

CORE CURRICULUM IN NEPHROLOGY

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

1. Xue JL, Ma JZ, Louis TA, Collins AJ: Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. *J Am Soc Nephrol* 12:2753-2758, 2001
2. 2002 Albert Lasker Award for Clinical Medical Research. *J Am Soc Nephrol* 13:3027-3030, 2002
3. Kinchen KS, Sadler J, Fink N, et al: The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 137:479-486, 2002
4. Vanholder R, De Smet SR: Pathophysiologic effects of uremic retention solutes. *J Am Soc Nephrol* 10:1815-1823, 1999

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

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- 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
 - Brachiocephalic 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

1. Pisoni RL, Young EW, Dykstra DM, et al: Vascular access use in Europe and the United States: Results from DOPPS. *Kidney Int* 61:305-316, 2002
2. Dhingra RK, Young EW, Hulbert-Shearon TE, et al: Type of vascular access and mortality in US hemodialysis patients. *Kidney Int* 60:1443-1451, 2002
3. Miller PE, Tolwani A, Luscyp CP, et al: Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 56:275-280, 1999

4. Oliver MJ, McCann RL, Indridason OS, et al: Comparison of transposed brachiobasilic fistulas to upper arm grafts and brachiocephalic fistulas. *Kidney Int* 60:1532-1539, 2001

5. Silva MB, Hobson RW, Pappas PJ, et al: A strategy for increasing use of autogenous hemodialysis access procedures: Impact of preoperative noninvasive evaluation. *J Vasc Surg* 27:302-308, 1998

6. Roy-Chaudhury P, Kelly BS, Miller MA, et al: Venous intimal hyperplasia in polytetrafluoroethylene dialysis grafts. *Kidney Int* 59:2325-2334, 2002

7. Marr KA, Sexton DJ, Conlon PJ, et al: Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med* 127:275-280, 1997

8. Beathard GA: Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. *J Am Soc Nephrol* 10:1045-1049, 1999

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 ($\mu\text{g/L}$) 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

1. Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, et al: Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. *J Am Soc Nephrol* 11:335-342, 2000
2. Fishbane S, Shapiro W, Dutka P, et al: A randomized trial of iron deficiency testing strategies in hemodialysis patients. *Kidney Int* 60:2406-2411, 2001
3. Fletes R, Lazarus JM, Gage J, Chertow GM: Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis* 37:743-749, 2001
4. Besarab A, Reyes CM, Hornberger J: Meta-analysis of subcutaneous versus intravenous Epoetin in maintenance treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 40:439-446, 2002
5. Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10:610-619, 1999
6. Besarab A, Bolton WK, Browne JK, et al: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and erythropoietin. *N Engl J Med* 339:584-590, 1998

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

“Traditional” risk factors

- 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

1. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697-701, 1974
2. Bostom AG, Lathrop L: Hyperhomocysteinemia in end-stage renal disease: Prevalence, etiology, and potential relationship to arteriosclerotic outcomes. *Kidney Int* 52:10-20, 1997
3. Himmelfarb J, Ikizler TA, Stenvinkel P, Hakim RM: The elephant in uremia: Reflections on oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 62:1524-1538, 2002
4. Herzog MD, Ma JZ, Collins AJ: Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery and impact of diabetes. *Circulation* 106:2207-2211, 2002
5. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32:S112-S119, 1998 (suppl 3)
6. Kaysen GA: The microinflammatory state in uremia: Causes and potential consequences. *J Am Soc Nephrol* 12:1549-1557, 2001
7. Klassen PS, Lowrie EG, Reddan DN, et al: Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 287:1548-1555, 2002
8. Zoccali C, Benedetto FA, Maas R, et al: Asymmetric dimethylarginine, C-reactive protein, and carotid intima-media thickness in end-stage renal disease. *J Am Soc Nephrol* 13:490-496, 2002
9. Goodman WG, Goldin J, Kuizon BD, et al: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342:1478-1483, 2000

