Choosing Wisely
Five Things Physicians and Patients

1. Don’t perform routine cancer screening for dialysis patients with limited life expectancies without signs or symptoms.
2. Don’t administer erythropoiesis-stimulating agents (ESAs) to chronic kidney disease (CKD) patients with hemoglobin levels greater than or equal to 10 g/dL without symptoms of anemia.
3. Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) in individuals with hypertension or heart failure or CKD of all causes, including diabetes.
4. Don’t place a peripherally inserted central catheter (PICC) in stage III-V CKD patients without consulting nephrology.
5. Don’t initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians.

Source: ABIM ASN 2012

1973 MEDICARE COVERS DIALYSIS TREATMENT

Initial projection, 1 in 5 patients would be medically suitable for dialysis.

Initial projection incidence = 40 per million
Current incidence = 350 per million.
WE’LL EXAMINE...
- Trend to early initiation of dialysis (MDRD eGFR > 10 ml/min/1.73m²)
- Conventional wisdom that have led to this trend
- Evidence of a mortality, morbidity, or quality of life benefit/harm from this trend to early initiation
- National and International Guidelines
- Renal function trajectory
- Indications to initiate dialytic therapy

FOR TODAY’S DISCUSSION
“EARLY START” = MDRD eGFR > 10 ml/min/1.73m²

Cockcroft Gault equation GFR is 2 – 3 ml/min higher than a given MDRD value

RENAL FUNCTION EQUATIONS
Cockcroft Gault
140 – Age X Weight (kg)/72 X Serum Creatinine, Corrected to a BSA of 1.73m²

MDRD
4 Variable (Most Widely Used)
Gives result that is ml/min/1.73m²
Adjusts for age, sex, race as markers of muscle mass

TREND TO EARLY INITIATION OF DIALYSIS 1996 - 2005

Opinion based guidelines, based on , have resulted in early initiation of dialysis.

A NEW PARADIGM: MUST BE A BENEFIT IN AT LEAST ONE
✓ MORTALITY
✓ MORBIDITY
✓ QUALITY OF LIFE
CONVENTIONAL WISDOM

- Level of dialytic clearance is associated with a survival/morbidity benefit and is comparable to RRF.
- Diabetics need to initiate dialysis earlier than non-diabetics.
- Nutrition can be improved with increased dialysis clearance.
- Low albumin and nutritional issues are synonymous.

MORE CONVENTIONAL WISDOM

- At low levels of renal function, (eGFR < 15 ml/min/1.73m²), most nephropathies progress relentlessly to minimal kidney function.
- Waiting until GFR is < 6 ml/min/1.73m² is dangerous.

Owen, NEJM, 1993

- Low URR associated with increased risk of death
- Serum albumin, as a predictor of mortality, 2\&times URR
- Diabetic patients had lower serum albumin and URR than non diabetics
- Increase of URR did not improve nutritional status

Conventional Wisdom ...

Diabetics need to initiate dialysis earlier than non-diabetics.

KT/V Urea/Creatinine Clearance and When to Commence Dialysis

63 patients
6 deaths
Correlated with KT/V urea
Minimum KT/V 1.05 liters per week

CANUSA
Starting Creatinine Clearance versus One Year Survival
< 3.8 ml/min = 73.6%
≥ 3.8 ml/min = 82.3%

Churchill, JASN, 1997
**WHEN TO INITIATE DIALYSIS?**

*Indices of malnutrition should be considered objective criteria for the initiation of dialysis.*

Hakim, JASN, 1995

This shift in indication may have been one of the prime movers to early dialysis initiation.

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**1997 K DOQI Guidelines**

NKF Workgroup recommended that initiation of dialysis be considered when the arithmetic mean of CCR and urea clearance fell below 10.5 ml/min/1.73² except in well-nourished, asymptomatic patients.

