Hemodialysis Complications
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INTRODUCTION

Hemodialysis is now used as a life-sustaining therapy for more than 300,000 patients in the United States who have end-stage renal disease. After work by pioneering physicians, including Kolff, Merrill, Scribner, and Schreiner, dialysis has become a standardized therapy. Beginning in 1973, legislation has entitled Medicare patients with end-stage renal disease to dialysis treatments irrespective of means, education, employment, or other medical conditions. As the incidence and prevalence of hemodialysis patients in the United States have grown, the age and number of comorbid diseases in patients initiating hemodialysis therapy also have increased. In recent years, hospitalization rates for hemodialysis patients have remained stable, whereas risk-adjusted mortality has improved slightly. Increased attention is being given to appropriate transitioning from chronic kidney disease care to the initiation of dialysis therapy, and controversies exist about optimal times for referral to nephrologists and initiation of dialysis therapy.

Loss of kidney function leads to uremic syndrome, a complex phenomenon involving dysfunction of many organ systems in the body. Uremic syndrome is attributable to the retention of numerous solutes normally excreted by healthy kidneys. Although many of these abnormalities can be improved with hemodialysis therapy, it also should be recognized that dialysis may potentiate or even worsen some uremic complications. As an example, use of heparin as an anticoagulant during hemodialysis exacerbates the tendency to gastrointestinal bleeding. The hemodialysis procedure also can contribute to uremic malnutrition through augmented amino acid losses in dialysate. Similarly, treatments designed to prevent one uremic complication can lead to another. As an example, oversuppression of secondary hyperparathyroidism can lead to adynamic bone disease.

For a nephrologist taking care of hemodialysis patients, the complex interrelationships between uremic syndrome, patient comorbidities, and effects of renal replacement therapy mandate considerable knowledge regarding potential complications. In essence, the nephrologist caring for hemodialysis patients is practicing “anephric” internal medicine.

ADDITIONAL READING


VASCULAR ACCESS

History

- Temporary vascular access: Kolff 1943
- External arteriovenous (AV) Quinton-Scribner shunt: 1960
  - Frequent thrombosis and infection
- Endogenous AV fistula (AVF): Brescia and Cimino 1966
  - Interpositional bridge grafts: 1960s
    - First autogenous saphenous veins
    - Bovine carotid arteries
    - Human umbilical veins
- Synthetic bridge grafts: 1970s
- Expanded polytetrafluoroethylene: late 1970s
Indwelling venous catheters
Tunneled cuffed double-lumen catheters: late 1980s
Subcutaneous vascular ports: early 2000s

Epidemiology
- Increasing vascular access–related morbidity and cost
- Large European and US practice pattern variation in vascular access use:
  - 80% versus 24% native AVF prevalence in Dialysis Outcomes and Practice Patterns Study
- Large US variation in vascular access use by dialysis facility:
  - Prevalence of AVFs ranges from 0% to 87%
- Central venous catheter use associated with increased relative mortality risk versus AVFs and AV grafts (US Renal Data System [USRDS] Study)
- US prevalence of AVF use is increasing (USRDS data and Medicare Clinical Performance Measures data)

Arteriovenous Fistulae
- Venous anatomy of the arm
- Types of AVFs:
  - Radiocephalic fistula
  - Brachiophecalic fistula
  - Brachiobasilic fistula
  - Brachial-perforating vein fistula (Gracz fistula)
- Preoperative ultrasonographic or venographic vein mapping
- AVF maturation:
  - Early thrombosis
  - Maturation failure
  - Surgical and endovascular ligation of tributary veins

Arteriovenous Grafts
- Advantages of low early thrombosis rate and short time between access creation and successful cannulation
- Increased long-term risk for infection and thrombosis versus AVFs
- AV graft thrombosis:
  - Accounts for 80% of all graft dysfunction
  - Related to venous stenosis in >90% of cases
  - Patency may be improved by vascular access monitoring and surveillance

Cuffed Venous Catheters
- Relatively easy placement
- Advantage of immediate usability
- High rate of infectious and thrombotic complications
- Catheter-related bacteremia:
  - Associated with serious morbidity and mortality
  - Treatment:
    - Catheter removal or guidewire exchange
    - Role of antibiotic lock solution
- Catheter-related thrombosis:
  - Thrombolytic therapy (urokinase, tissue plasminogen activator)
  - Mini-dose warfarin not proven effective
  - Right atrial thrombi
- Central vein stenosis:
  - Subclavian vein stenosis
  - Superior vena cava stenosis

