Ann & Robert H. Lurie Children's Hospital of Chicago®

Northwestern Medicine®
Feinberg School of Medicine

Major Infectious Complications

Mahima Keswani, MD
Ann & Robert H. Lurie Children's Hospital of Chicago
Assistant Professor of Pediatrics
Medical Director, Pediatric Dialysis

BEST CHILDREN'S HOSPITALS
U.S.News & WORLD REPORT
RANKED IN 10 SPECIALTIES
2020-21

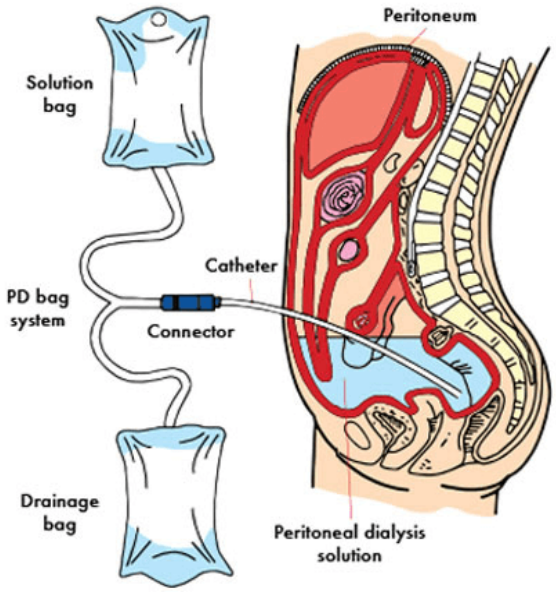
MAGNET RECOGNIZED
AMERICAN NURSES CREDENTIALING CENTER

Learning Objectives

- Describe the major Infectious Complications of Pediatric Chronic Dialysis
- Review the general approach to treatment
- Discuss associated risk factors and preventative measures

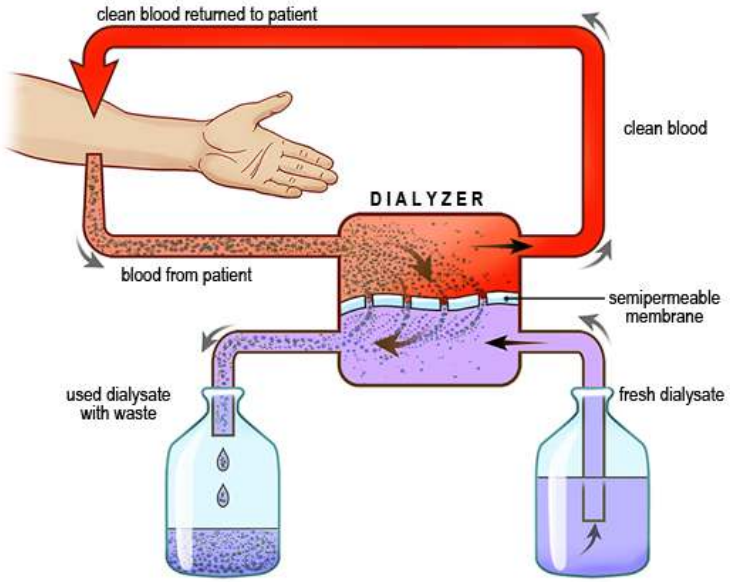
Modalities

Peritoneal Dialysis



Peritonitis
Exit Site Infection
Tunnel Infection

Hemodialysis



HD Catheter Associated Blood Stream Infection
Exit Site Infection
Tunnel Infection

Peritoneal Dialysis (PD) What's the big deal?

Ann & Robert H. Lurie Children's Hospital of Chicago®

- Most common initial dialysis modality in children WORLDWIDE

  Fadrowski J.J., Alexander S.R., Warady B.A. (2012) The Demographics of Dialysis in Children

- Infectious complications → Morbidity and Mortality

  Auron A, et al: Pediatr Nephrol 22: 578-585, 2007

- Most common reason for modality change (unwanted)

  Warady BA, et al: Perit Dial Int: S32-86, 2012

- Hospitalization Rate for Infection: PD >> HD >> Transplant

  United States Renal Data System (2017) 2017 USRDS annual data report: volume 2

- ESRD Deaths: CV >> PD Infection >> HD

  United States Renal Data System: ESRD database. Patients with ESRD aged 0-17 years at death, 2009-2018

Peritonitis

- Cloudy peritoneal effluent
- Abdominal pain, fever, chills, vomiting
- Cell Count: WBC > 100/mm3 ≥ 50% neutrophils
- Culture

Warady BA, et al: Perit Dial Int: S32-86, 2012

Pathogens

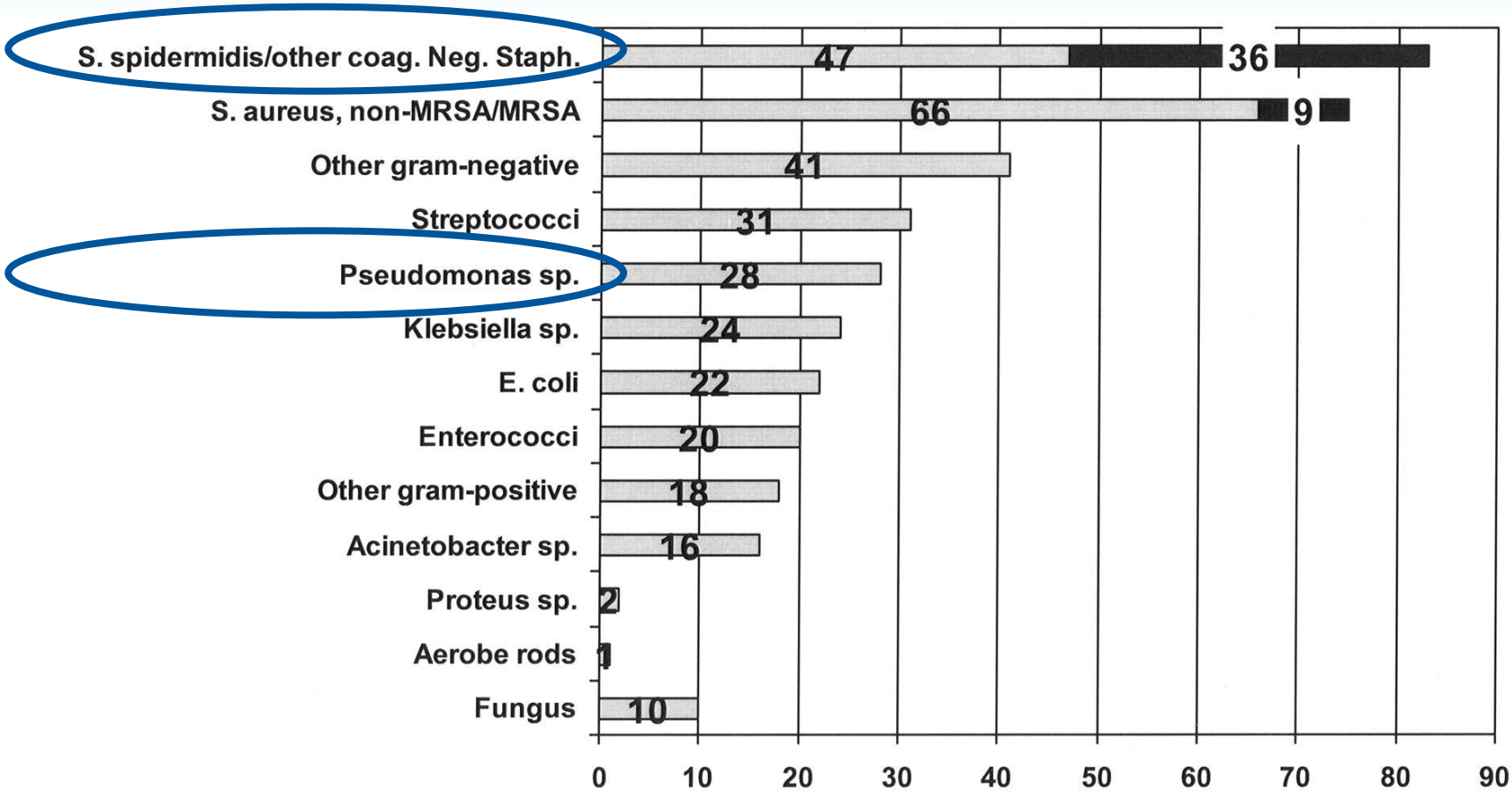
- IPPR
- 44% Gram Positive
- 25% Gram Negative
- 31% Culture Negative
- 2% Fungal

Bradley A. Warady et al. JASN 2007;18:2172-2179

- SCOPE
- 37.8% Gram Positive
- 19.5% Gram Negative
- 24.7% Culture Negative
- 7.7% Fungal

Christine B. Sethna et al. CJASN 2016;11:1590-1596

Pathogens: Worldwide

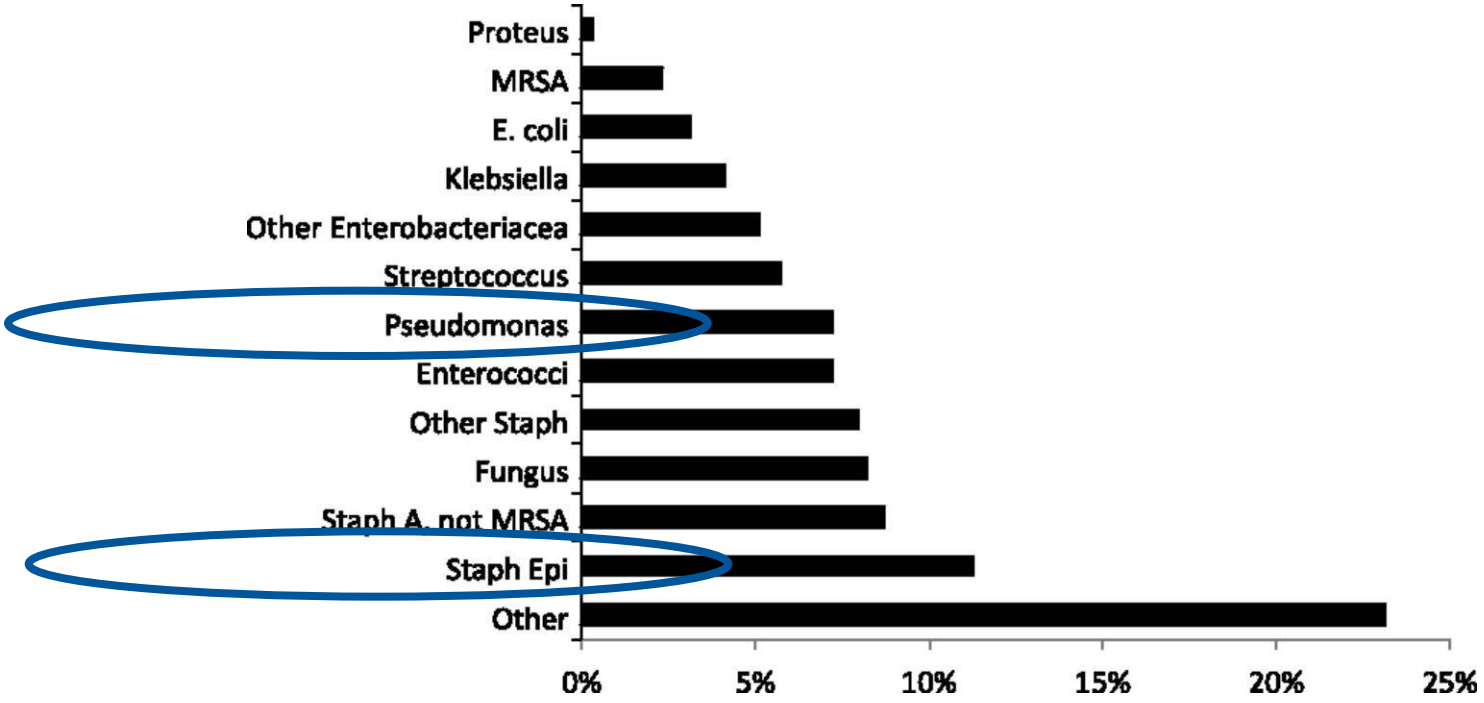


Bradley A. Warady et al. JASN 2007;18:2172-2179

JASN Journal of the American Society of Nephrology

Pathogens: US

Organisms cultured from patients with peritonitis.