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**MEASUREMENT OF DIALYSIS AND RESIDUAL RENAL CREATININE CLEARANCE**

170ml/min X 210 min = 35.7 liters
X 3 days per week = 107 liters

Creatinine Clearance of 10 ml/min
10 ml/min X 60 min X 24 hrs X 7 days = 100.8 liters

---

**RCT PD Patients**

Dialytic Clearance Did Not Provide Survival Benefit

ADEMEX, JASN, 2002

**RCT Hemo Patients**

Higher Doses of KT/V and High Flux = No Survival Benefit

HEMO Study, NEJM, 2002

Conventional Wisdom .... Level of dialytic clearance is associated with a survival/morbidity benefit and is comparable to RRF.

---

**Does early initiation of dialysis provide a survival benefit?**
Studies Examining the Issue Of Comorbidity Adjusted Early Initiation of Dialysis Versus Survival

- Traynor, JASN, 2002
- Beddu, JASN, 2003
- Kazimi, AJKD, 2005

NONE showed a comorbidity adjusted survival benefit!

Additional Large Population Based Studies Examining the Issue Of Comorbidity Adjusted Early Initiation of Dialysis Versus Survival

- Stel, NDT, 2009
- Sawhney, NDT, 2009
- Hwang, NDT, 2010
- LaSalle, KI, 2010
- Wright, CJASN 2010
- Clark, CMAJ, 2011
- Rosansky, Arch Int Med, 2011

NONE of these studies showed a survival benefit of early dialysis initiation!

Early Start of Dialysis May Be HARMFUL

- Rosansky, Arch Int Med, 2011
- 81,176 USRDS Hemodialysis Patients
- Treated Between 1996 - 2006
- Non-diabetic, 20 – 64 years old
- “Zero” Report Comorbidity
- Stratified by Serum Albumin

Healthy Cohort Study

- < .6 sensitivity for comorbidity reporting
- Higher eGFR = "poorer overall health"
- "Suspect comorbidity data” confounds eGFR vs. outcomes

- Weiner, Am J Kid Dis, 2011

Adverse effect of early start vs. survival

- Eliminated using 24 hour urine based creatinine clearance, especially if
  - lower BMI and lower serum albumin (<19 kg/m², < 2.5 g/dl)
  - diabetic

- Beddu, JASN, 2003
- Grootendorst, NDT, 2011

Healthy Cohort Study

- Overestimation of GFR minimized
- No diabetics, 6% BMI < 18.5
- 15% serum albumin < 2.5 gm/dl
- Non reported comorbidity equal across eGFR groups?

- Rosansky, Arch Int Med, 2011
SURVIVOR BIAS

"Survival of the fittest" Vs. Observational Studies

Does early initiation of dialysis have any comorbidity benefit?

NUTRITION?
CARDIAC MORBIDITY?
ENDOGENOUS RENAL FUNCTION?

The RCT IDEAL Study, recently published in the New England Journal of Medicine, also failed to show a survival advantage of early start.

NUTRITION

Hemodialysis:

- stimulates protein catabolism
- stimulates whole body degradation of protein including muscle protein.
- results in loss of aminoacids
- promotes dialyzer blood interaction/inflammation
- corrects metabolic acidosis
  - may decrease protein catabolism but study results are conflicting.
The HEMO study/nutritional aspects
- Increased dialytic clearance / had no effect on serum albumin or post dialysis weight
- All nutritional parameters, except for dietary protein energy intake, had small but statistically significant decline, average follow-up of 3 years.
- Decrease albumin associated with decrease synthesis and increased inflammation.

Conventional Wisdom ...
Nutrition can be improved with increased dialysis clearance.

Serum albumin comorbidity factor, not nutritional factor...
- Only in a state of negligible protein intake will albumin decline
- Albumin levels driven by non-dietary factors
- Severe nutritional deprivation, marasmus, anorexia nervosa, maintain normal albumin even with very low BMIs.
- Patients with chronic kidney diseases, albumin catabolism increases
- Associated inflammatory disorders - main reason for low albumin
- Metabolic acidosis increases albumin catabolism

Conventional Wisdom ...
Low albumin and nutritional issues are synonymous.

