatic procedures/disease (15%), hematologic disease (13%), and ob-gyn procedures (10%)
  - Few transfusions for renal disease (4%)
  - The renal patients, like most patients except the obstetric patients, were elderly
- Sensitization survey (Hardy, Lee, Terasaki 2001)
  - The small proportion of patients who received many transfusions was reduced by 1996
  - 30-40% of renal patients still received transfusions; a pattern that remained unchanged

Indications for ESAs: Transfusion Reduction?

- No improvement in cardiovascular disease endpoints or mortality
  - NHCT
  - CHOIR
  - CREATE
  - TREAT
- No improvement in exercise tolerance
- No improvement in health-related QOL
  - Indication removed from label by FDA in 2007

Transfusion Data from ESA Registration Studies

- No validated criteria for anemia intervention
- No protocol for transfusion
  - "Clinically indicated"
  - Most studies uncontrolled or open-label
- Little/no publically available information regarding:
  - Indication for transfusion
    - Anemia management vs Bleeding vs Surgical procedure
  - Hgb level at time of transfusion
  - # of units transfused
  - # units/person transfused
  - Serial PRA levels
  - Demographic information on transfused vs non-transfused pts
- Information, where available, limited to # patients transfused

Anemia & Transfusion: Canadian Group Study:
Hemodialysis 6 Month Study No DM Mean Age Mid 40s

Blood Parameter	Placebo	Hct target 9.5-11% vol Variable IV dose 3x/wk	Hct target 11.5-13% vol Variable IV dose 3x/wk
Baseline Hct	7.1±0.9 n=40	6.9±1.0 n=40	7.1±1.2 n=38
Hct at 6 mo (completers)	7.4±1.2 n=32	10.2±1.0 n=34	11.7±1.4 n=33
Hct at end (ITT)	----------	----------	----------
RBC transfusion (TF)			
# pts transfused	23	1	1
# units transfused	----------	----------	----------
# units/pt transfused	----------	----------	----------
# tf by *a priori* protocol established criteria	----------	----------	----------
# tf for hct <10	----------	---------- (GI bleed)	---------- (During surgery)
# tf for hct <7	----------	----------	----------
# pts transfused prior yr	7.3±8.3	6.6±6.8	5.6±6.4
TF dependent*	19	19	11
Anemia evaluation	Fe tests at t=0 & during study; Fe rx prn	Fe tests at t=0 & during study; Fe rx prn	Fe tests at t=0 & during study; Fe rx prn

*Protocol defined as ≥6 transfusions/year; >2 transfusions in 3 months if dialysis just started

Anemia & Transfusion: G88-011 Teehan 1989, Abels 1990: Pre-dialysis 8 Weeks No GFR Criteria Mean Age 57.1 Yrs)

Blood Parameter	Placebo	50 u/kg 3x/wk IV	100 u/kg 3x/wk IV	150 u/kg 3x/wk IV
Baseline Hct	M 29.9±4.1 n=17 F 28.4±3.1 n=12	M 29.7±3.8 n=18 F=28.4±2.6 n=10	M 29.4±4.7 n=17 F 27.0±2.1 n=11	M 28.2±5.6 n=17 F 29.7±3.3 n=13
Hct at 6 mo	----------	----------	----------	----------
Hct at end (ITT)	----------	----------	----------	----------
Hct ↑ of 6% vol	N=3	N=16	N=22	N=27
RBC Transfusion				
# pts TFed	----0-----	----0-----	----0----	----0----
# RBC units	----------	----------	----------	----------
# units/person TFed	----------	----------	----------	----------
# tf by *a priori* protocol using established criteria	----------	----------	----------	----------
# tf for hct <10	----------	----------	----------	----------
# tf for hct <7	----------	----------	----------	----------
# TFed prior yr	----------	----------	----------	----------
TF dependent*	----------	----------	----------	----------
Anemia evaluation	Fe, B-12, Folate tests at t=0. Folate given.	Fe, B-12, Folate at t=0. Folate given.	Fe, B-12, Folate at t=0. Folate given.	Fe, B-12, Folate at t=0. Folate given.**

*≥6 transfusions/year; >2 transfusions in 3 months if dialysis just started . **Multiple myeloma found incidentally

Other Erythropoietin Registration Studies

- Placebo-controlled (uncontrolled not included)
- Known, but unpublished
- Datasets not available
- FDA reviews not available

Study	Treatment	Blind	Length	N=	Comments
8701	Hemodialysis	Double	12 wk	68	Cited by sponsor as proof of transfusion reduction & QOL
8904	Peritoneal Dialysis	Double	12 wk	152	-----
H87-057	Pre-Dialysis	Double	12 wk	93	? published subsets: Kleinman 1989 n=14, Watson 1989

Other ESA Registration Studies:

Aranesp (darbepoetin α) & Mircera (methoxy polyethylene glycol epoetin β)

- Approved for anemia management in renal disease;
- Not approved for transfusion reduction.