Christine B. Sethna et al. CJASN 2016;11:1590-1596

CJASN

Treatment: General principles

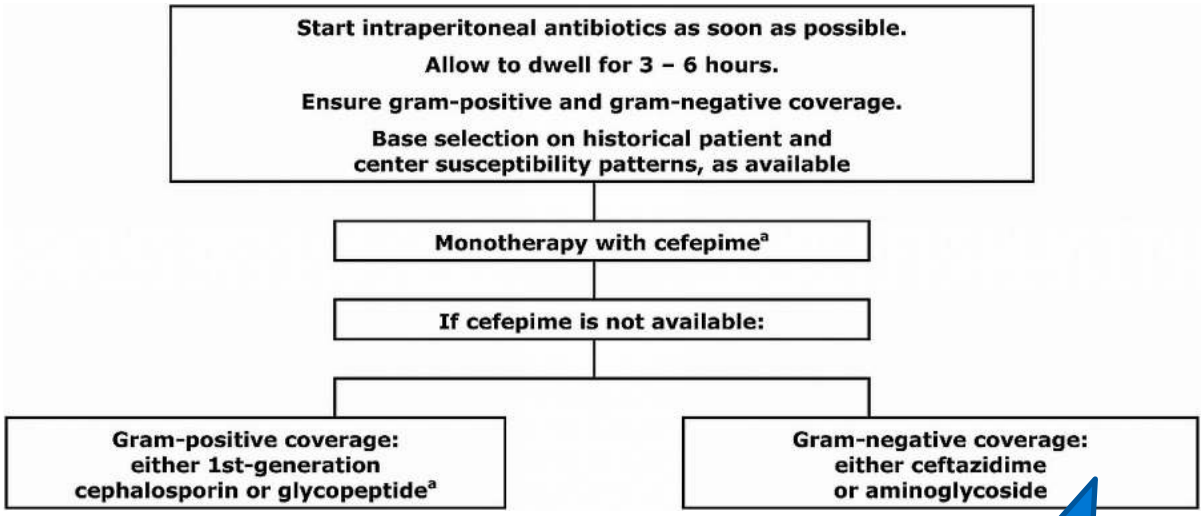


Figure 1 — Empiric therapy.

[a] If the center's rate of methicillin-resistant *Staphylococcus aureus* (MRSA) exceeds [illegible]%, or if [illegible]s history of MRSA infection or colonization, glycopeptide (vancomycin or teicoplanin) should be add[illegible]efe[illegible]ce the first-generation cephalosporin for gram-positive coverage. Glycopeptide use can also be [illegible] of severe allergy to penicillins and cephalosporins.

ANTIFUNGAL PPX

Treatment: Antibiotics

TABLE 5
Antibiotic Dosing Recommendations[a] for the Treatment of Peritonitis

Antibiotic type	Therapy type: Continuous[b] Loading dose	Continuous[b] Maintenance dose	Intermittent[b]
Aminoglycosides (IP)[c]			
Gentamicin	8 mg/L	4 mg/L	
Netilmycin	8 mg/L	4 mg/L	Anuric: 0.6 mg/kg
Tobramycin	8 mg/L	4 mg/L	Non-anuric: 0.75 mg/kg
Amikacin	25 mg/L	12 mg/L	
Cephalosporins (IP)			
Cefazolin	500 mg/L	125 mg/L	20 mg/kg
Cefepime	500 mg/L	125 mg/L	15 mg/kg
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg
Ceftazidime	500 mg/L	125 mg/L	20 mg/kg
Glycopeptides (IP)[d]			
Vancomycin	1000 mg/L	25 mg/L	30 mg/kg; repeat dosing: 15 mg/kg every 3–5 days
Teicoplanin[e]	400 mg/L	20 mg/L	15 mg/kg every 5–7 days
Penicillins (IP)[c]			
Ampicillin	—	125 mg/L	—
Quinolones (IP)			
Ciprofloxacin	50 mg/L	25 mg/L	—
Others			
Aztreonam (IP)	1000 mg/L	250 mg/L	—
Clindamycin (IP)	300 mg/L	150 mg/L	—
Imipenem–cilastin (IP)	250 mg/L	50 mg/L	—
Linezolid (PO)	<5 Years: 30 mg/kg daily, divided into 3 doses 5–11 Years: 20 mg/kg daily, divided into 2 doses ≥12 Years: 600 mg/dose, twice daily		
Metronidazole (PO)	30 mg/kg daily, divided into 3 doses (maximum: 1.2 g daily)		
Rifampin (PO)	10–20 mg/kg daily, divided into 2 doses (maximum: 600 mg daily)		
Antifungals			
Fluconazole (IP, IV, or PO)	6–12 mg/kg every 24–48 h (maximum: 400 mg daily)		
Caspofungin (IV only)	70 mg/m^2 on day 1 (maximum: 70 mg daily)	50 mg/m^2 daily (maximum: 50 mg daily)	

Treatment: Gram Positive

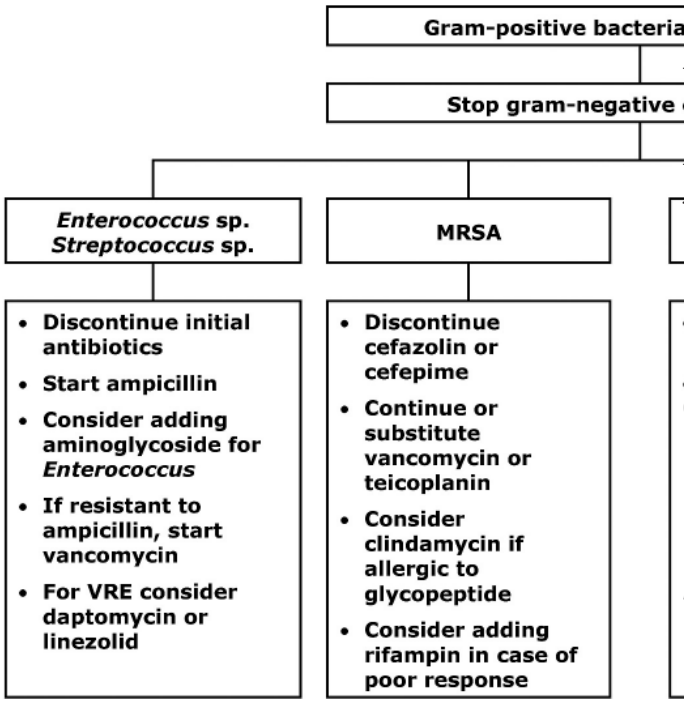


TABLE 6
Gram-Positive Bacteria: Recommended Antibiotics and Length of Therapy

Organism	Recommended antibiotics[a]	Length of therapy
Staphylococcus aureus		
Methicillin-resistant	Clindamycin *or* vancomycin *or* teicoplanin	3 Weeks
Methicillin-susceptible	Cefazolin *or* cefepime	3 Weeks
Coagulase-negative staphylococci	Cefazolin *or* cefepime *or* clindamycin *or* vancomycin *or* teicoplanin	2 Weeks
Enterococcus species	Ampicillin *or* vancomycin *or* teicoplanin	2–3 Weeks
Vancomycin-resistant	Ampicillin *or* linezolid	2–3 Weeks
Streptococcus species	Ampicillin *or* cefazolin *or* cefepime	2 Weeks

Figure 2 — Gram-positive organism on culture.
MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *S. aureus*; VRE = vancomycin-resistant enterococci.

Treatment: Gram Negative

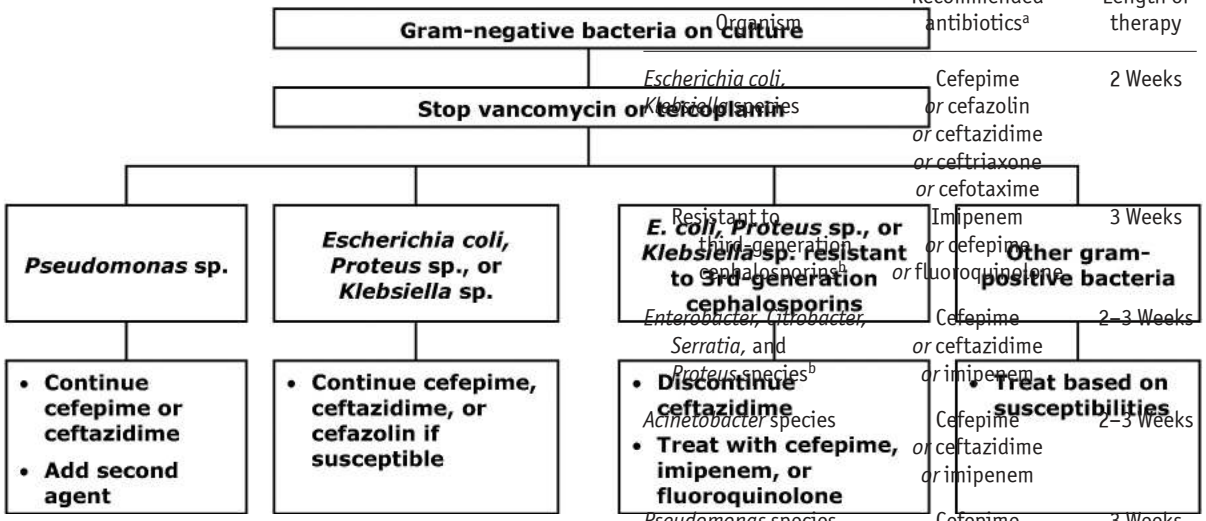


Figure 3 — Gram-negative organism on culture.

TABLE 7
Gram-Negative Bacteria: Recommended Antibiotics and Length of Therapy

Organism	Recommended antibiotics[a]	Length of therapy
Escherichia coli, *Klebsiella* species	Cefepime *or* cefazolin *or* ceftazidime *or* ceftriaxone *or* cefotaxime	2 Weeks
Resistant to third-generation cephalosporins[b]	Imipenem *or* cefepime *or* fluoroquinolone	3 Weeks
Enterobacter, *Citrobacter*, *Serratia*, and *Proteus* species[b]	Cefepime *or* ceftazidime *or* imipenem	2–3 Weeks
Acinetobacter species	Cefepime *or* ceftazidime *or* imipenem	2–3 Weeks
Pseudomonas species	Cefepime *or* ceftazidime *or* piperacillin *or* ticarcillin *or* imipenem *plus* aminoglycoside or fluoroquinolone	3 Weeks
Stenotrophomonas maltophilia	Trimethoprim–sulfamethoxazole *or* ticarcillin–clavulanic acid	3 Weeks

Unique Consideration: Culture Negative Peritonitis

- Treat broadly (gram +/gram – coverage) X 2 weeks
- Cefepime
- Ceftazidime + Cefazolin OR a glycopeptide

- ? Aminoglycoside

- If the initial cultures remain sterile at 72 hours and if signs and symptoms of peritonitis improved→ cefepime, ceftazidime, cefazolin, or a glycopeptide be continued for 2 weeks.
- Administration of an aminoglycoside be discontinued at 72 hours in patients with a sterile culture and clinical improvement

- Patients who fail to demonstrate clinical improvement after 72 hours

Unique Consideration: Fungal Peritonitis

- If fungi are identified by gram stain or culture of peritoneal effluent, therapy should consist of treatment with an antifungal agent and early catheter removal.