CARDIAC MORBIDITY
McIntyre KI 2009
- Hemodialysis recurrent ischemia
- Ultrafiltration volume drops in intradialytic BP
- “Stunned myocardium” even in pediatric patients
- Myocardial structural and function changes
- Spontaneous dysfunction heart failure

Pun KI 2009
Rates of sudden cardiac death by eGFR category:

<table>
<thead>
<tr>
<th>eGFR ml/min/1.73m²</th>
<th>Sudden Death per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>3.8</td>
</tr>
<tr>
<td>15 – 59</td>
<td>7.3</td>
</tr>
<tr>
<td>&lt;15</td>
<td>12</td>
</tr>
<tr>
<td>On dialysis</td>
<td>24</td>
</tr>
</tbody>
</table>

Endogenous Residual Renal Function

CANUSA
- For each 5 l/wk/1.73m² increase in GFR, 12% decrease in risk RR of death
- 250 cc increase urine out
- 36% decrease RR of death

Bargman JASN  2001

NECOSAD
- 1 cc increase in RRF = 12% decrease in mortality

Kendrick, CJASN, 2010

BENEFITS OF RRF
Beneficial effect on nutritional parameters
Suda, NDT, 2000
Correlates to:
- Decreased inflammation
- Lower LVH
More rapid decline, worse survival
Kendrick, CJASN, 2009

Improves:
- Survival, hemo and PD
- Fluid balance
- Phosphorus control
- Anemia
- Quality of life
Perl, Am J Kid Dis  2009
RRF Declines With Time on Dialysis

- Hemo Greater Than Peritoneal
- Hemo Decline 10.7% Per Mo.
- PD Decline 8.1% Per Mo.
- BP Control, with UF, can hasten decrease in RRF

NECOSAD Study
- Transient HRQOL benefit with early start
- Disappeared after one year of treatment

PCS QOL Score
- 10 point lower PCS = 1 gram serum albumin as survival predictor

ADEMEX
- Kt/V had no effect on quality of life
- Baseline QOL score predictor of survival and hospitalization

OTHER DIALYSIS INITIATION GUIDELINES

Australia New Zealand 2005
- Start at GFR less than 10 ml/min/1.73m²
- If evidence of uremia or its complications such as malnutrition
- If not symptomatic start dialysis when GFR falls below 6 ml/min/1.73m²

Canada 2008
GFR < 20 patients may need to start dialysis if symptomatic including Nutritional decreasing albumin or LBM not responsive to dietary interventions

United Kingdom 2000
- Start RRT for CKD 5
- Based on a discussion of risks benefits
- Consider starting at eGFR < 6 ml/min/1.73m² even if asymptomatic

In 2006, the NKF Workgroup
Updated Guidelines for Initiating Dialysis

"... at CKD stage 5, when eGFR is less than 15 ml/min/1.73m², nephrologists should examine the benefits, risks and disadvantages of beginning renal replacement therapy"

They also stated that the initiation of dialysis before CKD stage 5 may be appropriate for patients who have symptoms believed to be related to both their comorbidities and their level of RRF.
**ADDRESSING CONVENTIONAL WISDOM**

- At low levels of renal function, (eGFR < 15 ml/min/1.73m²), most nephropathies progress relentlessly to minimal kidney function.
- Waiting until GFR is < 6 ml/min/1.73m² is dangerous.

---

**Low eGFR Dialysis Initiation**

Hwang, NDT, 2010
23,351 Taiwan Patients
Median eGFR = 4.7 ml/min/1.73m²

- Inverse relationship between eGFR and survival
- < 3.29 ml/min/1.73m² reference group
- eGFR > 6.52 ml/min/1.73m²
- HR 2.44 vs. reference group

---

**Definition of Renal Function Trajectory**

MDRD eGFR change per year

---

**With stable diet, weight/muscle mass,**

**Renal Trajectory**

May be more important than an “accurate” GFR.