- Pivotal studies were non-inferiority studies;
- Designed to show equivalence with antecedent ESAs.

Unpublished Aranesp study 211 (on dialysis, ESA naïve or no recent ESA, 20 wks, n=120) showed that more patients in the darbepoetin arm (27%) than in the epo arm (16%) were transfused at least once. *FDA reviewer wrote "In any case, the data do not make the case that ARANESP decreased the need for RBC transfusions, given the directionally opposite trend".*

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080442.htm

ESRD Management

- The majority of ESRD patients are treated with hemodialysis
- Although the annual incidence of transplant recipients is relatively low, the prevalence is substantially higher—reflecting demographics of the transplant population and/or the therapeutic impact of transplantation

	NEW (INCIDENT) PATIENTS					TOTAL (PREVALENT) PATIENTS				
AGE	HD	PD	TX	UNK	TOTAL	HD	PD	TX	UNK	TOTAL
0-19	636	419	183	7	**1,245**	1,228	838	5,086	57	**7,209**
20-44	11,656	1,153	676	19	**13,504**	46,089	5,560	42,989	300	**94,938**
45-64	37,141	2,717	1,325	56	**41,239**	136,608	11,470	79,941	415	**228,434**
65-74	23,492	1,183	282	29	**24,986**	76,155	4,752	21,630	90	**102,627**
75+	26,961	904	34	18	**27,917**	73,535	3,132	4,727	40	**81,434**
TOTAL	**99,886**	**6,376**	**2,500**	**129**	**108,891**	**333,615**	**25,752**	**154,373**	**902**	**514,642**

USRDS 2009 Report 2007 data. CMS has limited information on pre-dialysis patients because they are not covered by CMS unless they are otherwise covered by age (≥65 yrs) or other disability (<65 yrs)

ESRD Management

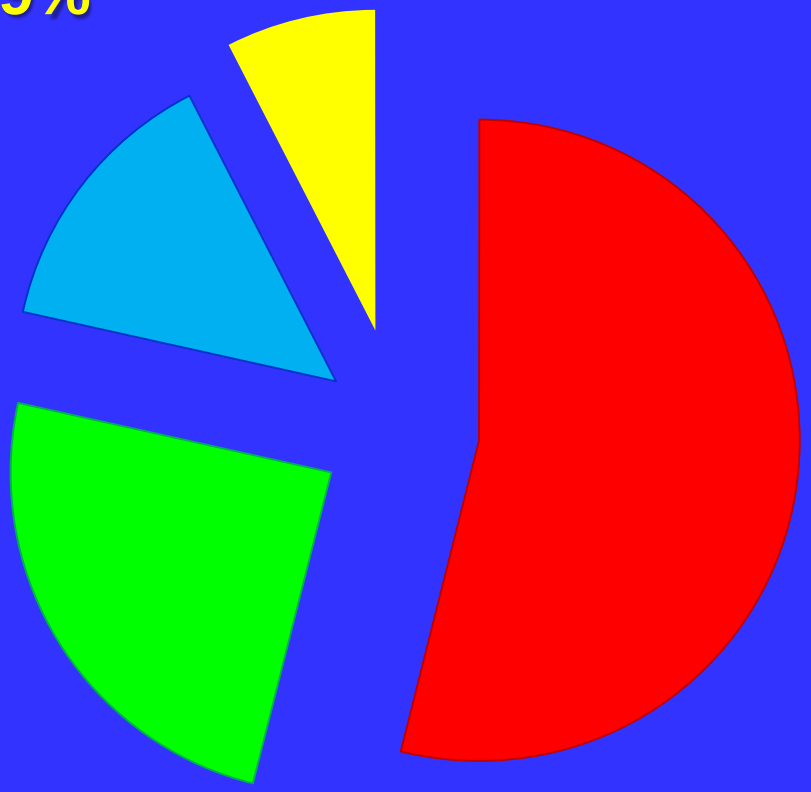
	Incidence		Prevalence		ESRD Treatment	
Age	#	%	#	%	Dialysis:Transplant	
0-19	**1,245**	**1.1**	**7,209**	**1.4**	**1 : 2.4**	**Primarily Transplant**
20-44	**13,504**	**12.4**	**94,938**	**18.4**	**1.2 : 1**	**Dialysis~Transplant**
45-64	**41,239**	**37.9**	**228,434**	**44.4**	**1.8 : 1**	**Dialysis:Transplant**
65-74	**24,986**	**23.0**	**102,627**	**19.9**	**3.7 : 1**	**Primarily Dialysis**
75+	**27,917**	**25.6**	**81,434**	**15.8**	**16.2 : 1**	**Primarily Dialysis**

Age is a major predictor of mortality in ESRD. The likelihood of dying in the 1st year of dialysis compared to 0-44 yr-old cohort is 2x if 44-64 yrs and 4-6x if 75+ yrs.

