Associations of Chronic Kidney Disease with Infectious Disease

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Tufts University School of Medicine, Boston, MA

KDIGO Controversies Conference, Amsterdam, The Netherlands
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Objectives

• What is known?
  ⇨ Review the evidence

• What can be done with what is known?
  ⇨ Provide clinical practice recommendations

• What needs to be known?
  ⇨ Provide clinical research recommendations
# Review of the Evidence

## Main Topics
- CKD and 5 chronic infectious diseases (CID) of global importance
- Vaccination strategies in CKD
- Potential pitfalls of GFR estimates in infectious disease

## Other Topics
- CKD and acute infectious diseases
  - Pneumonia
  - Sepsis
- CKD-T (transplant) and infectious disease
- CKD and infectious disease in children
The CKD-CID Complex
The CKD-CID Complex
Original CKD Conceptual Framework: CID $\Rightarrow$ CKD

Susceptibility factor $\Rightarrow$ Initiation factor $\Rightarrow$ Progression factor $\Rightarrow$ End-stage factor

HIV, HCV, HBV
Conceptual Framework: CKD in the Natural Course of CID

CKD can be present at any stage during the course of CID
Is CKD a Risk Multiplier for CID?
Stage-5 CKD-D and Infectious Disease: What Have We Learned?

The Analogy with CVD!
Infection 2nd Leading Cause of Death (15%) in Dialysis Patients Following CVD

Total Death Rate = 176 deaths per 1000 patient years

USRDS 2003 Annual Report
Sepsis-Related Mortality of Dialysis Patients Compared with the General Population

Pulmonary Infectious Mortality of Dialysis Patients Compared with the General Population

Annual Mortality (%) vs Age (years)

- Dialysis Population
- General Population

10-fold increase in mortality for the Dialysis Population compared to the General Population

Sarnak & Jaber: Chest 120:1883-1887, 2001
Susceptibility of Patients with CKD to Infections

Virulence of microorganisms

Dialysis-related Factors (for CKD-5-D)

Impaired Host Immunity
Pathogenesis of Infections in CKD

Virulence of microorganisms

Dialysis-related Factors (for CKD-5-D)

- Neutrophil dysfunction
- Monocyte dysfunction
- Impaired T-cell activation
- Impaired humoral responses

Impaired Host Immunity
What About CKD as a Risk Multiplier in Patients with CID?

1. Prevalence of CKD in CID

2. Association of CKD with CID-associated adverse outcomes
Infections of Global Importance

Overall burden of 874 million

- TB: 15 million
- HIV: 40 million
- HCV: 170 million
- Malaria: 300 million
- HBV: 350 million

www.who.int
### Proposed Framework: CKD as a Risk/Prognostic Factor for Infectious Diseases

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<th>Infectious disease (ID)</th>
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<td></td>
</tr>
<tr>
<td>TB</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HIV and CKD
HAART and Incidence of HIVAN: A 12-Year Cohort Study

HIVAN incidence (per 1000 person-years)

- No antiretroviral therapy: 26
- Nucleoside analogue therapy: 14
- Highly-active antiretroviral therapy: 7

Lucas GM et al: AIDS 18:541-6, 2004
CDC National Surveillance of Dialysis-Associated Diseases, 1995-2002 U.S.
- HIV/AIDS -

Finelli L et al: *Seminars in Dialysis* 18:52-61, 2005
Proteinuria/Increased Serum Creatinine in HIV-Infected Patients