---

**Renal Function Trajectory**

846 AASK
Bayesian Model

- 41% non-linear or prolonged non-progression
- 8.7% had both a stable/improved trajectory interval and then rapid decline interval

---

**Non-linear Decline**

Li, AJKD, 2012
Patterns of Renal Function Trajectory

- Flat/Stable
- Improvement
- Linear Decline
- Interrupted Decline by AKI or ACE/ARB
- High Variability
- Rapid Decline
- Slow Decline

COMPETING RISK OF DEATH VS. NEED FOR DIALYSIS

"Most patients with CKD die before they need RRT."

Jaar, CJASN, 2008

Elderly CKD 4/5
Risk of death exceeds risk of definite need for RRT

Conway, NDT, 2009
Demoule, NDT, 2011
O’Hare, KI, 2007

How Often is Renal Trajectory Flat or Up?

- 3,047 patients
- 10 year study
- Mean Age = 75
- eGFR Range = 25 – 55 ml/min/1.73m²
- 27% Had No Decline in GFR
  - Average change -1.03 ml/min/1.73m²/yr

Erikson, KI, 2006

4,231 CKD 4 patients
Mean Age = 67
Mean rate of change -2.65 ml/min/1.732/yr

67% had stable renal function over 2 years
If RRF down > 5 ml/min/1.732/yr, 76% went on hemodialysis.
If RRF down < 5 ml/min/1.732/yr, 27% went on hemodialysis.

Levin, Am J Kid Dis, 2008
When to Initiate Dialysis?

Attending multidisciplinary pre-dialysis clinic
- Better biochemistry parameters at start of therapy and fewer hospitalizations
- Lower chance of death in 3 year follow up after dialysis initiation.

Goldstein, Am J Kid Dis, 2004

Multidisciplinary care - pre dialysis and four months post initiation
- 22% decrease in mortality
- 8% decrease in hospitalizations

Wingard, CJASN, 2009

CMS mandate to improve HRQOL, optimize medical, psychological, and social intervention.

Finkelstein, KI, 2009

What is the contribution of 3 x weekly non-dialytic care to morbidity, mortality and quality of life?

IDEAL RCT Study
8x8 Patients
Mean Age = 60.4

- Early start = eGFR 7.2 ml/min/1.73m², late start = eGFR 9.0 ml/min/1.73m²
- No significant survival difference between early and late starts

EDITORIAL REGARDING IDEAL RCT
- "Just in time dialysis"
- Contends most nephrologists start dialysis on the basis of clinical factors rather than numerical data such as eGFR.

Lamierre, NEJM, 2010
Clinical Symptoms at Dialysis Initiation

- Non-specific nature of symptoms correlate to comorbidity
- Low serum albumin, older age, more symptoms
- Fatigue, nausea, anorexia most common symptoms

Curtis, Clin Nephrol, 2002

Nephrologists’ Opinions on Dialysis Initiation 1999 Questionnaire

Most important factor:
- Uremia .................38%
- GFR ....................32%
- Nutrition ............20%

Decision for early start:
- DM ......................90%
- Malnutrition .......72%
- Improved QOL ......39%

Ledbe, NDT, 2001

ERBP Guidelines
When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study

MDRD eGFR not useful to decide on when to initiate
- Support for pre-dialysis clinics
- Emphasis on preparation of patients for dialysis, before GFR < 55 ml/min/1.73m² and before they become symptomatic
- Consider dialysis at GFR < 35 when any symptoms of uremia, including deterioration of nutritional status
- Patients with eGFR declining over 4 ml/min/yr/1.73m² and diabetics need close supervision
- If this is not feasible and the uremic symptoms may be difficult to detect
- Consider a planned start to dialysis while asymptomatic

Tattersal, NDT, 2011

ERBP Guidelines Continued

“High quality evidence that patients will have uremic symptoms” before eGFR of 6 ml/min/1.73m²

“Delaying dialysis until there are symptoms would carry a risk of harm or death due to uremia.”