USRDS 2009 Report 2007 data

Likelihood of Transplantation within 3 yrs of ESRD Registration

Overall 17.9%



USRDS 2009 Report
Data from 2004

Transplant Rejection/Failure

Rejection

- Cellular-mediated
- Humoral-mediated
  - Pre-formed antibodies
  - De-novo antibodies

Failure may reflect

- Donor traits e.g., age
- Recipient traits e.g., underlying renal disease
- Surgical expertise
- Compliance

Timing and biopsies help determine cause(s)

Panel Reactive Antibodies (PRA)

- Developed in the 60s by Patel & Terasaki
- Global test
- The percentage of the pool of local donors to which a patient had reactive antibodies
- Used local blood donor samples as a surrogate for the organ donor pool
- *For example, a 50% PRA level would be a cross-match incompatible with 50% of donors*

Panel Reactive Antibodies (PRA)

Putative Causes of PRA Elevation

- Prior Transplant
- Multiple pregnancies
- Transfusions
  - UNOS/transplant centers do not rigorously collect data on transfusions
- Other
  - Hardy, Lee, Terasaki 2001 13% w/o risk factors +PRA False positive?
  - PRA sample collection before or after dialysis session, statin use,…

➢ UNOS collects PRA data for clinical use and CMS/USRDS, but does not adjudicate on the basis of test type, which can differ by maker and over time. PRA levels reported to UNOS have increased over the last 15 yrs (Cecka 2009) despite extensive ESA penetrance.

➢ Current data collection limitations impact the types of analyses that can be performed and the conclusions that can be drawn

Panel Reactive Antibodies (PRA)

PRA=Relatively non-specific surrogate for sensitization risk

--Low level, but still experience antibody-mediated rejection

--High level (what is too high?) & not experience rejection of a specific organ

Development of methods to measure specific antibodies to specific HLA antigens

--Solid-phase tests with single HLA antigens produced by rDNA technology

→Specific Patient Profiles

→CPRA based on the percentage of actual organ donors that express one or more unacceptable HLA antigens in the patient's profile. (Database 12,00 donors) Recipients are not offered futile organs.

Active Waitlist Patients and PRA: 1999 to 2008

Peak PRA	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Total	36,951	39,958	42,219	44,262	45,475	45,290	46,106	47,039	48,677	50,624
0-9%	22,184	24,629	26,615	27,818	28,624	28,774	28,908	28,736	29,209	28,898
10-79%	7,766	7,847	8,025	8,633	8,915	8,936	9,369	9,925	10,631	11,310
80%+	4,793	5,147	5,327	5,732	6,053	6,107	6,743	7,489	7,923	8,688
Unknown	2,208	2,335	2,252	2,079	1,883	1,473	1,086	889	914	1,728
0-9%	60.0%	61.6%	63.0%	62.8%	62.9%	63.5%	62.7%	61.1%	60.0%	57.1%
10-79%	21.0%	19.6%	19.0%	19.5%	19.6%	19.7%	20.3%	21.1%	21.8%	22.3%
80%+	13.0%	12.9%	12.6%	13.0%	13.3%	13.5%	14.6%	15.9%	16.3%	17.2%
Unknown	6.0%	5.8%	5.3%	4.7%	4.1%	3.3%	2.4%	1.9%	1.9%	3.4%

OPTN/SRTR Data as of May 4, 2009

Sensitized Patient Options

- Better characterization of sensitization
- Induction therapy (rituximab)
- IV Immunoglobulin
- Plasmapheresis
- Paired donor programs (multi-patient/donor swaps)
- Experimental e.g., rh C1 Inhibitor

Sensitized and ABO-incompatible Transplants

	PRA 80+			ABO Incompatible				
Year	Total*	MM > 0	MM = 0	Total	A2-B	A->B	AB->O	B->A
1999	116	82	31	26	4	7	13	6
2000	138	86	50	31	0	2	25	4
2001	172	125	45	26	4	4	19	3
2002	168	135	32	39	2	6	28	5
2003	250	201	48	52	6	9	36	7
2004	261	220	37	64	1	7	51	6
2005	347	283	60	79	4	15	55	9
2006	340	271	68	95	2	19	68	8
2007	316	272	43	91	0	9	66	16
2008	320	260	53	90	4	23	54	13