- We suggest that, after catheter removal, anti- mycotic therapy be administered for 2 weeks or longer after complete resolution of the clinical symptoms of infection.

Unique Consideration: Relapsing Peritonitis

- Relapsing Peritonitis = peritonitis recurs with the same organism as in the preceding episode within 4 weeks of completion of antibiotic treatment
- Reinitiate empiric therapy for relapsing
- Consider instillation of a fibrinolytic agent be considered after diagnosis of a first peritonitis relapse that is not explained by extraluminal pathology (Tunnel infection, intra-abdominal abscess etc)
- In the setting of relapsing peritonitis associated with a persistent or recurrent tunnel infection, or a second peritonitis relapse → catheter removal

Indications for Catheter Removal

- refractory bacterial peritonitis
- fungal peritonitis is established
- exit-site or tunnel infection in conjunction with peritonitis with the same bacteria (particularly S. aureus and P. aeruginosa), except CNS
- Simultaneous catheter removal and replacement for a refractory exit-site or tunnel infection
- Simultaneous removal and replacement of the peritoneal catheter after clearing of the peritoneal effluent (white blood cells < 100/mm3) in repeated relapsing bacterial peritonitis (2C).
- Minimum period of 2 – 3 weeks between catheter removal and insertion of a new catheter for fungal, enteric, and refractory bacterial peritonitis

Outcomes

76.6% of infections resolved with antimicrobial treatment alone,
12.2% required permanent removal of the catheter,
and 6% resulted in catheter removal with subsequent catheter replacement and reinsti
(other outcomes =5.2%)

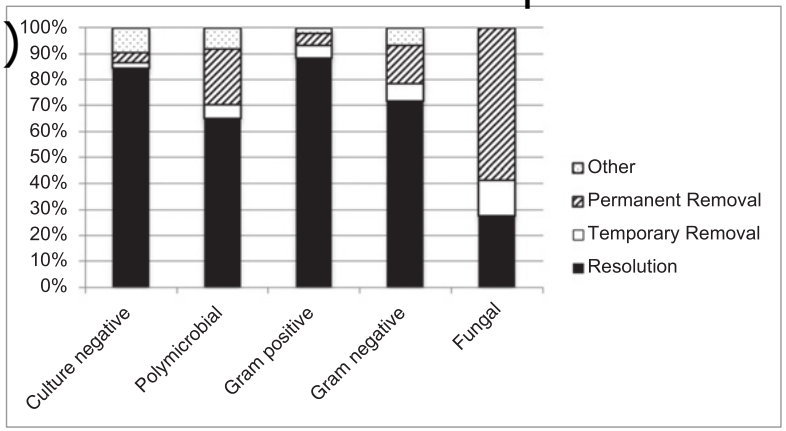


Figure 2. | Outcomes of peritonitis by organism.

Hospitalization was required in 59.6% of peri- tonitis episodes and varied by organism
(gram negative =71.1%; fungal =66.7%; gram positive =62.3%; polymicro- bial =57.5
culture negative =44.7%; P,0.01)

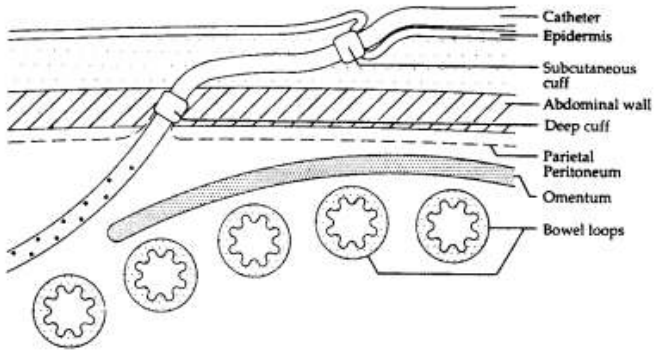
Modifiable Risk Factors/Preventive Measures

- Insertion Bundle (Intra-operative+Post operative)
- Training Bundle
- Follow Up Care Bundle

Intra-operative

Guideline 2.1: Data from the 2008 North American Pediatric Renal Trials and Collaborative Studies report showed that use of the double-cuff Tenckhoff catheter with a swan-neck tunnel and a downward-directed exit site was associated with a better annualized peritonitis rate and a longer time to a first peritonitis episode when
catheter charac-
imilar data on the

dy BA, et al: Perit Dial Int: S32-86, 2012



ownward position
given prior to

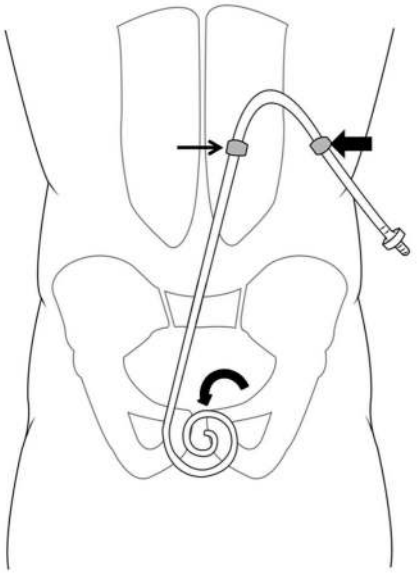
FIGURE 1 Two-cuff Tenckhoff catheter in proper position with deep cuff in abdominal musculature, parietal peritoneum reflecting along the catheter, superficial cuff near exit site, and epidermis reflecting along the catheter.

t-operative days,
acted by a

- Sterile procedure is used for all exit-site dressing changes until the exit-site is healed
- PD catheter is immobilized until exit-site is healed
- PD catheter is not used for peritoneal dialysis for at least 14 post-operative days

PD, peritoneal dialysis

Neu A, et al: Pediatr Ne



Intra-operative

Pre-operative antibiotics

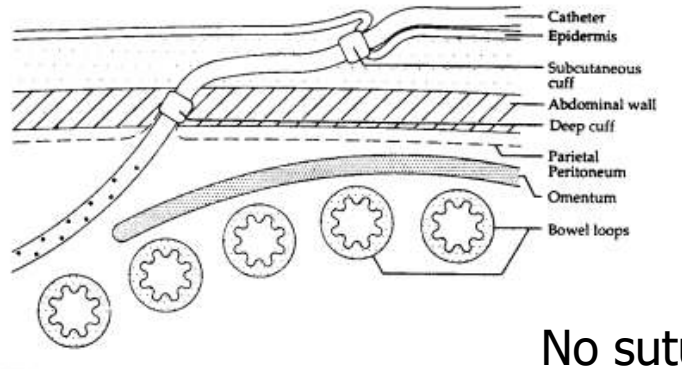
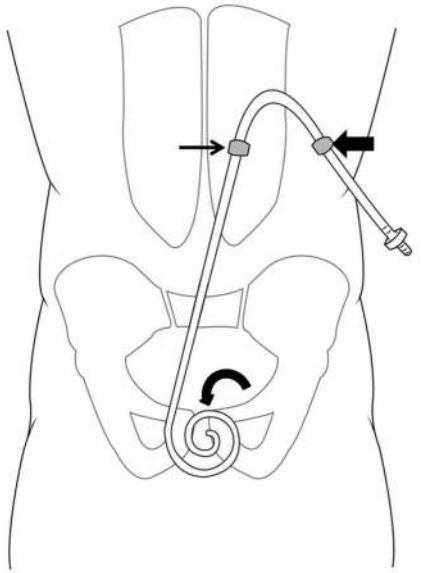


FIGURE 1 Two-cuff Tenckhoff catheter in proper position with deep cuff in abdominal musculature, parietal peritoneum reflecting along the catheter, superficial cuff near exit site, and epidermis reflecting along the catheter.

No sutures at the exit site

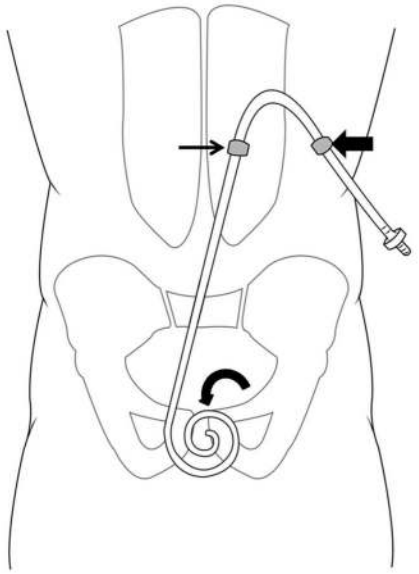


Intra-operative

Table 4. Rate ratio models for peritonitis

Variables	Crude Rate Ratio (95% CI)	*P* Value	Adjusted Rate Ratio[a] (95% CI)	*P* V
Age group, yr		<0.001		
<2	Reference		Reference	
2–5	0.81 (0.62 to 1.06)	0.12	0.59 (0.22 to 1.59)	
6–12	0.61 (0.51 to 0.73)	<0.001	0.66 (0.27 to 1.61)	
13–17	0.59 (0.49 to 0.71)	<0.001	0.68 (0.25 to 1.85)	
≥18	0.96 (0.65 to 1.44)	0.85	1.06 (0.23 to 4.95)	
Race		<0.001		
Nonblack	Reference		Reference	
Black	1.66 (1.42 to 1.95)		1.61 (0.93 to 2.80)	
Gastrostomy tube	1.49 (1.29 to 1.72)	<0.001	1.30 (0.69 to 2.45)	
Vesicostomy or stoma	1.36 (1.10 to 1.69)	<0.01	1.04 (0.52 to 2.06)	
Incontinence	1.53 (1.32 to 1.77)	<0.001	1.29 (0.56 to 3.01)	
Touch contamination	1.75 (1.51 to 2.02)	<0.001	2.22 (1.44 to 3.43)	<
Patient performs PD themselves	0.70 (0.59 to 0.81)	<0.001	1.17 (0.63 to 2.17)	
Upward orientation	3.14 (2.42 to 4.08)	<0.001	4.20 (1.49 to 11.89)	<
Plastic adapter	1.33 (1.15 to 1.54)	<0.001	1.38 (0.86 to 2.22)	
Insertion compliance		0.001		0.67
No	Reference		Reference	
Yes	0.62 (0.47 to 0.82)		0.91 (0.57 to 1.44)	
Training compliance		0.43		NA
No	Reference		NA	
Yes	0.88 (0.64 to 1.21)		NA	
Follow-up compliance		<0.001		<0.001
No	Reference		Reference	
Yes	0.50 (0.40 to 0.62)		0.49 (0.30 to 0.80)	<0.01

95% CI, 95% confidence interval; PD, peritoneal dialysis; NA, not applicable.
[a]All significant variables in crude model were included in addition to sex and patient clustering.