- Markers of HIV-related kidney disease:
  - HIVAN
  - Other HIV-related glomerular diseases
  - Nephrotoxicity of HIV-related drugs
- Indicators of poor health status as a result of:
  - Hypertension
  - Diabetes mellitus
  - Cardiovascular disease
## Summary of HIV-CKD Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Sample size</th>
<th>Renal predictor variable</th>
<th>Outcome variable</th>
<th>Results (multivariate analyses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewden C (2002)</td>
<td>Multicenter prospective cohort study (France)</td>
<td>1155 HIV-infected adults</td>
<td>Baseline and post-treatment (4-month) sCr &lt; normal (0.9 [male] or 0.8 [female] mg/dl)</td>
<td>Mortality</td>
<td>• Baseline HR 2.4 (1.3, 4.3) • 4-month HR 2.5 (1.0, 6.1)</td>
</tr>
<tr>
<td>Gardner LI (2003)</td>
<td>Prospective cohort study (USA)</td>
<td>885 HIV-infected and 425 at-risk HIV negative women</td>
<td>Baseline renal abnormalities: proteinuria (≥ 2+) and/or sCr ≥ 1.4 mg/dl</td>
<td>Mortality</td>
<td>HR 2.5 (1.9, 3.3)</td>
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<td>Baseline renal abnormalities: proteinuria (≥ 2+) and/or sCr ≥ 1.4 mg/dl</td>
<td>Condition-specific hospitalizations</td>
<td>• Overall hospitalization HR 1.5 (1.3, 1.8) • Hosp. AIDS defining illness HR 1.7 (1.1, 2.7) • Hosp. renal conditions HR 5.0 (2.3, 11.0) • Hosp. hepatic conditions HR 1.8 (1.1, 2.8)</td>
</tr>
</tbody>
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| Szczech LA (2004) | Prospective cohort study (USA) | 2038 HIV-infected women                          | Proteinuria ($\geq 1+ \geq 2$ visits) Inverse sCr decrease | new AIDS-defining illness (ADI) and death before and after widespread use of HAART | Pre-HAART ADI  
• Proteinuria HR 1.3 (1.1, 1.6)  
Post-HAART ADI  
• 1/sCr↓ HR 1.4 (1.0, 2.1)  
Pre-HAART Death  
• Proteinuria HR 1.3 (1.1, 1.8)  
• 1/sCr↓ HR 1.7 (1.1, 2.7)  
Post-HAART Death  
• Proteinuria HR 2.2 (1.3, 3.7) |
| Levin A (2006) | Prospective cohort study (Canada) | 2629 HIV-infected adults initiating antiretroviral therapy | eGFR (MDRD 4-variable equation) < 60 ml/min/1.73 m² | Mortality                                                                          | eGFR < 60 ml/min/1.73 m²  
HR 1.65 (1.01, 2.71) |
# Proposed Framework: CKD as a Risk/Prognostic Factor for Infectious Diseases

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<td>++ AIDS defining illness Hospitalization</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guidelines for Management of CKD in HIV/AIDS

- Published Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients
- HIV Medicine Association of the Infectious Diseases Society of America (IDSA)
- 15 members: 7 nephrologists, 8 infectious disease specialists
- Guidelines adopt KDOQI Guidelines to estimate kidney function

Clinical Infectious Disease 40:1559-85, 2005
HBV, HCV and CKD
Association between HCV Seropositivity and Albuminuria: NHANES III (N = 15,029)

No association with low eGFR (< 60 ml/min/1.73 m²)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Adjusted odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>0.8</td>
<td>* P = 0.05</td>
</tr>
<tr>
<td>40-59</td>
<td>1.8</td>
<td>* P = 0.05</td>
</tr>
<tr>
<td>&gt;= 60</td>
<td>2.5</td>
<td>** P = 0.01</td>
</tr>
<tr>
<td>All ages</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race, educational status, smoking status, diabetes, and hypertension

HBV, HCV, and Proteinuria (≥ 1+) in Southern Taiwan (n = 9,934)