Vascular Access Monitoring and Surveillance
- Attempts to identify access dysfunction before thrombosis
- Assumes benefit from elective correction of stenotic lesions
- Vascular access monitoring techniques:
  - Physical examination
  - Static and dynamic venous pressure monitoring
  - Vascular access blood flow monitoring
  - Measurements of access recirculation
  - Vascular access imaging
- Multidisciplinary vascular access monitoring programs

ADDITIONAL READING
ANEMIA

Pathogenesis
- Erythropoietin deficiency
- Shortened erythrocyte survival

Complications of Anemia in Kidney Disease
- Left ventricular hypertrophy and/or dilatation
- Decreased exercise capability
- Increased intradialytic hypotension
- Decreased quality of life
- Increased sexual dysfunction
- Decreased cognitive capacity

Treatment

Packed red blood cell transfusions
- Transfusion reactions
- Transfusion-associated hepatitis
- HLA presensitization

Erythropoietic agents
- Erythropoietin
- Darbepoetin

Treatment with erythropoietic agents
- Intravenous versus subcutaneous administration
- Target hemoglobin (Hb) level:
  - Kidney Disease Outcomes Quality Initiative clinical practice guidelines, 11 to 12 g/dL (110 to 120 g/L)
  - Improved morbidity, quality of life, and mortality with higher Hb levels in observational databases
- Improved quality of life and morbidity with higher target Hb levels in some randomized clinical trials
- Greater mortality with “normalized” target Hb in 1 large randomized clinical trial of patients with cardiovascular disease
- Resistance to erythropoietic agents:
  - Uremic toxicity (inadequate dialysis)
  - Inflammation
  - Increased blood loss:
    - Dialyzer blood loss
    - Frequent phlebotomy
    - Gastrointestinal bleeding
- Hemolysis:
  - Kinking of dialysis tubing
  - Thermal erythrocyte injury
- Iron deficiency (discussed next)
- Pure red cell aplasia
- Hyperparathyroidism
- Complications of erythropoietic therapy:
  - Hypertension
  - Hyperkalemia
  - Development of iron deficiency
  - Increased vascular access thrombosis
  - Seizures (rare)

Treatment of iron deficiency
- Oral iron salts
- Intravenous iron
- Iron dextran
- Iron sucrose
- Iron gluconate

Complications of intravenous iron
- Anaphylactic reactions (iron dextran)
- Free iron toxicity
- Excess iron deposition (hemochromatosis)
- Increased oxidative stress
- Possible increased cardiovascular toxicity
- Possible increase in infectious complication rate

Biochemical parameters for monitoring iron therapy
- Serum ferritin (indirect measure of storage iron):
  - Ferritin <100 ng/mL (µg/L) usually reflects iron deficiency
  - Serum ferritin also an acute-phase reactant
Percentage of transferrin saturation (TSAT):
- Assesses availability of circulating iron
- <20% TSAT an indicator of iron deficiency
- Serum iron level and TSAT affected by inflammation
- Percentage of hypochromic cells
- Reticulocyte Hb content:
  - Measures iron status at level of reticulocyte

**Additional Reading**

**Cardiovascular Disease**
- High prevalence of morbidity and mortality in dialysis population
- Accounts for >50% of deaths
- Related to arrhythmia, cardiomyopathy, ischemic heart disease, and other
- Concerns for accelerated atherosclerosis in dialysis patients: Scribner 1960s
- Increased vascular calcification
- High incidence of amputation for peripheral vascular disease

**Risk Factors for Atherosclerosis in Hemodialysis Patients**

- Hypertension
- Dyslipidemia
- Smoking

**“Nontraditional” risk factors**
- Endothelial dysfunction:
  - Hyperhomocysteinemia
  - Asymmetric dimethylarginine (nitric oxide inhibitor)
- Acute-phase inflammatory response:
  - C-Reactive protein
  - Proinflammatory cytokines (interleukin 6)
- Other acute-phase reactants
- Increased oxidative stress:
  - Reactive aldehyde accumulation
  - Thiol group oxidation
  - Myeloperoxidase-catalyzed oxidant stress

**Treatment of Atherosclerotic Coronary Artery Disease**

**Medical therapy**
(Few large randomized clinical trials in the dialysis population)
- Statins
- Antiplatelet agents
- β-Blockers (carvedilol)
- Homocysteine-lowering therapy
- Antioxidants (vitamin E, N-acetylcysteine)

**Atherosclerosis screening tests**
- Ambulatory electrocardiography
- Nuclear medicine studies
- Stress echocardiography