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 ≥ 1.2 g/kg of body weight per day

- Recommended daily energy intake:
 - 35 kcal/kg of body weight per day for people aged ≤ 60 years
 - 30 to 35 kcal/kg of body weight per day for people aged ≥ 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

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

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

1. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. *Am J Kidney Dis* 37:S66-S70, 2001 (suppl 2)
2. Caglar K, Fedje L, Dimmitt R, et al: Therapeutic effects of oral nutritional supplementation during hemodialysis. *Kidney Int* 62:1054-1059, 2002
3. Pupim LB, Flakoll PJ, Brouillette JR, et al: Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest* 110:483-492, 2002
4. Kalantar-Zadeh K, Block G, McAllister CJ, et al: Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 80:299-307, 2004

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

1. Sarnak MJ, Jaber BL: Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int* 58:1758-1764, 2000
2. Tokars JI, Finelli L, Alter MJ, Arduino MJ: National surveillance of dialysis-associated diseases in the United States, 2001. *Semin Dial* 17:310-319, 2004
3. Rangel MC, Coronado VG, Euler GL, Strikas RA: Vaccine recommendations for patients on chronic dialysis. *Semin Dial* 13:101-107, 2000
4. Hoen B, Paul-Dauphin A, Hestin D, Kessler M: EPIBACDIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 9:869-976, 1998
5. Lewis SL, Van Epps DE: Neutrophil and monocyte alterations in chronic dialysis patients. *Am J Kidney Dis* 9:381-395, 1987

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 β_2 -microglobulin proteins
- Diagnosis by means of imaging techniques and clinical syndrome
- Therapy:
 - Hemofiltration or high-flux hemodialysis to remove β_2 -microglobulin
 - Symptomatic relief
 - Carpal tunnel syndrome surgery
 - Joint replacement
 - Renal transplantation

ADDITIONAL READING

1. Goodman WG, Juppner H, Salusky IB, Sherrard DJ: Parathyroid hormone (PTH), PTH-derived peptides, and new PTH assays in renal osteodystrophy. *Kidney Int* 63:1-11, 2003
2. Slatopolsky E, Finch J, Clay P, et al: A novel mechanism for skeletal resistance in uremia. *Kidney Int* 58:753-761, 2000
3. Slatopolsky E, Brown A, Dusso A: Pathogenesis of secondary hyperparathyroidism. *Kidney Int Suppl* 73:S14-S19, 1999
4. Teng M, Wolf M, Lowrie E, et al: Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349:446-456, 2003
5. Chertow GM, Burke SK, Raggi P, Treat to Goal Working Group: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62:245-252, 2002

6. Block GA, Martin KJ, de Francisco AL, et al: Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 350:1516-1525, 2004

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 \times 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 \times 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

1. Fine A, Zacharias J: Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy. *Kidney Int* 61:2210-2217, 2002
2. Ahmed S, O'Neill KD, Hood AF, et al: Calciphylaxis is associated with hyperphosphatemia and increased osteopon-

tin expression by vascular smooth muscle cells. *Am J Kidney Dis* 37:1267-1276, 2001

3. Mazhar AR, Johnson RJ, Gillen D, et al: Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int* 60:324-332, 2001

4. Wilmer WA, Magro CM: Calciphylaxis: Emerging concepts in prevention, diagnosis, and treatment. *Semin Dial* 15:172-186, 2002

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 vasodilatation
- 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 vasodilators)
- 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 kallikrein-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 (eg, *Mycobacterium chelonae*) 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

1. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA: Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. *Am J Kidney Dis* 33:920-926, 1999
2. Epstein A, Kay G, Plumb V: Considerations in the diagnosis and treatment of arrhythmias in patients with end-stage renal disease. *Semin Dial* 2:31-37, 1990
3. Dheen S, Henrich WL: Preventing dialysis hypotension: A comparison of usual protective maneuvers. *Kidney Int* 59:1175-1181, 2001