*Includes living donor transplants where HLA MM information is missing.
SRTR Analysis, August 2009

Renal Transplantation in Sensitized Patients

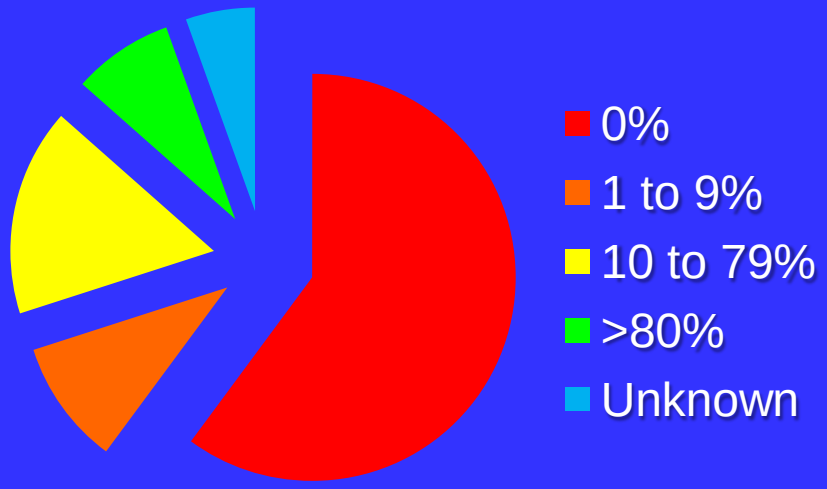
~300-350 transplants are performed annually in wait-listed patients with PRA ≥80%

→~12%% of such incident wait-listed patients or

→~4% of such prevalent wait-listed patients

(2.3% of incident patients are transplanted in year 1)

PRA Level in Incident Wait-listed Patients (2007)



Summary

- There are research gaps in transfusion use and criteria for anemia intervention in acute/chronic settings.
- Therapeutic intervention with transfusions for patients with hb >10 g/dl and most patients with hb levels between 7-10 g/dl is not warranted.
- Although physiologic replacement levels of ESAs may have a role in ESRD patients with significant anemia and ESA responsiveness, the data in support of the transfusion reduction indication are limited.
- ESAs do not eliminate the need for transfusions in many patients because the transfusions are given for renal (and non-renal) related disease.