Prevalence of Viral Hepatitis

- HBSAg-positive rate
- Anti-HCV positive rate

* P < 0.001

Prevalence of Proteinuria

- Proteinuria quantified with automated reader on 2 separate visits

Multivariate Analyses of Variables Associated with Proteinuria

9,934 subjects

8,696 nondiabetic subjects

<table>
<thead>
<tr>
<th>Variables&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (+)</td>
<td>3.735</td>
<td>3.133–4.453</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (+)</td>
<td>1.974</td>
<td>1.673–2.329</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-HCV (+)</td>
<td>1.648</td>
<td>1.246–2.179</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI (kg m&lt;sup&gt;-2&lt;/sup&gt;)</td>
<td>1.078</td>
<td>1.055–1.102</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.014</td>
<td>1.000–1.028</td>
<td>0.044</td>
</tr>
<tr>
<td>Triglycerides (mg dL&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>1.002</td>
<td>1.001–1.002</td>
<td>&lt;0.001</td>
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OR, odds ratio; CI, confidence interval. <sup>a</sup>Variables included: age, sex, body mass index (BMI), alanine aminotransferase (ALT) level, total cholesterol level, triglyceride level, presence of diabetes, presence of hypertension, presence of antibodies to hepatitis C virus (anti-HCV), seropositive for hepatitis B surface antigen (HBsAg). For the continuous variables, OR represents one unit increase in the value of the variable tested.

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<th>95% CI</th>
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<tr>
<td>Hypertension (+)</td>
<td>1.963</td>
<td>1.611–2.392</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-HCV (+)</td>
<td>1.847</td>
<td>1.332–2.561</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg m&lt;sup&gt;-2&lt;/sup&gt;)</td>
<td>1.086</td>
<td>1.057–1.116</td>
<td>&lt;0.001</td>
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<td>Triglycerides (mg dL&lt;sup&gt;-1&lt;/sup&gt;)</td>
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# HBV Pretreatment Characteristics and 6-Month Mortality (N = 154)

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<th>Predictor variable</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>3.54 (2.03, 6.18)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.27 (0.14, 0.52)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.56 (1.35, 1.81)</td>
</tr>
<tr>
<td>HBV DNA positivity</td>
<td>5.16 (1.21, 21.93)</td>
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### Proposed Framework for CKD as Risk Factor for Infectious Diseases

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<td>HCV</td>
<td>HCV Ab(+): proteinuria ($\geq 1$+) = 10.2% eGFR &lt; 60 ml/min/1.73 m$^2$ = 2.0% (95% CI 1.1, 3.6%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>HBV</td>
<td>HBS Ag(+): proteinuria ($\geq 1$+) = 6.4%</td>
<td>?</td>
<td>+</td>
</tr>
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Reported Malarial Nephropathies in Endemic Areas

- **Acute malarial nephropathy:**
  - *Plasmodium falciparum*
  - Southeast Asia, India, and sub-Saharan Africa
  - Incidence:
    - Native patients in endemic areas: 1-5%
    - Non-immune Europeans: 25-30%

- **Chronic malarial nephropathy:**
  - *Plasmodium malariae* and *P. Vivax*
  - African children
  - Chronic glomerulopathy

TB and Chronic Kidney Disease

- 7- to 53-fold increased risk of TB in stage-5 CKD compared to the general population
- High incidence of extra-pulmonary disease
- High prevalence of anergy to tuberculin skin test
  - Two-step tuberculin skin testing (booster phenomenon)
  - Annual screening in dialysis units (stage-5 CKD-D)

Dogan E et al: Ren Fail 27:425-8, 2005
CDC National Surveillance of Dialysis-Associated Diseases, 1995-1997 U.S.
- Active Tuberculosis -

Prevalence of Tuberculin Sensitivity and Anergy in Stage-5 CKD in an Endemic Area

Prevalence of Tuberculin Sensitivity

- ESRD patients: 44% (N = 108)
- Age- and sex-matched healthy controls: 66% (N = 100)

* P = 0.002

Prevalence of Anergy

- ESRD patients: 44%
- Age- and sex-matched healthy controls: 16%

* P < 0.001

Cumulative Prevalence of a Positive Tuberculin Skin Test in Hemodialysis Patients

$N = 224$

Booster injection administered at a 7-day interval

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<tr>
<td>HCV</td>
<td>HCV Ab(+): proteinuria = 10.2% eGFR $&lt; 60$ ml/min/1.73 m$^2$ = 2% (95% CI 1.1, 3.6%)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>HBV</td>
<td>HBS Ag(+): proteinuria = 6.4%</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Malaria</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>TB</td>
<td>CKD-5-D point prevalent active TB = 6.8%</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
What About Vaccination in CKD?