Tattersal, NDT, 2011

IDEAL Protocol Violations

<table>
<thead>
<tr>
<th>Reason for not starting dialysis in assigned GFR range (protocol violations)</th>
<th>Randomized to early start group but started with GFR &lt; 10 ml/min/1.73 m² (n=175)</th>
<th>Randomized to late start group but started with GFR &gt; 7 ml/min/1.73 m² (n=377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia</td>
<td>5</td>
<td>234</td>
</tr>
<tr>
<td>Physician discretion</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Delay in access creation</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Unavailability of resources</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Sudden improvement in GFR</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

Tattersal, NDT, 2011

WHAT IS UREMIA?

BetterMedicine.com

“Uremia is a state in which the blood urea nitrogen level, an indicator of nitrogen waste products, is elevated. In uremia, the kidneys’ failure to filter nitrogen waste properly leads to excessively high levels of nitrogen wastes in the bloodstream. Uremia is life-threatening because too much nitrogen in the blood is toxic to the body. Symptoms of uremia include confusion, loss of consciousness, low urine production, dry mouth, fatigue, weakness, pale skin or pallor, rapid heart rate (tachycardia), edema (swelling), and excessive thirst. Uremia may also be painful.”

Tattersal, NDT, 2011
“The term uremia, which literally means urine in the blood, was first used by Piorry to describe the clinical condition associated with renal failure.

Uremia can occur once the creatinine clearance is below 10-20 mL/min, and it is heralded by the clinical onset of nausea, vomiting, fatigue, anorexia, weight loss, muscle cramps, pruritus, mental status changes, visual disturbances, and increased thirst. Uremic encephalopathy can progress to seizures, stupor, coma, and, eventually, death.”

“Because uremia mostly is a consequence of kidney failure, its signs and symptoms often occur concomitantly with other signs and symptoms of kidney failure, such as hypertension due to volume overload, hypocalcemic tetany, and anemia due to erythropoietin deficiency. These, however, are not signs or symptoms of uremia. Still, it is not certain that the symptoms currently associated with uremia actually are caused by excess urea, as one study showed that uremic symptoms were relieved by initiation of dialysis, even when urea was added to the dialysate to maintain the blood urea nitrogen level at approximately 90 mg per deciliter (that is, approximately 32 mmol per liter).”

“Addressing Conventional Wisdom

- At low levels of renal function, (eGFR < 15 ml/min/1.73m²), most nephropathies progress relentlessly to minimal kidney function.
- Waiting until GFR is < 6 ml/min/1.73m² is dangerous.

ERBP Dialysis Initiation Guidelines Critique

- No comprehensive literature review
- Did not include the possible harm study
- MedScape called the Rosansky Archives article the number one “Game Changer” article for nephrology for 2011.
- The IDEAL cross-overs were not 72% “uremia”
- eGFR is useful, interpret with care if low, declining muscle mass

Wikipedia

“Because uremia mostly is a consequence of kidney failure, its signs and symptoms often occur concomitantly with other signs and symptoms of kidney failure, such as hypertension due to volume overload, hypocalcemic tetany, and anemia due to erythropoietin deficiency. These, however, are not signs or symptoms of uremia. Still, it is not certain that the symptoms currently associated with uremia actually are caused by excess urea, as one study showed that uremic symptoms were relieved by initiation of dialysis, even when urea was added to the dialysate to maintain the blood urea nitrogen level at approximately 90 mg per deciliter (that is, approximately 32 mmol per liter).”