Post operative

Table 1 Peritoneal Dialysis Catheter Insertion Bundle

Intra-operative care

- PD catheter exit-site orientation is in the lateral or downward position
- A single dose of a first generation cephalosporin is given prior to incision
- No sutures are placed at catheter exit site

Post-operative care

- Exit-site dressing is not changed for the first 7 post-operative days, unless soiled, loose or damp and if changed, conducted by a healthcare professional
- Sterile procedure is used for all exit-site dressing changes until the exit-site is healed
- PD catheter is immobilized until exit-site is healed
- PD catheter is not used for peritoneal dialysis for at least 14 post-operative days

PD, peritoneal dialysis

Neu A, et al: Pediatr Nephrol: 29:1477-1484, 2014

Post-op

Table 3 Risk of early onset peritonitis

Variable	OR (95%)	*P* value
Age group		
< 1 year	1.1 (0.6, 1.9)	0.723
> 1 year	Reference	
Early dressing change		
Yes	1.5 (0.8, 2.9)	0.216
No	Reference	
Concurrent G-tube placement		
Yes	1.9 (0.8, 4.4)	0.117
No	Reference	
Concurrent HD catheter placement		
Yes	0.5 (0.2, 1.5)	0.300
No	Reference	
Adaptor type		
Plastic	1.4 (0.9, 2.2)	0.187
Titanium	Reference	
Orientation		
Upward	1.3 (0.6, 3.1)	0.532
Lateral/downward	Reference	
Early PD catheter use		
Yes	1.9 (1.2, 3.1)	0.001
No	Reference	

And beyond

Table 2 Peritoneal Dialysis Patient and Care Giver Training Bundle[a]

- Training performed by a qualified registered nurse
- Trainer to trainee (or family) ratio 1:1
- Appropriate teaching aides such as photographs, mannequin or apron used during training
- Training should cover all elements specified in ISPD guidelines [7, 12]
- Training should include specific procedures for:
  - -hand hygiene according to the world health organization guidelines [24]
  - -exit-site care
  - -aseptic connection technique
- Post-training concept and demonstration test administered at completion of training and again at one-month post-training visit
- Home visit performed

Neu A, et al: Pediatr Nephrol: 29:1477-1484, 2014

TABLE 4
Antifungal and Antibacterial Prophylaxis in Peritoneal Dialysis (PD) Patients

Situation	Indication	Antimicrobial
Presence of risk factors for fungal peritonitis	• High baseline rate of fungal peritonitis in the PD unit • PEG placement	Nystatin PO 10 000 U/kg daily Fluconazole 3–6 mg/kg IV or PO every 24–48 hours (maximum: 200 mg)
Touch contamination	• Instillation of PD fluid after disconnection of system • Disconnection during PD	Cefazolin (125 mg/L IP), or vancomycin (25 mg/L IP) if known colonization with MRSA Culture result, if obtained, directs subsequent therapy
Invasive dental procedures	• Manipulation of gingival tissue or of the periapical region of teeth, or perforation of the oral mucosa	Amoxicillin (50 mg/kg PO; maximum: 2 g) *or* ampicillin (50 mg/kg IV or IM, ; maximum: 2 g) *or* cefazolin (25 mg/kg IV; maximum: 1 g) *or* ceftriaxone (50 mg/kg IV or IM; maximum: 1 g) *or* clindamycin (20 mg/kg PO; maximum: 600 mg) *or* clarithromycin (15 mg/kg PO; maximum: 500 mg) *or* azithromycin (15 mg/kg PO; maximum: 500 mg)
Gastrointestinal procedures	• High-risk procedures (esophageal stricture dilation, treatment of varices, ERCP, and PEG)	Cefazolin (25 mg/kg IV; maximum: 2 g) *or* clindamycin (10 mg/kg IV; maximum: 600 mg) *or,* if high risk for MRSA, vancomycin (10 mg/kg IV; maximum: 1 g)
	• Other gastrointestinal or genitourinary procedures	Cefoxitin/cefotetan (30–40 mg/kg IV; maximum: 2 g) Alternatives: Cefazolin (25/kg IV; maximum: 2 g) *plus* metronidazole (10 mg/kg IV; maximum: 1 g) *or* clindamycin (10 mg/kg IV; maximum: 600 mg) *plus* aztreonam (30 mg/kg IV; maximum: 2 g)

Neu A, et al: Pediatr Nephrol: 29:1477-1484, 2014

Table 3 Peritoneal Dialysis Catheter/Exit-Site Follow-up Care Bundle[a]

- Objective score of exit-site using International Pediatric Peritoneal Dialysis Network (IPPN) scoring tool (Table 5) (7, 25)
- Review key aspects of each of the following:
  - hand hygiene
  -exit-site care
  -aseptic technique
- Query for touch contaminations or other break in aseptic technique and whether they were treated according to ISPD guidelines [7]
- Repeat concept and demonstration test administered every 6 months
- Patient/care giver receives training after a peritonitis episode

Do the bundles work?

- Follow up Bundle
- Follow up Bundle X 3 yrs
- Follow up Bundle 7 yr (accepted for publication)

Sethna

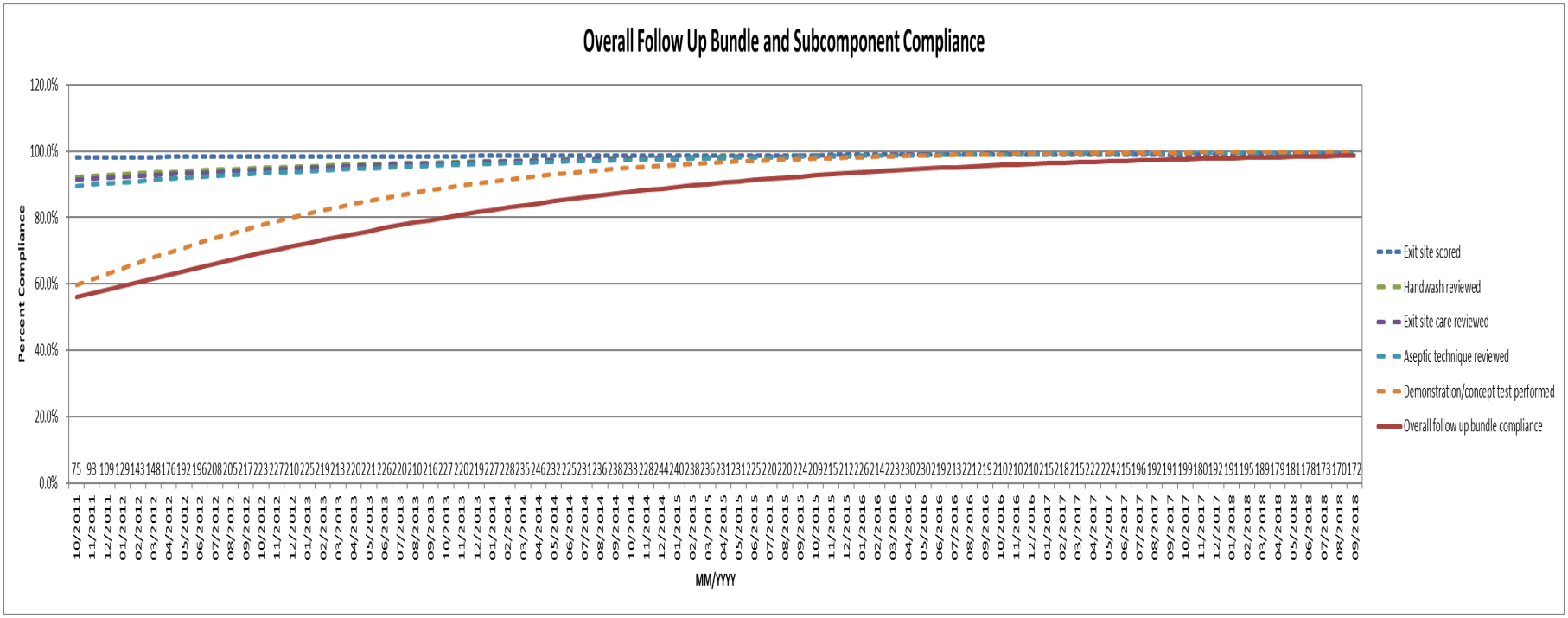
Table 4. Rate ratio models for peritonitis

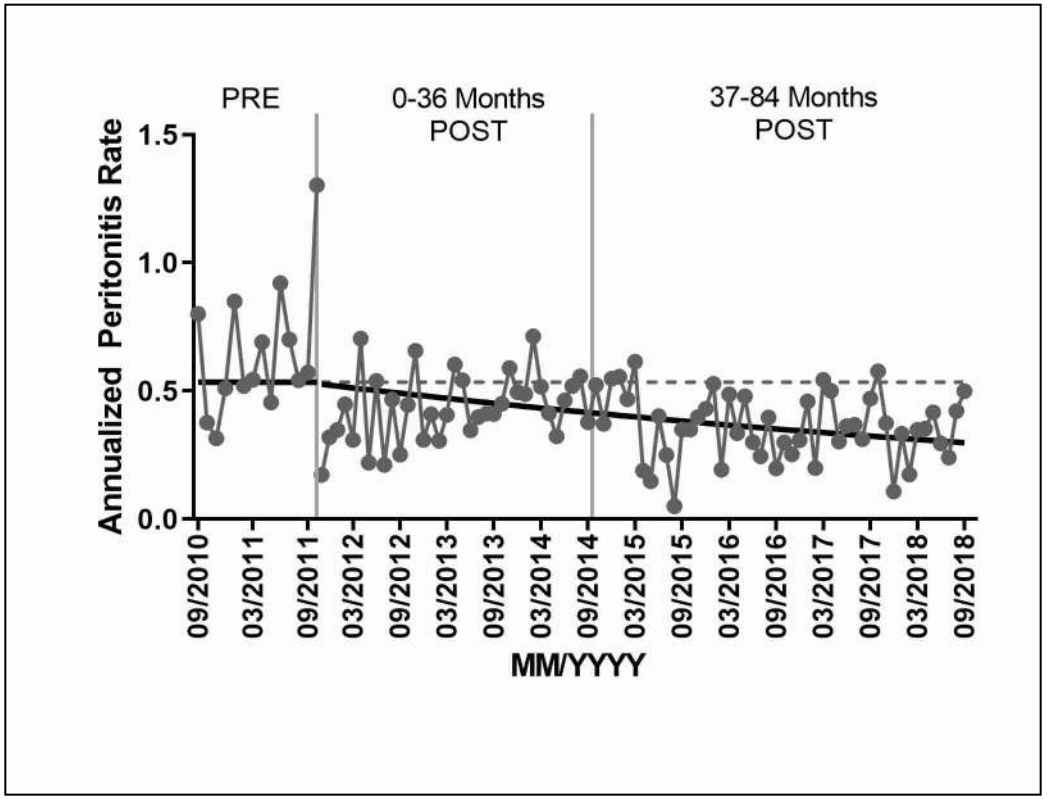
Variables	Crude Rate Ratio (95% CI)	*P* Value	Adjusted Rate Ratio[a] (95% CI)	*P* Value
Age group, yr		<0.001		0.15
<2	Reference		Reference	
2–5	0.81 (0.62 to 1.06)	0.12	0.59 (0.22 to 1.59)	0.28
6–12	0.61 (0.51 to 0.73)	<0.001	0.66 (0.27 to 1.61)	0.35
13–17	0.59 (0.49 to 0.71)	<0.001	0.68 (0.25 to 1.85)	0.44
≥18	0.96 (0.65 to 1.44)	0.85	1.06 (0.23 to 4.95)	0.94
Race		<0.001		0.09
Nonblack	Reference		Reference	
Black	1.66 (1.42 to 1.95)		1.61 (0.93 to 2.80)	
Gastrostomy tube	1.49 (1.29 to 1.72)	<0.001	1.30 (0.69 to 2.45)	0.37
Vesicostomy or stoma	1.36 (1.10 to 1.69)	<0.01	1.04 (0.52 to 2.06)	0.92
Incontinence	1.53 (1.32 to 1.77)	<0.001	1.29 (0.56 to 3.01)	0.54
Touch contamination	1.75 (1.51 to 2.02)	<0.001	2.22 (1.44 to 3.43)	<0.001
Patient performs PD themselves	0.70 (0.59 to 0.81)	<0.001	1.17 (0.63 to 2.17)	0.60
Upward orientation	3.14 (2.42 to 4.08)	<0.001	4.20 (1.49 to 11.89)	<0.001
Plastic adapter	1.33 (1.15 to 1.54)	<0.001	1.38 (0.86 to 2.22)	0.18
Insertion compliance		0.001		0.67
No	Reference		Reference	
Yes	0.62 (0.47 to 0.82)		0.91 (0.57 to 1.44)	
Training compliance		0.43		NA
No	Reference		NA	
Yes	0.88 (0.64 to 1.21)		NA	
Follow-up compliance		<0.001		<0.001
No	Reference		Reference	
Yes	0.50 (0.40 to 0.62)		0.49 (0.30 to 0.80)	<0.01

95% CI, 95% confidence interval; PD, peritoneal dialysis; NA, not applicable.
[a]All significant variables in crude model were included in addition to sex and patient clustering.