Guidelines for Vaccinating
Kidney Dialysis Patients and
Patients with Chronic
Kidney Disease

summarized from
Recommendations of the Advisory Committee on
Immunization Practices (ACIP)
## CDC Vaccination Recommendations for Patients with CKD

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommended</th>
<th>May Use If Otherwise Indicated</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>DTaP/Tdap/Td</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>X (see p. 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza (TIV)</td>
<td>X (see p. 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza (LAIV)</td>
<td></td>
<td>X (see p. 4)</td>
<td></td>
</tr>
<tr>
<td>Japanese Encephalitis</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Meningococcal</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>X (see p. 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polio (IPV)</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Smallpox</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Typhoid</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Yellow Fever</td>
<td></td>
<td>X*</td>
<td></td>
</tr>
</tbody>
</table>

*No specific ACIP recommendation for this vaccine exists for renal dialysis patients and patients with chronic renal disease.

†Children with primary immunodeficiency disorders and both children and adults who have received hematopoietic, hepatic, or renal transplants are at risk for severe or prolonged rotavirus gastroenteritis and can shed rotavirus for prolonged periods. [*Prevention of Rotavirus Gastroenteritis Among Infants and Children: Recommendations of the Advisory Committee on Immunization Practices* †Unpublished]
Decreased Responses to Vaccination in Patients with Stage-5 CKD

• Protective antibody levels not easily achieved
  – Impaired macrophage function
  – ↓ T-cell activation and proliferation
  – ↓ B-cell count and IgG production

• Protective antibody levels fall rapidly
# Doses and Schedules of Hepatitis B Vaccines for Patients with CKD

Adapted from CDC. Recommendations for Preventing Transmission of Infections Among Chronic Hemodialysis Patients. *MMWR* 2001; 50 (No. RR-5):Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Recombivax HB</th>
<th>Engerix B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td>Volume</td>
</tr>
<tr>
<td>≥20 years of age: Predialysis*</td>
<td>10 μg</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>≥20 years of age: Dialysis-dependent</td>
<td>40 μg</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>&lt;20 years of age†</td>
<td>5 μg</td>
<td>0.5 mL</td>
</tr>
</tbody>
</table>

* Immunogenicity might depend on degree of renal insufficiency.
† Special formulation.
‡ Doses for all persons aged <20 years approved by the U.S. Food and Drug Administration. For hemodialysis patients, higher doses might be more immunogenic.

Message lost in translation
Immunogenicity of Hepatitis B Vaccine Declines with Age and CKD

CDC: MMWR 50 (No. RR-5), 2001
Fraser GM et al: J Hepatol 21:450-4, 1994
Antibody Response to Engerix-B and Recombivax-HB Vaccination in Stage-5 CKD-D (N = 14,456)

Odds ratio for antibody response to Engerix (vs. Recombivax) = 1.96 (95% CI 1.56, 2.45) adjusted for age, gender, race, diabetes, vintage, BSA, hemoglobin, and eKt/V

Pneumococcal Vaccine: Antibody Response in Dialysis Patients

Linnemann CC et al: Arch Int Med 146:1554-6, 1986
Influenza Vaccination Rates in CKD-5-D are Below U.S. National Objectives

- HD: 49%
- PD: 39%
- Whites: 60%
- Non-Whites: 30%
- 2000 Objective: 60%
- 2010 Objective: 90%

Dialysis Patients

General Population

MMWR 50:532-37, 2001
Odds of Hospitalization and Death are Lower among Vaccinated Dialysis Patients

What About Other Vaccines?

- Other vaccines such as diphteria, tetanus, polio (DTP) and are not well studied in CKD
- The usual schedule is recommended if indicated
- Protection is likely to be suboptimal as with other vaccines

Workgroup Tasks: Clinical and Research Recommendations

• Should we screen for CKD in chronic infectious diseases (HBV, HCV, and HIV)?

• Should we vaccinate in earlier stages of CKD (e.g. stage 4)?

• Do we need better tools to estimate kidney function in chronic infectious diseases (HBV, HCV, and HIV)?