**Coronary artery revascularization**
- Thrombolytic therapy
- Coronary artery bypass graft surgery
- Percutaneous coronary interventions

**Cardiomyopathy and Congestive Heart Failure**
- High prevalence of alterations in left ventricular geometry:
  - Left ventricular hypertrophy
  - Left ventricular dilatation
  - Independent risk factors for mortality
  - Related to chronic volume and pressure overload

**Cardiac Arrhythmias and Sudden Death**
- Frequent cause of dialysis-associated cardiovascular mortality
- High frequency and severity of atrial and ventricular arrhythmias
- Increase Q-T dispersion in dialysis patients
Vascular Calcification

- Frequently observed, even in young hemodialysis patients
- High prevalence of medial calcification
- Detectable by means of electron-beam computed tomography
- Related to serum phosphorus and calcium \( \times \) phosphorus product:
  - May be associated with calcium-containing phosphorus binders
  - May be associated with excess use of vitamin D products

ADDITIONAL READING


Hemodialysis-Induced Catabolism

- Dialysis membrane biocompatibility
- Inflammatory mediators from dialysate

Hormonal Alterations

- Insulin-like growth factor 1 (IGF-1)/growth hormone axis
- Hypercortisolism
- Alterations in adipokine levels (leptin, adiponectin)

Markers of Nutritional Status

Biochemical Markers of Visceral Protein Stores

- Serum albumin (also a negative acute-phase reactant)
- Serum prealbumin (also a negative acute-phase reactant)
- Blood urea nitrogen and creatinine (indirect measures of dialysis adequacy in addition to nitrogen intake and muscle mass surrogates)
- Serum IGF-1 (level that connotes malnutrition in uremia not fully established)

Body Composition

- Dual-energy x-ray absorptiometry (DEXA)
- Bioelectrical impedance (BIA)
- High interpatient variation between DEXA and BIA in dialysis patients

Other Markers

- Subjective global assessment
- Dietary protein intake:
  - Urea nitrogen appearance rate or protein catabolic rate
  - Dietary recall

PROTEIN-CALORIE MALNUTRITION

- Highly prevalent in hemodialysis patients
- Associated with increased morbidity and mortality

Pathogenesis of Malnutrition

- Inadequate protein and/or calorie intake
- Recommended daily dietary protein \( \geq 1.2 \) g/kg of body weight per day
- Recommended daily energy intake:
  - 35 kcal/kg of body weight per day for people aged \( \leq 60 \) years
  - 30 to 35 kcal/kg of body weight per day for people aged \( \geq 60 \) years
- Increased resting energy expenditure
- Amino acid losses in dialysate:
  - 5 to 8 g of free amino acids per dialysis session with low-flux dialyzers
  - 30% greater amino acid losses with high-flux dialyzers
**Nutritional Therapy**
- Initiation of hemodialysis (can increase serum albumin and IGF-1 levels and body mass)
- Oral nutritional supplementation
- Intradialytic parenteral nutrition
- Vitamin and trace element supplementation
- Few controlled studies in hemodialysis patients

**ADDITIONAL READING**

**INFECTION AND IMMUNITY**

**Second Leading Cause of Death in Hemodialysis Patients**
- Infection-related mortality 12% to 22% in patients with end-stage renal disease
- Septicemia responsible for >75% of infectious deaths
- Sepsis-related mortality 100- to 300-fold greater in dialysis patients than general population

**Risk Factors for Septicemia**
- Diabetes mellitus
- Older age
- Hypoalbuminemia
- Catheters for vascular access
- Reprocessing of dialyzers

**Pathogenesis of Infection and Altered Immunity**
- Most infections caused by catalase-producing bacteria (eg, Staphylococcus species)
- Opportunistic infections less frequent
- Altered granulocyte function in uremia (altered chemotaxis, adherence, phagocytosis, and reactive oxygen species production)
- Malnutrition and iron exposure may affect phagocytic cell function
- Bioincompatible hemodialysis membranes may increase infection rate
- Increased antibiotic resistance in hemodialysis patients:
  - Methicillin-resistant Staphylococcus aureus infections
  - Vancomycin-resistant Enterococcus

**Viral Infections in Hemodialysis Patients**

**Hepatitis B infections**
- Decreasing prevalence in hemodialysis units:
  - Universal precautions
  - Use of hepatitis B vaccine
  - Decreased transfusion use secondary to erythropoietic agents

**Hepatitis C infection**
- Leading cause of liver disease in hemodialysis patients
- Declining incidence in hemodialysis units
- Minority of seropositive patients with hepatic enzyme abnormalities
- Nosocomial transmission of hepatitis C virus documented in dialysis units
- Characteristically chronic, indolent, and fluctuating clinical course