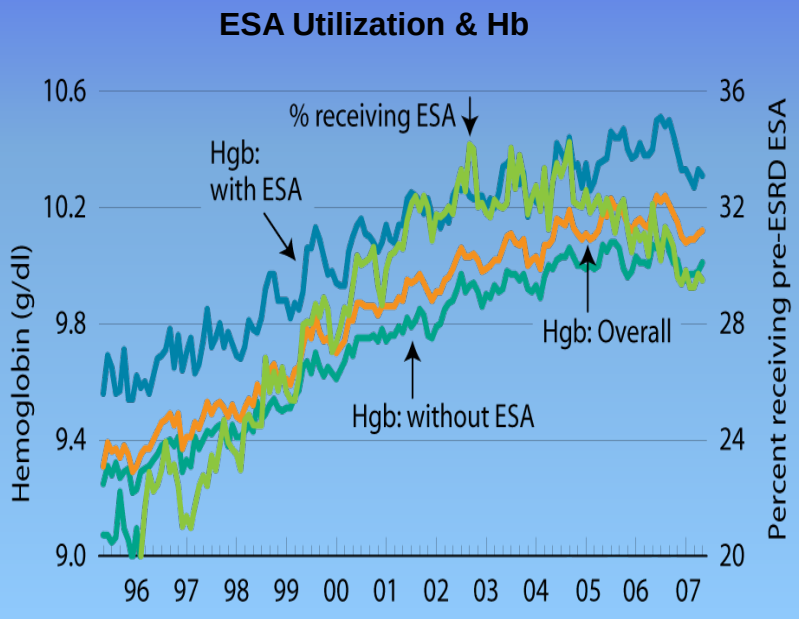
Summary

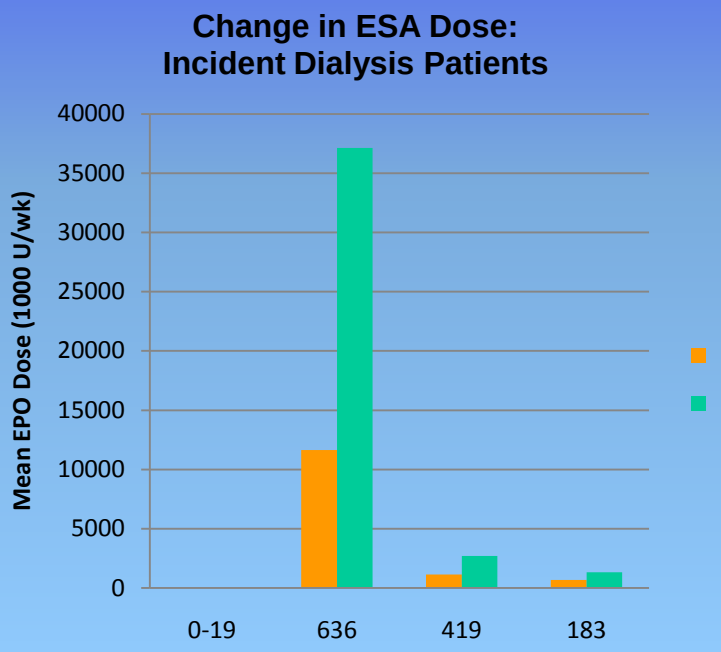
- PRA are non-standardized and non-specific tests, which have changed over time.
- Patient characteristics other than PRA impact on transplant suitability. Most transplant recipients are young and w/o co-morbid disease.
- The relationships between transfusions, PRA, and renal transplant outcomes are not straightforward. Current data collection limits analyses.
- There are options for sensitized patients.

Ancillary Slides

Anemia & ESA Use: X-sectional Data (USRDS)

- Temporal ↑ in ESA use in dialysis patients
- Temporal ↑ in ESA use prior to 1st dialysis
- Temporal ↑ in ESA use in less severe anemia
- Temporal ↑ in ESA dose



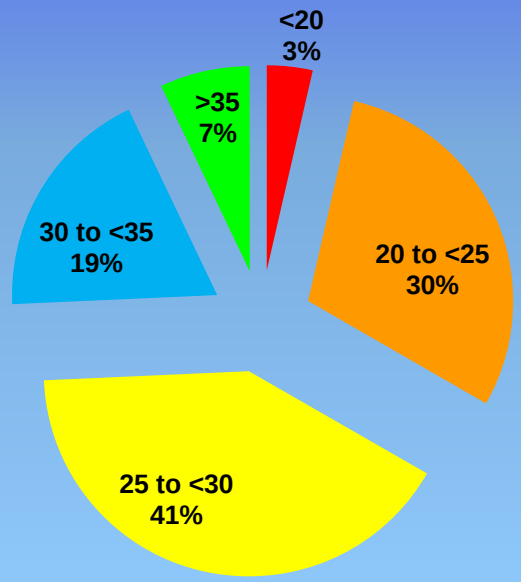


Anemia Prevalence: Historical Perspective

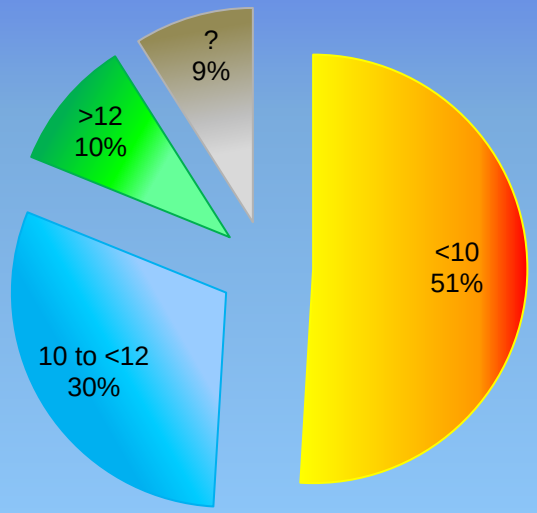
- Anemia long a recognized phenomenon
- Change in severity over time; temporal ↑ in Hb in ESA-naïve patients
- (Change in patient population & advances in patient management)