In contrast, there was significantly lower provider compliance with the follow-up bundle in the peritonitis group compared with the group without peritonitis (67.2% versus 71.0%, respectively; $P<0.001$). Compliance with the individual elements of review of hand washing (84.1% versus 88.8%, respectively), exit site care (86.1% versus 89.4%, respectively), and aseptic technique (82.1% versus 87.3%, respectively) was significantly lower in those patients with peritonitis compared with the no peritonitis group (all $P<0.001$). Compliance with exit site scoring

Neu 7 yr


Overall Follow Up Bundle and Subcomponent Compliance
Percent Compliance
120.0%
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
MM/YYYY
Exit site scored
Handwash reviewed
Exit site care reviewed
Aseptic technique reviewed
Demonstration/concept test performed
Overall follow up bundle compliance


PRE
0-36 Months
POST
37-84 Months
POST
Annualized Peritonitis Rate
1.5
1.0
0.5
0.0
09/2010
03/2011
09/2011
03/2012
09/2012
03/2013
09/2013
03/2014
09/2014
03/2015
09/2015
03/2016
09/2016
03/2017
09/2017
03/2018
09/2018
MM/YYYY

Exit Site Infections: Skin + Tunnel

GUIDELINE 18 – DIAGNOSIS OF CATHETER-RELATED INFECTION

18.1 We suggest that an objective scoring system be used to monitor the status of the PD catheter exit site (2B).

18.2 We suggest that a diagnosis of a catheter exit-site infection be made in the presence of pericatheter swelling, redness, and tenderness (exit-site score of 2 or greater in the presence of a pathogenic organism and 4 or greater regardless of culture results) (2B).

18.3 We suggest that a tunnel infection be defined by the presence of redness, edema, and tenderness along the subcutaneous portion of the catheter, with or without purulent drainage from the exit site (exit-site score of 6 or greater) (2B).

TABLE 9
Exit-Site Scoring System[a]

Indication	Score[b] 0	1	2
Swelling	No	Exit only (<0.5 cm)	Including part of or the entire tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain on pressure	No	Slight	Severe
Secretion	No	Serous	Purulent

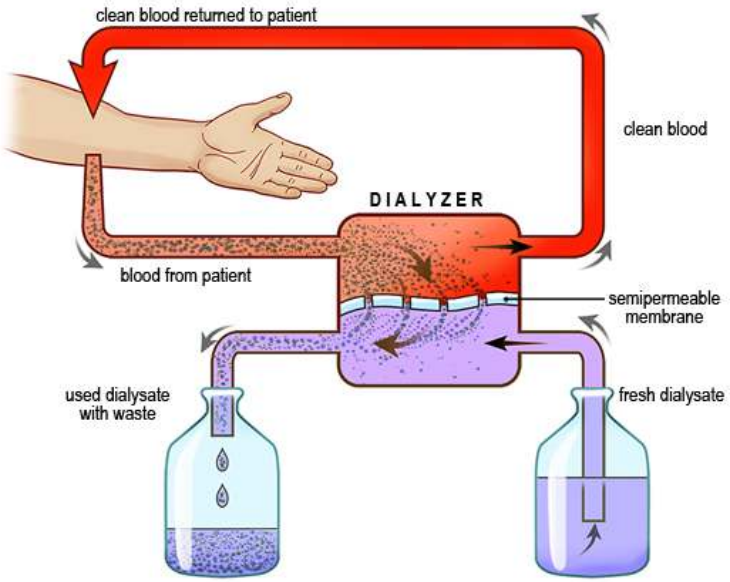
[a] From Schaefer *et al.* (159).
[b] Infection should be assumed with a cumulative exit-site score of 4 or greater.

Schwartz Paper

- MSSA most common Gram-positive organism, identified in 35% of isolates,
- MRSA occurring in 6.5% of isolates.
- Pseudomonas was the most common Gram-negative isolate (18% of isolates).
- a very young age providing protection from ESI (children < 2 years) and an older age (children 6–12 years) then predisposing to ESI.
- Exit site infection-associated peritonitis was rare, occur- ring in only 13 ESIs (6%)
- Of all ESIs,
- 84% resolved with antibiotic provision.
- included PD catheter removal (in 12%)
- and progressive infections (peritonitis or extension to tunnel; in 4%).
- ESI complications twofold more frequently seen with ESIs involving the tunnel than with infections confined to the exit site (28 vs. 12%; p = 0.01).
- Moreover, as a result of the orig- inal ESI or an ensuing complication, 24% of ESIs required hospitalization.

- Among children with ESI, 38% had an IPPN score of > 0 at the follow-up visit prior to the infection, whereas only 18% of those who remained without ESI had a score of > 0 at the last follow-up visit ($p < 0.001$).
- A higher IPPN score at these follow-up visits was strongly associated with a subsequent ESI before the next follow-up visit.
- The follow-up bundle stipulates that exit site care should be reviewed at each follow-up visit. Documentation of such site review at the last follow-up visit was found in 81% of children who developed ESI compared to 89% without ESI ($p = 0.048$).
- ESI contributed to signifi- cant patient morbidity, with nearly 25% of ESIs requiring hospitalization, including PD catheter removal in 10% of these, underscoring why prevention or early identification of ESI is a key component of PD care.
- Similarly, lower provider adherence to care bundles at the patient level resulted in higher ESI rates in this cohort. Children with ESI were less likely to have documentation of initial exit site care training. Children with ESI were also less likely to have documentation of site care review at the last follow-up visit. MODIFIABLE RISK FACTOR

Hemodialysis



HD Catheter Associated Blood Stream Infection
Exit Site Infection
Tunnel Infection

What's the big deal? (USRDS)

- Hemodialysis (HD) catheter-associated blood stream infections (CA-BSI) are a significant cause of morbidity and mortality. Infection is the second leading cause of mortality and the leading cause of hospitalizations in pediatric end stage renal disease (ESRD), with the highest rates in children on peritoneal dialysis (PD) and HD, compared with those with a kidney transplant [1].

- , the reported pediatric HD CA-BSI rates of 1.1-10/1000 catheter days [11–15] correspond to a rate of 3.3-30/100 patient months (Olea)

HD Catheter Associated BSI: Definition

Lack of Uniformity in the Definition

- Surveillance definition
- CLABSI
  - BSI is considered to be associated with a central venous catheter if the catheter was in use during the 48-h period before development of the BSI.
  - May overestimate true number of Catheter Related Blood Stream Infections
- Clinical Definition
- IDSA
- KDOQI

HD Catheter Associated BSI: Definition

Ann & Robert H. Lurie Children's Hospital of Chicago®

- KDOQI[1]+ IDSA[2] clinical definition:
- KDOQI: Same organism from a semiquantitative culture of the catheter tip (>15 CFU/catheter segment) *and* from a BC in a symptomatic patient with no other apparent source of infection
- **Probable:** Defervescence of symptoms after antibiotic therapy with or without removal of the catheter, in the setting in which BC confirms infection, but catheter tip does not (or catheter tip does, but blood does not) in a symptomatic patient with no other apparent source of infection.
- **Possible:** Defervescence of symptoms after antibiotic treatment or after removal of catheter in the absence of laboratory confirmation of BSI in a symptomatic patient with no other apparent source of infection.

- IDSA:
- Bacteremia/fungemia in a patient with an intravascular catheter with at least 1 positive BC and with clinical manifestations of infections (ie, fever, chills, and/or hypotension) and no apparent source for the BSI except the catheter
  AND
  One of the following should be present:
  A positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10^3 CFU/catheter segment) culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and peripheral blood.
  Simultaneous quantitative BC with a >5:1 ratio catheter versus peripheral.
  Differential time period of catheter culture versus peripheral BC positivity of >2 h.

Implications of HD Catheter Associated BSI

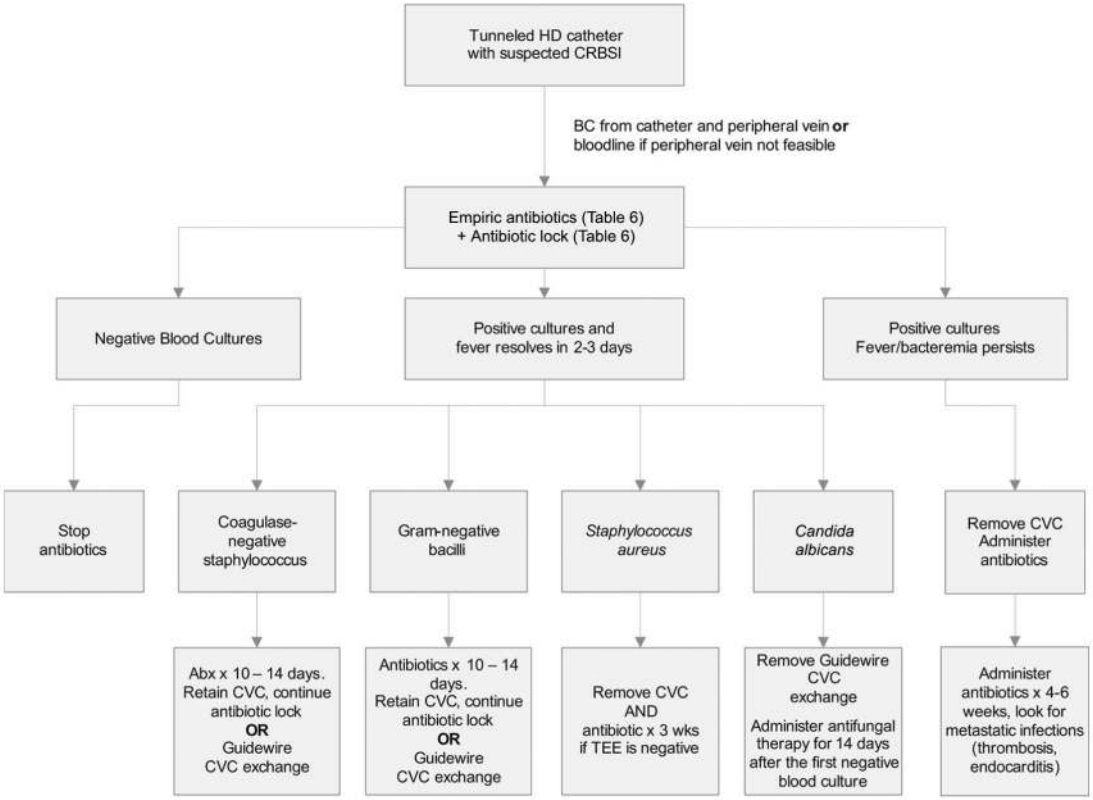
Ann & Robert H. Lurie Children's Hospital of Chicago®

- Complications of Hemodialysis Catheter Bloodstream Infections: Impact of Infecting Organism.AUFarrington CA, Allon M SOAm J Nephrol. 2019;50(2):126. Epub 2019 Jun 26. BACKGROUNDCatheter-related bloodstream infections -(CRBSI) are associated with a high burden of morbidity and mortality, but the impact of infecting organism on clinical outcomes has been poorly studied.
- METHODSThis retrospective analysis of a prospective vascular access database from a large academic dialysis center investigated whether the organism type affected the clinical presentation or complications of CRBSI.
- RESULTSAmong 339 patients with suspected CRBSI, an alternate source of infection was identified in 50 (15%). Of 289 patients with CRBSI, 249 grew a single organism and 40 were polymicrobial. Fever and/or rigors were presenting signs in≥90% of patients with

HD BSI: Pathogens

- Gram-positive organisms are responsible for most hemodialysis catheter-related infections. Coagulase-negative staphylococci and *S. aureus* together account for 40 to 80 percent of cases in most studies [3,19,25-29]. Gram-negative organisms account for 20 to 40 percent, and polymicrobial infections are implicated in 10 to 20 percent of all episodes of catheter-related bloodstream infections (CRBSIs) [3].