DiMicco, NDT, 2009

30 patients
Initial eGFR ≤ 11
- Prospective study start at eGFR 6 ml/min/1.73m²
- Used nine indications to start, one was uremia
- Half of the patients had no indication to start by eGFR 6 ml/min/1.73m²
- Only seven (23%), of the 30 patients had any of nine listed indications, one of which was “uremia”
- Eight patients did not start dialysis after 21.8 months

This Discussion EXCLUDES End Stage Liver Disease or Heart Failure where Dialysis is not used as a treatment for ESRD, but as a management tool.
Three Additional Scenarios

1. ARF to ESRD
2. ARF on CRF to ESRD
3. Gradual Loss of Renal Function to ESRD

WE WILL ADDRESS #3

KDIGO 2013 GUIDELINES

5.3: TIMING THE INITIATION OF RRT

5.3.1: We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m². (2B)

New Definition for the New Paradigm

ESRD = eGFR ≤ 5 ml/min/1.73m²

Suggested reference point for dialysis initiation

eGFR > 5 - 9 ml/min/1.73m²

For uremia related:

- Pericarditis
- Coagulopathy
- Gastroenteropathy
- Anorexia
- Encephalopathy
- Volume Overload/Hypertension - Not Responsive to Diuretic Therapy

Stabilization of Elderly Early Starts
CONCLUSIONS

1. The US incident hemodialysis population with initial MDRD eGFR 1-10 ml/min/1.73m² increased from < 10 to > 50% between 1996 and 2008.

2. Early initiation of dialysis cannot be justified since it does not provide a mortality, morbidity or quality of life benefit.

3. Serum albumin level is a strong predictor of dialysis patient mortality.

4. Conventional wisdom of relating albumin levels to nutritional state appears to be wrong.

5. Low serum albumin is a marker of comorbidity and poor prognosis.

6. Despite general acceptance of the practice, there is no evidence that diabetic patients benefit from early dialysis initiation.

7. The two randomized controlled trials examining the effect of dialytic clearance on survival have shown that increasing dialytic clearance is not accompanied by a survival benefit.

8. Residual renal function correlates with dialysis patient survival. Every effort should be made to preserve patients residual renal function.

9. Renal function trajectory must be considered in the decision to prepare a patient for dialytic therapy. Younger patients and patients with heavy proteinuria are more likely to have a rapid decline in residual renal function. Elderly patients have a slower decline of residual renal function.

10. Available studies do not support the conventional wisdom that at low levels of renal function, (MDRD eGFR < 6ml/min/1.73m²), renal function will inevitably decline rapidly. Presumptive dialytic therapy in these patients is not justified on the basis of eGFR levels alone.

11. Use of multidisciplinary interventions in patients with eGFR in the 10-20 ml/min/1.73m² range is strongly encouraged and may decrease the high initial mortality of the incident dialysis population.

12. Multidisciplinary pre-dialysis clinics may be of great benefit to the elderly population who choose maximal conservative management and whose renal function may decline at a rate that will not require dialysis.

13. Recent observational studies utilizing large national and international databases and the randomized controlled trial, IDEAL, have demonstrated that dialytic therapy at eGFR levels of 5-9 ml/min/1.73m² or less may be the most appropriate time to consider dialysis initiation. Definitive uremic complications at higher levels of renal function are appropriate reason to initiate dialysis.

14. The decision to initiate dialysis must be a patient/physician joint decision with full disclosure.

Choosing Wisely
Five Things Physicians and Patients

1. Don't perform routine cancer screening for dialysis patients with limited life expectancy without signs or symptoms.

2. Don't administer erythropoiesis-stimulating agents (ESAs) in chronic kidney disease (CKD) patients with hemoglobin levels greater than or equal to 10 g/dL without symptoms of anemia.

3. Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) in individuals with hypertension or heart failure or CKD of all causes, including diabetes.

4. Don't place a peripherally inserted central catheter (PICC) in stage III-IV CKD patients without consulting nephrology.

5. Don't initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians.

Don't initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians.

The decision to initiate chronic dialysis should be part of an individualized, shared decision-making process between patients, their families, and their physicians. This process includes eliciting individual patient goals and preferences and providing information on prognosis and expected benefits and harms of dialysis within the context of these goals and preferences. Limited observational data suggest that survival may not differ substantially for older adults with a high burden of comorbidity who initiate chronic dialysis versus those managed conservatively.
QUESTIONS