Eggers 2000

1990 Congress-OTA-H-451 (Hct [vol %])



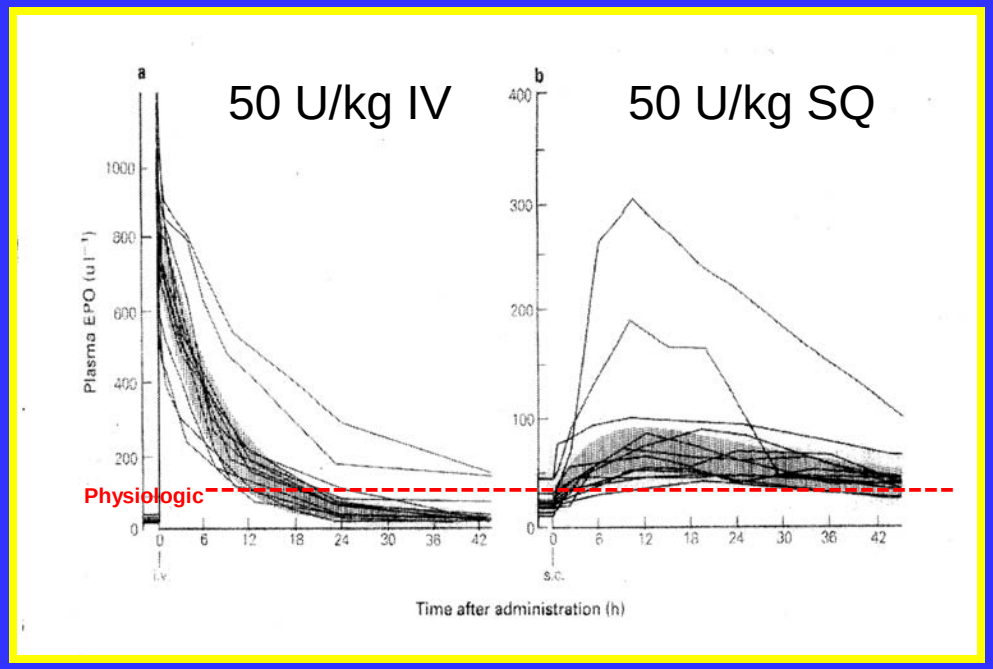
2008 USRDS (Hb [g/dl])



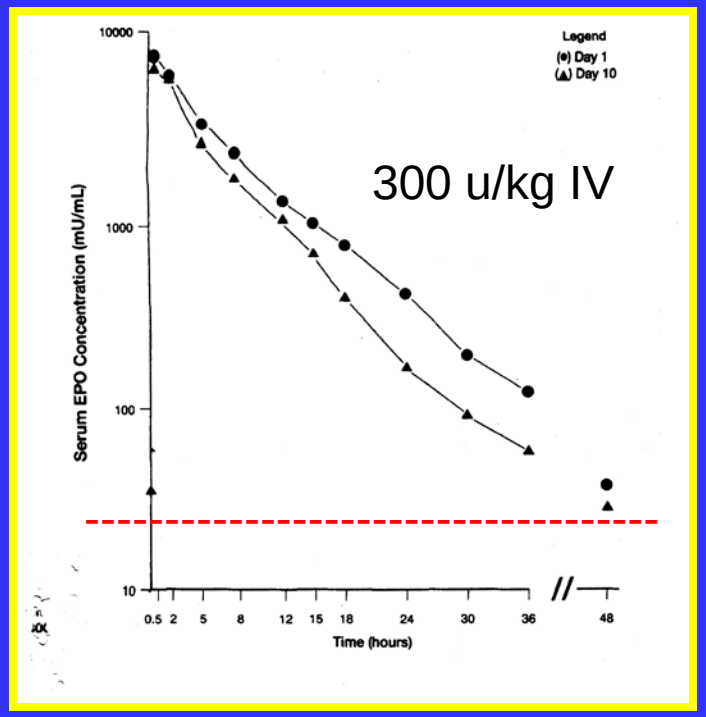
(5.7% ESA use; no nephrologist)

Serum Levels: Physiologic & Pharmacologic

- Serum levels of epo are supraphysiologic for many hours to days (SQ < IV).
- Supraphysiologic exposure is present even at low dosing.
- Supraphysiologic exposure is even greater at higher dosing.



Brockmoller 1992



McMahon 1989

ESA Resistance: Putative/Established Etiology

Defects in the hormone

Defects in/suppression of hormone production

Cytokines, e.g., IL-1, TNF, interferons, & TGF (Means 1992)

Inhibitors to hormone binding

Antibodies to receptor (Casadevall 1996)

Antibodies to hormone receptor

Receptor mutations or defects in post receptor pathways

C-terminus domain exerts negative erythropoiesis control; Up-regulation mutation known (de la Chapelle 1993)

Alterations in target tissue environment/structure

Marrow fibrosis due to ESAs (Animal data, FDA 1989; Kennedy 2006)

Osteitis Fibrosa Cystica (Bhadada 2009, Rao 1993)