- SCOPE paper


Tunneled HD catheter with suspected CRBSI
BC from catheter and peripheral vein **or** bloodline if peripheral vein not feasible
Empiric antibiotics (Table 6) + Antibiotic lock (Table 6)
Negative Blood Cultures
Positive cultures and fever resolves in 2-3 days
Positive cultures Fever/bacteremia persists
Stop antibiotics
Coagulase-negative staphylococcus
Gram-negative bacilli
Staphylococcus aureus
Candida albicans
Remove CVC Administer antibiotics
Abx x 10 – 14 days. Retain CVC, continue antibiotic lock **OR** Guidewire CVC exchange
Antibiotics x 10 – 14 days. Retain CVC, continue antibiotic lock **OR** Guidewire CVC exchange
Remove CVC AND antibiotic x 3 wks if TEE is negative
Remove Guidewire CVC exchange
Administer antifungal therapy for 14 days after the first negative blood culture
Administer antibiotics x 4-6 weeks, look for metastatic infections (thrombosis, endocarditis)

HD Catheter BSI: Treatment (IDSA)

Ann & Robert H. Lurie Children's Hospital of Chicago®

- WHAT ARE THE UNIQUE ASPECTS OF MANAGING PATIENTS WHO ARE RECEIVING HEMODIALYSIS THROUGH CATHETERS FOR WHOM CATHETER-RELATED INFECTION IS SUSPECTED OR PROVEN? Recommendations 53 Peripheral blood samples should be obtained for culture from vessels that are not intended for future use in creating a dialysis fistula (e.g., hand veins) (A-III). 54 When a peripheral blood sample cannot be obtained, blood samples may be drawn during hemodialysis from bloodlines connected to the CVC (B-II). Mermel et al. Page 19 Clin Infect Dis. Author manuscript; available in PMC 2014 May 30. NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript 55 In patients with suspected CRBSI for whom blood cultures have been obtained and for whom antibiotic therapy has been initiated, antibiotic therapy can be discontinued if both sets of blood cultures have negative results and no other source of infection is identified (B-II). 56 When a peripheral blood sample cannot be obtained, no other catheter is in place from which to obtain an additional blood sample, there is

Preventative Measures

- Fistula: USRDS numbers
- SCOPE: Bundle adherence
- NTDS

HD Catheter: Exit Site and Tunnel Infection: Definition

- IDSA: Hyperemia, induration, and/or tenderness **≤2 cm** from catheter exit site. May be associated with fever and purulent drainage from the exit site. It may or may not be associated with bacteremia. If there is purulent drainage, it should be collected and sent for Gram staining and culture.

- IDSA: Tenderness, hyperemia, and/or induration that extends **>2** cm from the exit site and along the subcutaneous tunnel. It may or may not be associated with bacteremia. If there is purulent drainage, it should be collected and sent for Gram staining and culture.

HD Catheter: Exit Site and Tunnel Infection: Treatment IDSA

Ann & Robert H. Lurie Children's Hospital of Chicago®

What are the unique aspects of treating long-term CVC or implanted catheter-related infections other than hemodialysis catheters?			
44.	Patients with tunnel infection or port abscess require removal of the catheter, incision and drainage if indicated, and 7–10 days of antibiotic therapy in the absence of concomitant bacteremia or candidemia.	A-II	[19, 264]
45.	For patients with suspected exit site infection, obtain cultures of any drainage from the exit site and blood cultures	A-II	[19]
46.	Uncomplicated exit site infections (i.e., those without systemic signs of infection, positive blood culture results, or purulence) should be managed with topical antimicrobial agents on the basis of the exit site culture results (e.g., mupirocin ointment for *S. aureus* infection and ketoconazole or lotrimin ointment for *Candida* infection	B-III	
47.	If an uncomplicated exit site infection fails to resolve with topical therapy or if it is accompanied by purulent drainage, then systemic antibiotics should be administered on the basis of the antimicrobial susceptibility of the causative pathogen; the catheter should be removed if treatment with systemic antibiotics fails	B-II	[19]
48.	If other vascular sites are unavailable and/or the patient is at increased risk for bleeding diathesis in the setting of CRBSI not complicated by an exit site or tunnel infection, then exchange the infected catheter over a guidewire	B-III	[73]
	In such situations, an antimicrobial-impregnated catheter with an anti-infective intraluminal surface should be considered for catheter exchange		

Northwestern Medicine®
Feinberg School of Medicine

Growth and Recombinant Growth Hormone Therapy

John D Mahan, MD

Professor, Department of Pediatrics

Nationwide Children's Hospital

The Ohio State University College of Medicine

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

THE OHIO STATE UNIVERSITY

No Conflicts to Disclose

Overview

1. Why is **growth** in children with CKD so important
2. How to improve growth in children with CKD
3. Describe new evidence about additional benefits of therapies directed to the GH-IGF-1 Axis in CKD

Growth: A Paramount Concern !

Overview

1. Why i
   so im
2. How t
   with C
3. Descr
   additi
   direct

cern !

Objectives

1. Describe why growth is so important to children with CKD and their families
2. Provide best approaches, including recombinant Growth Hormone (GH) treatment, to promote growth in children with Chronic Kidney Disease (CKD)
3. Describe potential additional benefits of therapies directed to the GH-IGF-1 Axis in CKD

Growth is the Paramount Outcome in Children with CKD!!!

4 Questions

1. Why is Growth in Children with CKD so Important?
2. What are Modifiable Causes of Growth Failure in Children with CKD?
3. How Does GH Work to Improve Growth in CKD?
4. How is GH Used in Children with CKD?

Q1: Why is Growth in Children with CKD so Important?

Patient MH

Identical twin with Prune Belly Syndrome

Twin unaffected

LRD (father) transplant 1 week prior to 6th birthday with bilateral nephrectomy and orchidopexy

Patient MH

Age (yr)	Wt (kg)	Wt SDS	Ht (cm)	Ht SDS	Wt/Ht SDS	Cr (mg)	GFR (mL/min/1.73 m^2)
6	25.5	1.96	115.9	-0.04	2.16	0.6	106
9.6	33.3	0.95	132.2	-0.4	1.38	1.1	66
11.2	31	-0.87	135.6	-1.33	0.23	1.8	41
12.9	37.6	-0.8	139	-1.89	1.07	1.5	46

On CSA/Imm/Pred post transplant; rejection x 1, treated with solumedrol

Patient MH

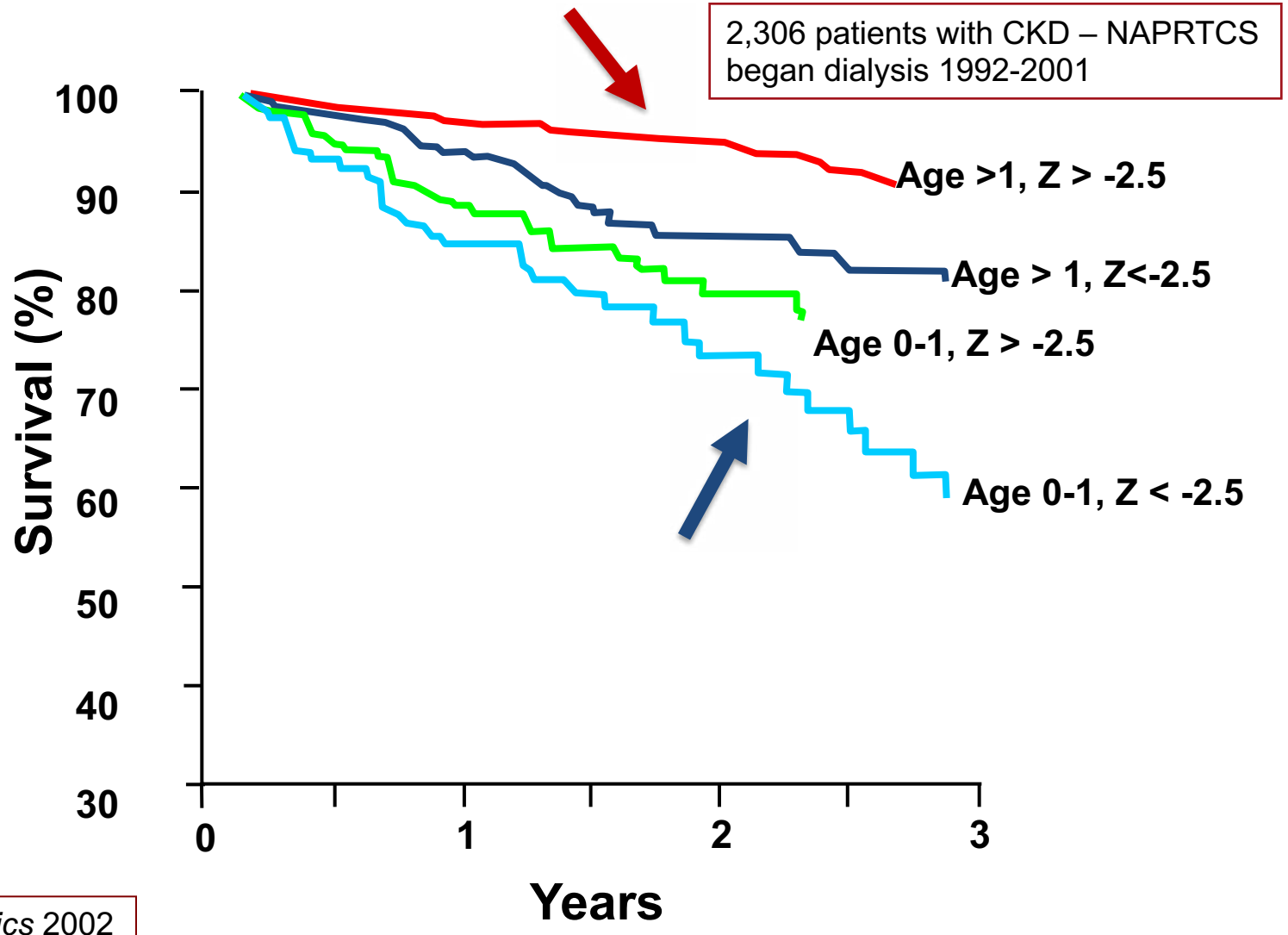
Ag (y	GFR (in/1.73 m²)
6	106
9.	66
11	41
12	46

On CSA/Imm/Pred post transplant; rejection x 1, treated with solumedrol

Better Growth in Childhood CKD is Associated with Better

- **Survival** [Furth 2002; Ku 2016]
- **Morbidity** (hospitalizations, infections, etc) [Furth 2002; Li 2019]
- **Adult height** [Hoekken-Kolega 2001; Haffner 2000]
- **Satisfaction with adult life** [Boyer 2004; Rosenkrantz 2005]
- **Childhood physical and social functioning** [Al-Uzri 2013]
- **Patient/Parent perspective** [Reynolds 1995]
- **Bone mineralization** [Nawrot-Wawrzyniak 2013]