**Human immunodeficiency virus infection**
- Increasing in hemodialysis patients
- Not routinely screened for in most dialysis centers
- Treatment with highly active antiretroviral therapy

**Vaccination in Hemodialysis Patients**

**Hepatitis B vaccine**
- 3 doses of recombinant vaccine intramuscularly recommended
- 50% to 75% of dialysis patients develop protective antibody levels after 3 doses
- Revaccination recommended if no seroconversion

**Pneumococcal vaccine booster**
- Recommended for all hemodialysis patients older than 2 years
>75% of patients respond to vaccine
Revaccination every 5 years in adults

**Influenza vaccine**
- Recommended annually for hemodialysis patients

**Childhood vaccines**
- Generally recommended for children on dialysis therapy, eg:
  - Measles, mumps, and rubella vaccines
  - Varicella vaccine
  - Inactivated polio virus vaccine
  - Diphtheria, tetanus, and pertussis vaccines
  - *Haemophilus influenzae* type B conjugate vaccine
  - Oral poliovirus vaccine not recommended

**Additional Reading**

**Renal Osteodystrophy**

**Secondary Hyperparathyroidism (SHPT)**
- High bone turnover renal osteodystrophy
- Osteitis fibrosa
- Characterized by high serum parathyroid hormone (PTH) levels

**Pathogenesis of SHPT**
- Renal phosphorus retention and hyperphosphatemia
- Hypocalcemia
- Low calcitriol levels
- Skeletal resistance to PTH

**Signs and symptoms of SHPT**
- Bone pain
- Proximal muscle weakness
- Spontaneous tendon rupture
- Pruritus
- Metastatic and extraskeletal calcifications

**Assays for PTH**
- Intact PTH assay: measures 1-84 and 7-84 peptides
- Biointact or whole PTH assays: measure 1-84 peptide only
- Amino acid 7-84 PTH fragment:
  - May bind to alternate PTH receptor
  - Antagonizes activity of 1-84 PTH
  - May account for observed skeletal resistance to PTH activity
- Other:
  - Total alkaline phosphatase
  - Bone-specific alkaline phosphatase
  - Osteocalcin

**Treatment of SHPT**
- Decrease phosphorus intake:
  - Phosphorus-restricted diet
- Use of phosphorus binders:
  - Calcium-containing phosphorus binders (calcium acetate, calcium carbonate)
  - Non–calcium-containing phosphorus binders (aluminum hydroxide, sevelamer hydrochloride, lanthanum carbonate)
- Administration of vitamin D analogues:
  - Calcitriol
  - Paricalcitol
  - Doxercalciferol
- Calcimimetic agents
- Parathyroidectomy:
  - Reserved for severe refractory hyperparathyroidism
  - Subtotal parathyroidectomy usually recommended:
    - Recurrence of hyperparathyroidism after 5 years in 20% to 30% of patients
    - Careful monitoring for hypocalcemia required postoperatively

**Osteomalacia**
- Prevalence decreasing because of elimination of aluminum-containing phosphate binders from common clinical practice
• Associated with bone pain, frequent fractures, and marked musculoskeletal disability
• Radiologically characterized by pseudofractures or Looser zones

Adynamic Bone Disease
• Characterized by slow rate of bone formation
• Prevalence increasing in dialysis patients
• More prevalent in peritoneal dialysis patients, older patients, and patients with diabetes
• Lower PTH values than in other patients with renal osteodystrophy
• Related to vitamin D treatment
• Increased fracture and mortality rate
• Histologically similar to osteomalacia:
  ■ Absence of large osteoid seams

Dialysis-Related Amyloidosis
• Seen in patients on long-term hemodialysis therapy
• Characterized by carpal tunnel syndrome, chronic joint pain, and destructive arthropathy
• Amyloid fibrils contain β2-microglobulin proteins
• Diagnosis by means of imaging techniques and clinical syndrome
• Therapy:
  ■ Hemofiltration or high-flux hemodialysis to remove β2-microglobulin
  ■ Symptomatic relief
  ■ Carpal tunnel syndrome surgery
  ■ Joint replacement
  ■ Renal transplantation

ADDITIONAL READING

CALCIFIC UREMIC ARTERIOLOPATHY
CALCIPHYLAXIS

Clinical Presentation
• Skin disorder characterized by arteriolar calcification in dermis
• Presents as painful red nodules or plaques
• Progresses to ulcerative lesions with necrotic centers and violaceous borders