Other Myelofibrosis

Alterations in target tissue function

Diseases with Physiologic Inhibitors- Cytokines, e.g., IL-1, TNF, interferons & TGF (Means 1992)

Infection (Occult, Overt) (Elliot 2009, Nassar 2002)

Anemia of chronic disease

Malnutrition-inflammation complex syndrome (Kalantar-Zadeh 2003)

Inflammatory Disease , e.g., IBD (Schreiber 1996), ***?Type 2 DM***

Diseases with Toxins

Uremia & dialysis adequacy (Ifudu 1996, Markson 1956, Radtke 1981, Wallner 1981, Zappacosta 1982)

Diseases with progenitor dysfunction or accelerated apoptosis, e.g., Myelodysplastic Syndromes

Frank deficiency in required or supportive hematologic factors

Nutrients, e.g., Fe, folate (van Wyck 1989)

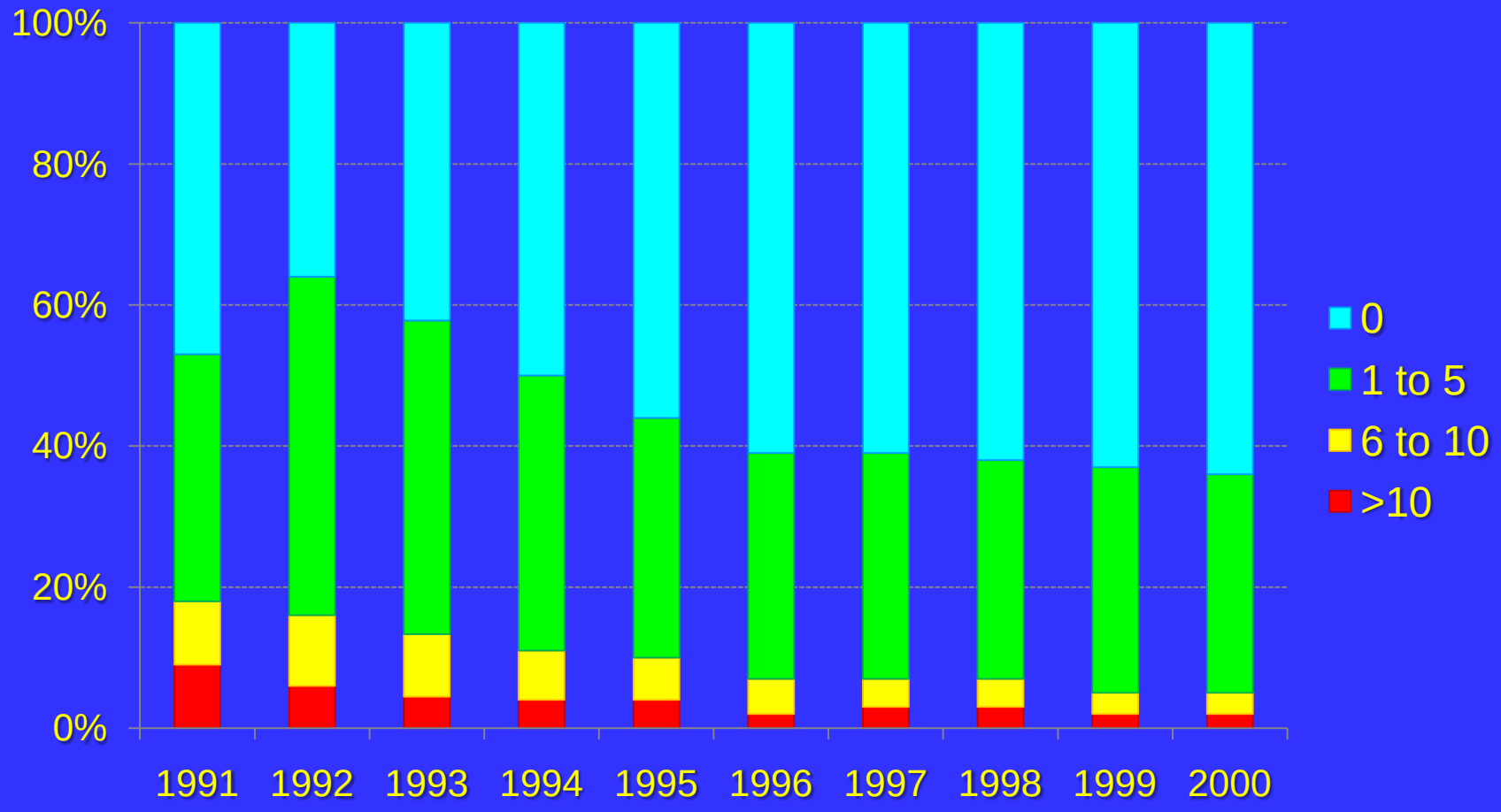
Impairment of hematologic co-factors

Fe by Vitamin C deficiency (Altallah 2006) **& ? Vitamin D deficiency** (Amato 2005, Goicoechea 1998)