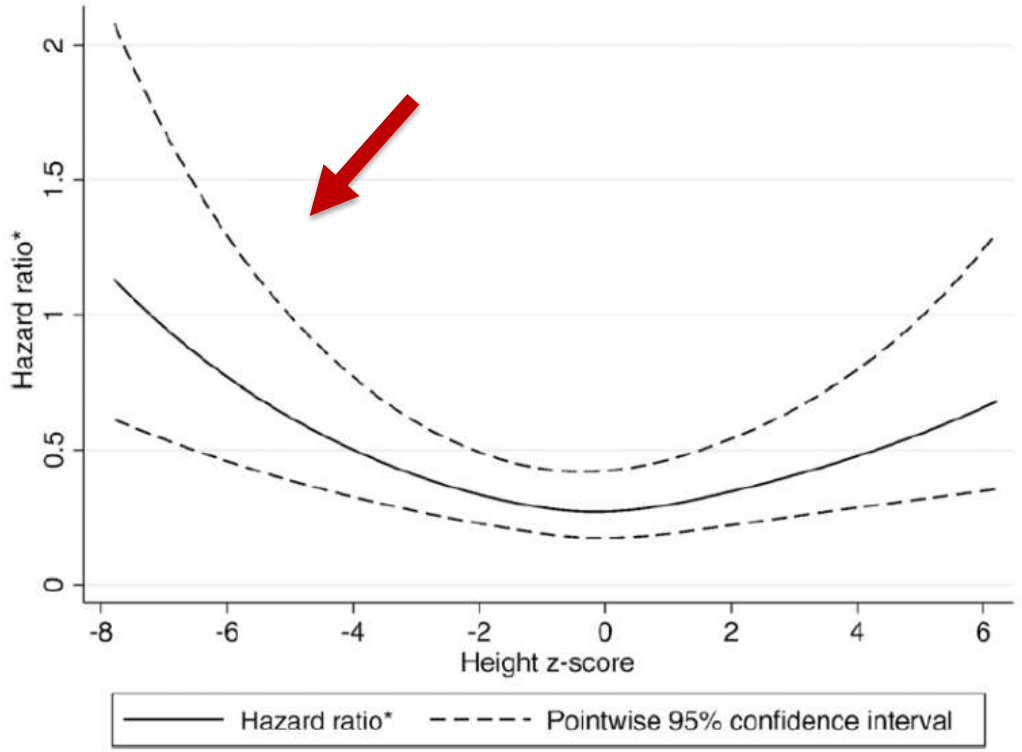
Growth Failure in Children with CKD is Associated with Poorer Survival



Furth S, *Pediatrics* 2002

Children with Short Stature at Initiation of RRT Have Increased Mortality

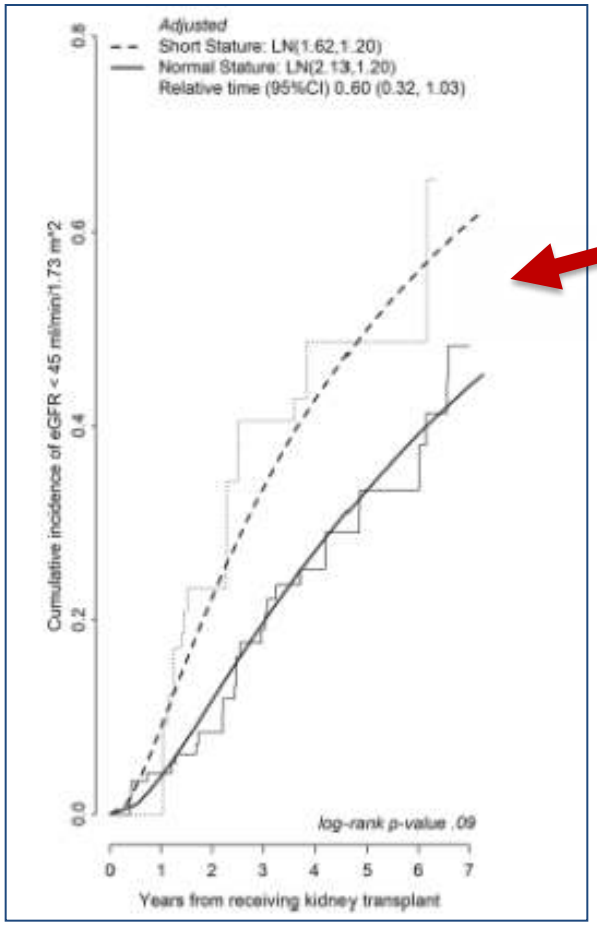
USRDS, retrospective
13,218 children (2-19 yo)
First RRT 1995-2011
1721 deaths



Short children = higher risk of cardiac & infection deaths
Tall children = higher risk of cancer deaths

Ku E. *CJASN* 2016

Short Stature at Time of Renal Transplant is Associated with Faster Time to Poor Kidney Function



CKiD, 138 children
Renal Tx mean age 13 yo
Median time to eGFR <45 = 6.6 yrs
20% (28) short stature before Tx

Children with short stature = lower SES, nephrotic proteinuria, higher BP, lower mid-parental height before transplant

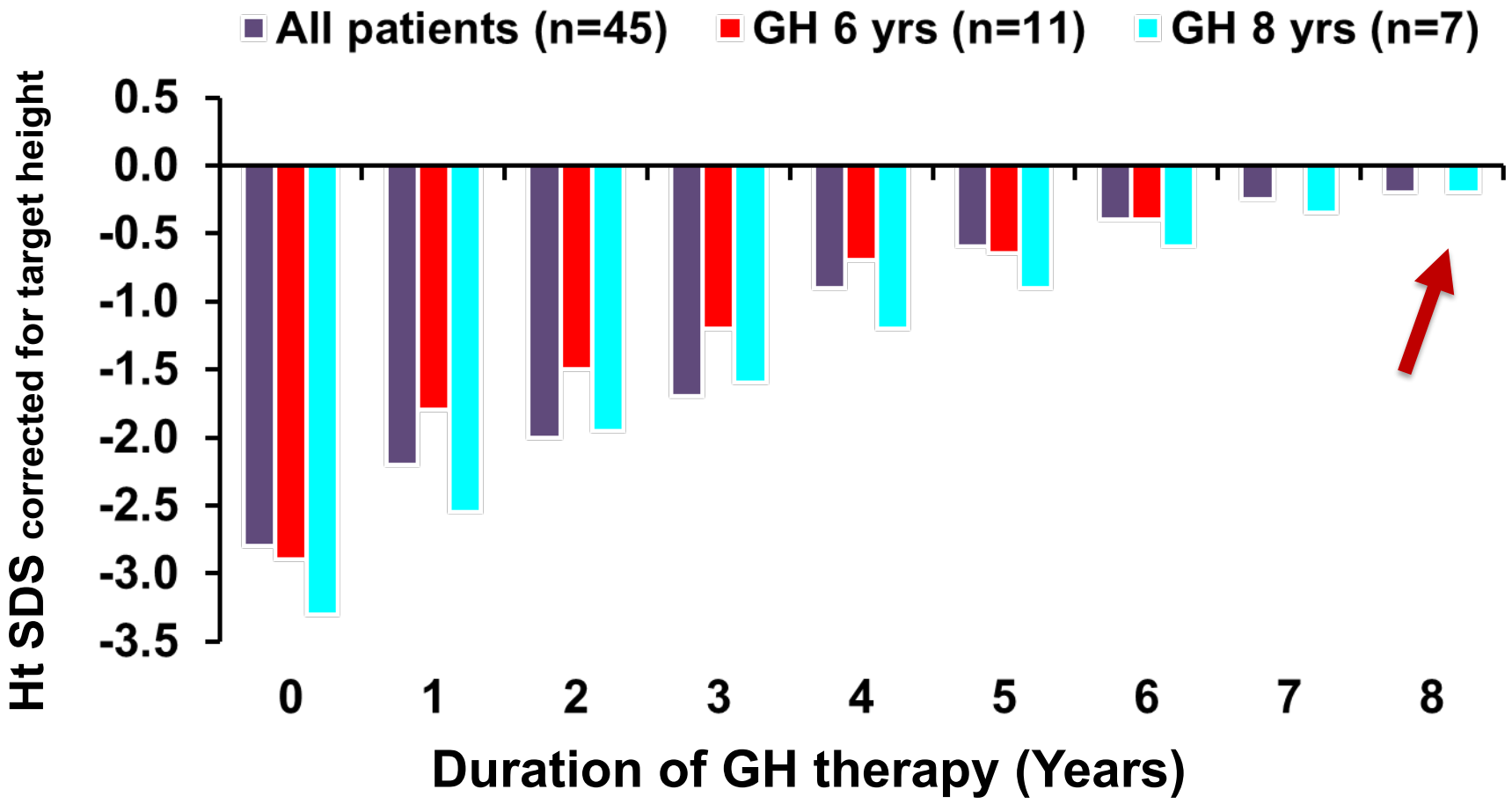
After adjustment for above variables, children with growth failure had 40% shorter time to eGFR <45 ml/min/1.73 m^2

Li Y. *Ped Neph 2019*

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

THE OHIO STATE UNIVERSITY

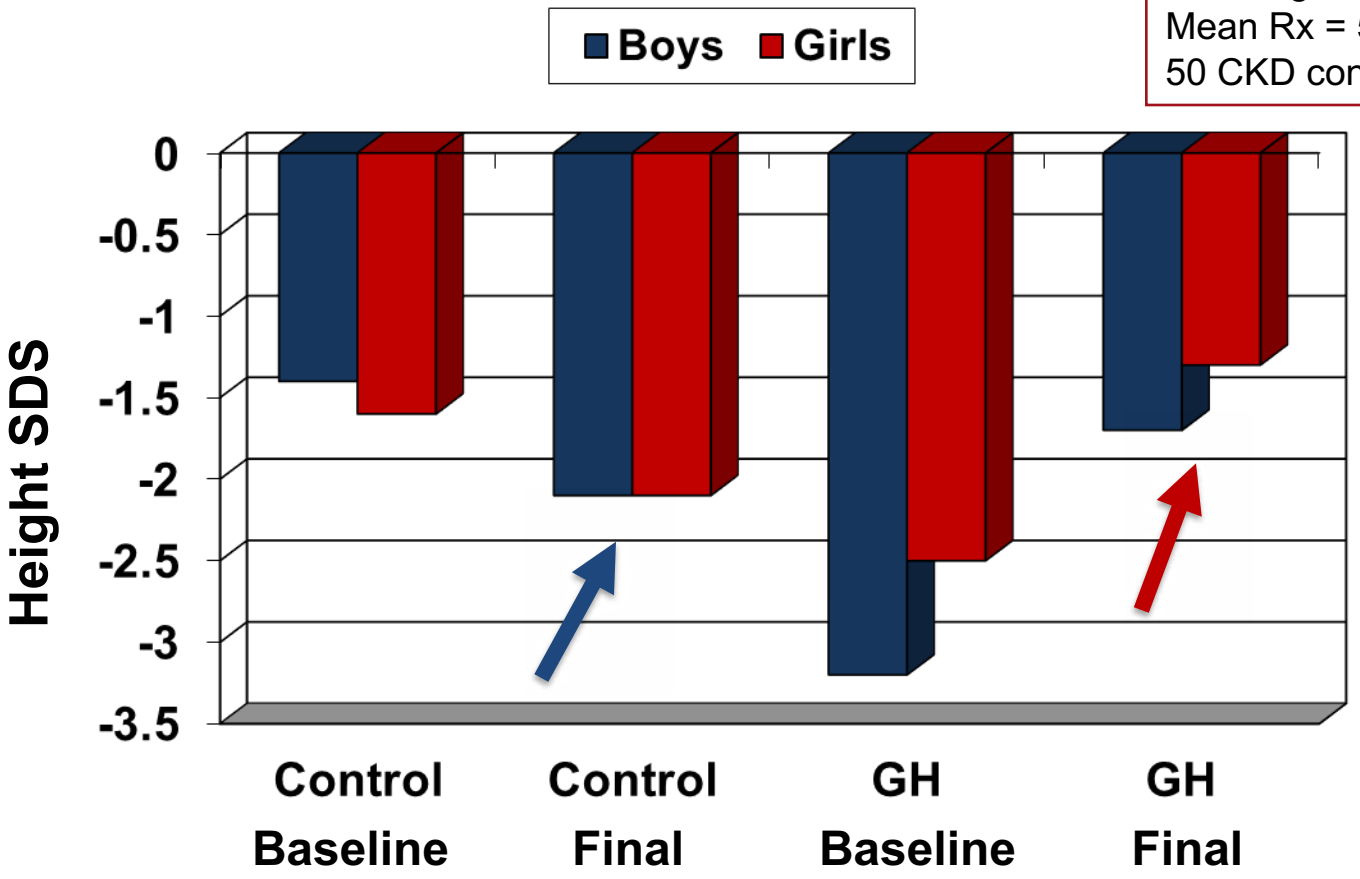
Long-Term Intervention (GH Therapy) Continues to Improve Growth in Children with CKD