Pathogenesis
• Largely reported as case reports or case series
• Definitive data on pathogenesis lacking
• Frequently associated with hyperparathyroidism or high calcium × phosphorus product
• Female sex, white race, obesity, and hypoalbuminemia are risk factors

Pathobiology
• Medial calcification in small arterioles
• Low levels of serum fetuin A (endogenous inhibitor of mineralization)
• Fat necrosis

Prognosis and Therapy
• Overall high morbidity/mortality
• Corticosteroids may be helpful in early plaque stage
• Control calcium × phosphorus product
• Consider daily dialysis
• Consider discontinuation of vitamin D analogues
• Consider parathyroidectomy if PTH > 500 pg/mL (ng/L)
• Additional therapies reported as possibly beneficial in small case series:
  ■ Hyperbaric oxygen
  ■ Bisphosphonate therapy (pamidronate)

ADDITIONAL READING
2. Ahmed S, O’Neill KD, Hood AF, et al: Calciphylaxis is associated with hyperphosphatemia and increased osteopon-

INTRADIALYTIC COMPLICATIONS

Hypotension
- Most common acute complication of hemodialysis (incidence, 15% to 30%)
- More common in older patients and women

Pathogenesis of hypotension
- Plasma volume removal (convective and diffusive)
- Thermal energy transfer causing vasodilation
- Autonomic dysfunction
- Dialysis membrane biocompatibility
- Antihypertensive medications

Treatment of intradialytic hypotension
- Decreased ultrafiltration rate (<1.5 L/h)
- Increased dialysate sodium concentration
- Increased dialysate calcium concentration
- Variable sodium and/or ultrafiltration modeling
- Decreased dialysate temperature
- Use of biocompatible membranes
- Minimize short-acting antihypertensives within 4 hours of dialysis (especially vaso-dilators)
- Midodrine, 5 to 10 mg, administered 30 to 60 minutes before hemodialysis

Muscle Cramps
- Occur with up to 20% of dialysis treatments
- Pathogenesis uncertain, but frequently related to acute extracellular volume contraction

Treatment of muscle cramps
- Decreased ultrafiltration rate
- Administration of normal or hypertonic saline
- Pharmacologic agents (quinine sulfate, diazepam, vitamin E, carnitine)
- Increased estimated dry weight

Dialysis Disequilibrium Syndrome
- Characterized by nausea, vomiting, headaches, and fatigue
- Can result in life-threatening seizures, coma, and arrhythmias
- Pathogenesis from rapid rates of change in solute concentration and pH in the central nervous system
- Most commonly occurs with high initial solute concentrations

Treatment strategies to reduce disequilibrium
- Use of smaller surface area dialyzers
- Reduced rates of blood and dialysate flow
- Cocurrent (rather than countercurrent) dialysate flow
- High dialysate sodium
- Intravenous administration of diazepam

Arrhythmias and Angina

Incidence of atrial arrhythmia is common
- Changes in potassium concentration
- Can be precipitated by hypotension and coronary ischemia
- Treatment similar to that for patients with normal renal function

Cardiac arrest
- Uncommon in outpatient dialysis
- Related to day of week and dialysate potassium concentration

Dialyzer Reactions

First-use syndrome
- Anaphylactoid reaction to new dialyzers made of cuprophane:
  - Alternative pathway complement activation
  - Ethylene oxide exposure
- Anaphylactoid reaction to polyacrylonitrile dialysis membranes in patients administered angiotensin-converting enzyme inhibitors:
  - Bradykinin generation through the kal-likrein-kininogen pathway
- Treatment with epinephrine and steroids

Water, Dialysate Composition, and Extracorporeal Circuit Complications
- High level (120 to 200 L) of dialysate exposure per treatment
Toxic water system treatment contaminants
- Chloramine (hemolysis)
- Copper (anemia)
- Aluminum (osteomalacia and encephalopathy)
- Fluoride (bone disease and cardiac arrhythmias)

Infectious complications
- Endotoxin exposure (pyrogenic reactions) from contaminated dialysate or reuse
- Infectious outbreaks (e.g., Mycobacterium chelonei) related to improper dialyzer reuse

Treatment (prevention) of water and dialysate problems
- American Association of Medical Instrumentation standards
- Properly configured water treatment system:
  - Sand filter
  - Carbon beds
  - Reverse osmosis
  - Deionization (optional)
  - Filters
  - Periodic surveillance of water and dialysate composition and quality
- Other complications:
  - Air embolism
  - Increase shear stress (hemolysis)

ADDITIONAL READING