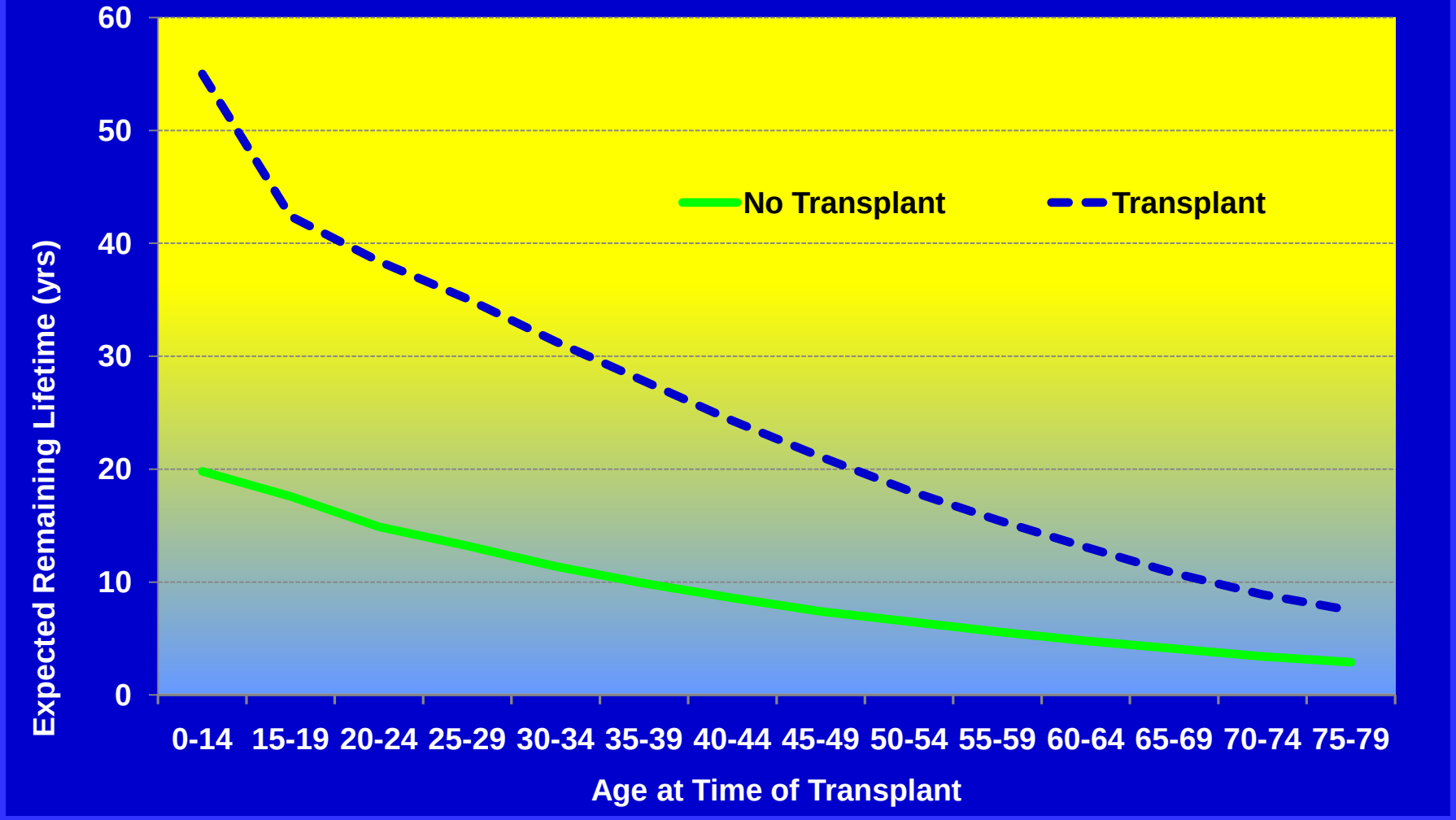
Fe by Al toxicity (Bia 1989, Caramelo 1995)

Secular Transfusion Use Trends

Hardy, Lee, Terasaki 2001



USRDS LIFESPAN PROJECTIONS (2009 Report)



Not based on randomized data. Inherent bias in transplant candidate selection.