Hokken-Koelega A. *J Ped Endrocrinol Metab* 2001
Hokken-Koelega A. *Ped Neph* 2000

Final Adult Height is Better in Children with CKD Treated with GH Therapy

38 short with CKD
Mean age 10.4 yr at GH Rx
Mean Rx = 5.3 yrs
50 CKD controls



Haffner D. *N Engl J Med* 2000

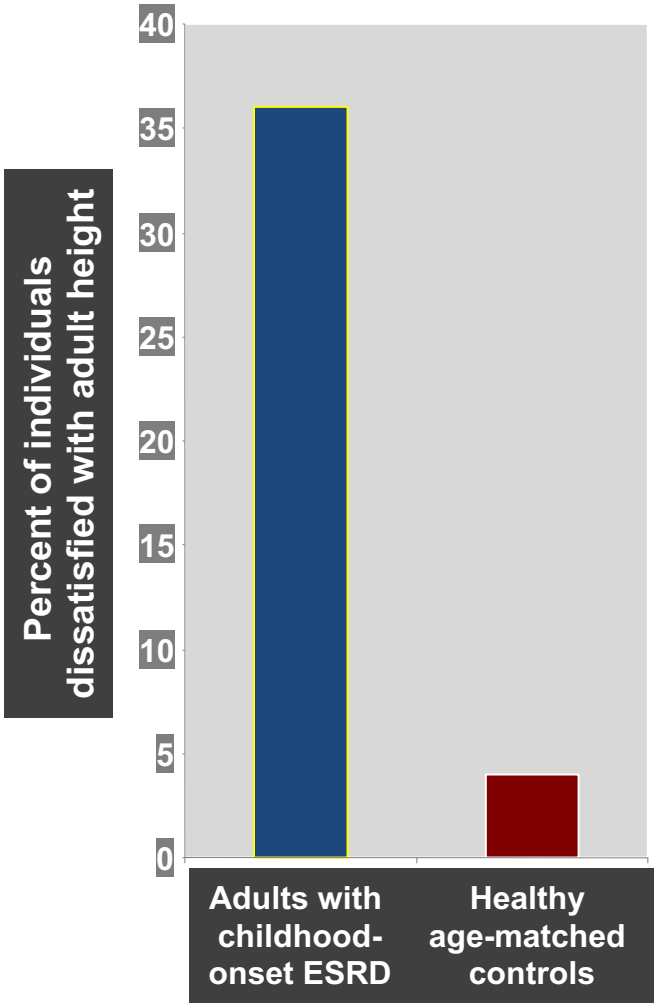
Social Outcome Following Renal Transplantation is Greatly Influenced by Adult Height

Adult height significantly correlated with:	
Characteristic	P value
Year of transplantation	0.04
Higher educational level achieved	<0.001
Higher rate of paid employment	0.02
Greater likelihood of marriage	<0.0001
Greater likelihood of independent living	0.0003

N = 244; mean age = 31.7; mean age Tx = 11.9

Broyer M. *Transplantation* 2004

Height Dissatisfaction in Adults with Childhood CKD Impacts Adult Quality of Life



Mean adult height SDS score: –1.56 ± 1.55

Height satisfaction correlated with height SDS score (*r* = 0.42; *P* = .006)

Quality of life correlated significantly with height satisfaction (*r* = 0.41; *P* = .008)

N = 39; mean age = 26.7

Rosenkranz J. *Ped Neph* 2005

Growth in Children with CKD IMPACTS on QOL

CKiD, 483 children &/or parents
Peds QL (4.0) on 2 visits

Chronic Kidney Disease in Children

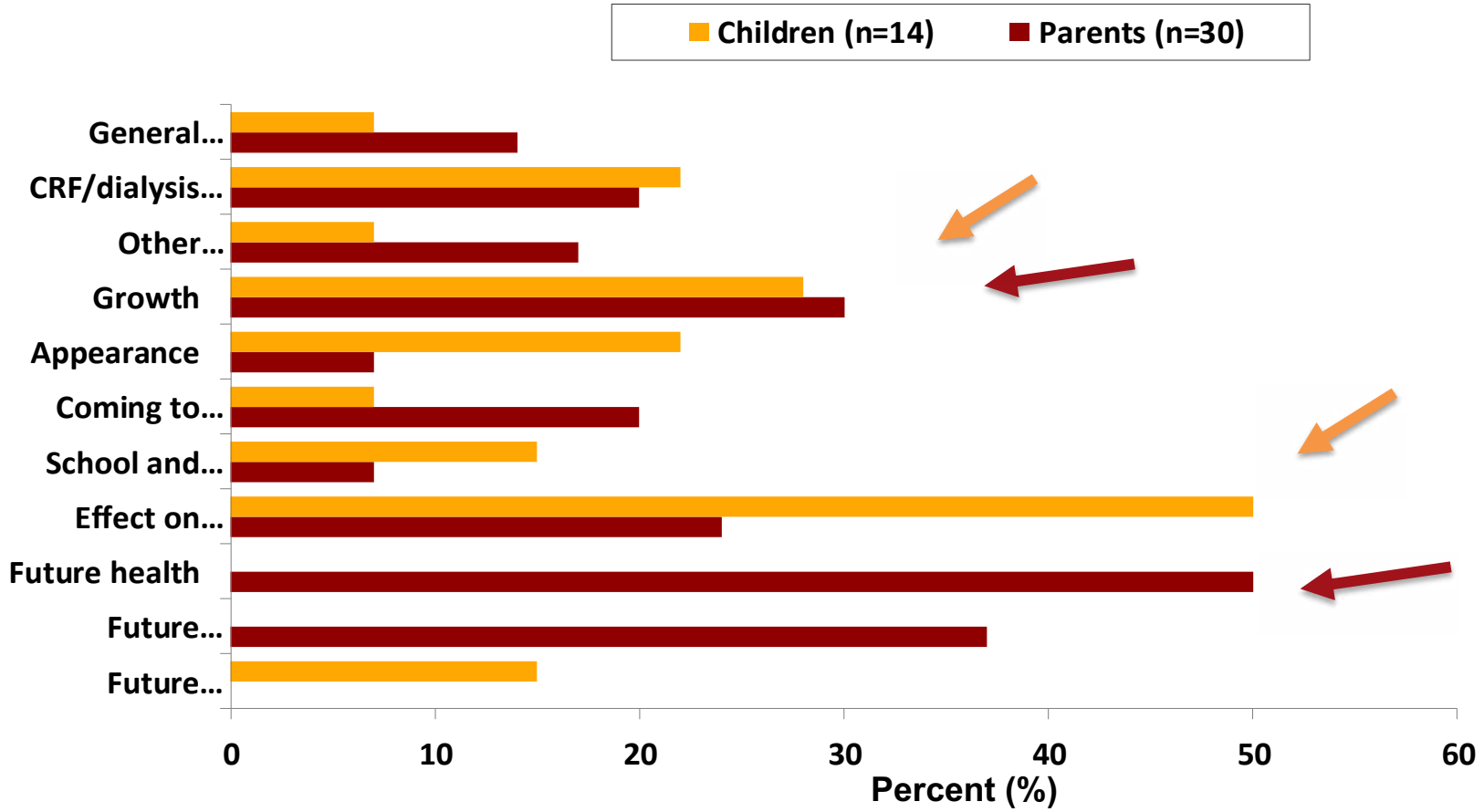
Participants split into Normal Height or Short Stature groups

Multivariate modeling: *significant association between both*

- ***catch-up growth***
- ***growth hormone use***

Improved child physical functioning social functioning
[based on parent reports]

Growth Concerns Children with CKD and Their Parents



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

THE OHIO STATE UNIVERSITY

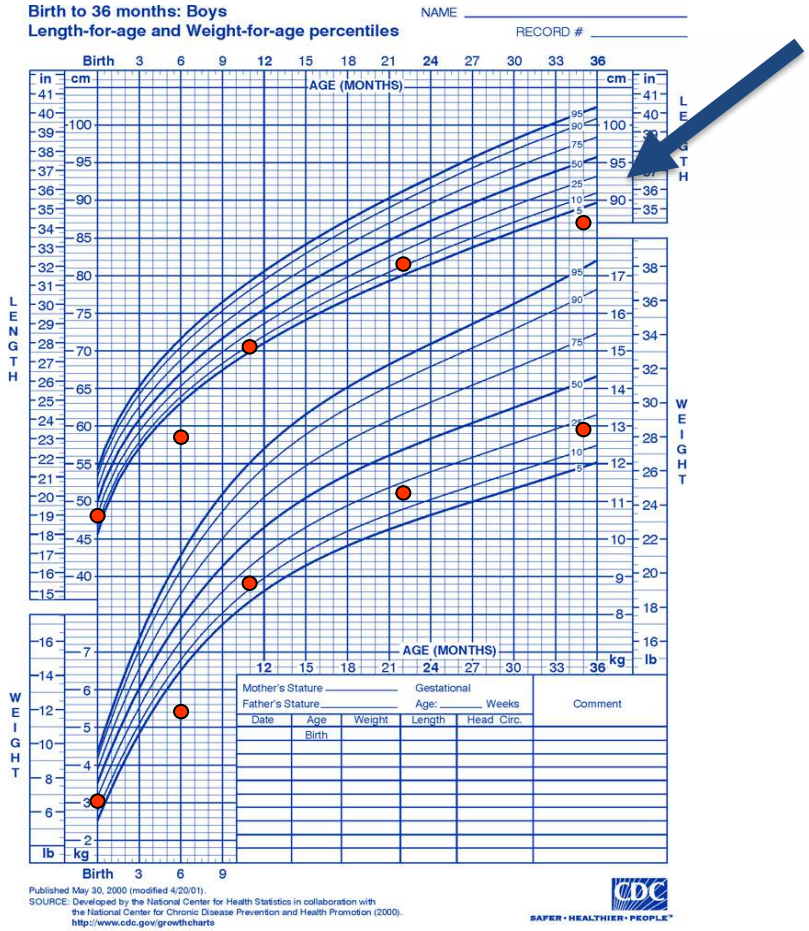
Reynolds JM
Arch Dis Child 1995

Patient MH – Subsequent Outcome

	Age (yr)	Wt (kg)	Wt SDS	Ht (cm)	Ht SDS	Wt/Ht SDS	Cr (mg)	GFR (mL/min/1.73 m^2)
	6	25.5	1.96	115.9	-0.04	2.16	0.6	106
	9.6	33.3	0.95	132.2	-0.4	1.38	1.1	66
	11.2	31	-0.87	135.6	-1.33	0.23	1.8	41
GH started	12.9	37.6	-0.8	139	-1.89	1.07	1.5	46
	13.2	37.2	-0.87	143	-1.33	0.23	1.4	56
	15.4	49.2	-0.75	160.5	-1.84	1.07	1.7	52
	17.6	61.3	-0.79	175.5	-0.21	0.2	2.6	37

On CSA/Imm/Pred post transplant; rejection x 1, treated with solumedrol

Q2: What are Modifiable Causes of Growth Failure in Children with CKD?



Variables That Can Contribute to Growth Failure in Individual Child with CKD*

Growth Failure May Occur at Any Level of CKD (GFR)
Growth Does Not Typically Improve with Dialysis
Growth Failure is Related to Multiple Factors

Non-Modifiable

Age of onset of CKD
Abnormal birth history
Primary renal disease
Degree of renal dysfunction
Genetic factors (parental ht)
Delayed puberty?
Steroid and other therapies

Modifiable

Protein and Calorie deficiency
Abnormal protein metabolism
Metabolic acidosis
CKD-MBD
Salt-wasting/concentration defect

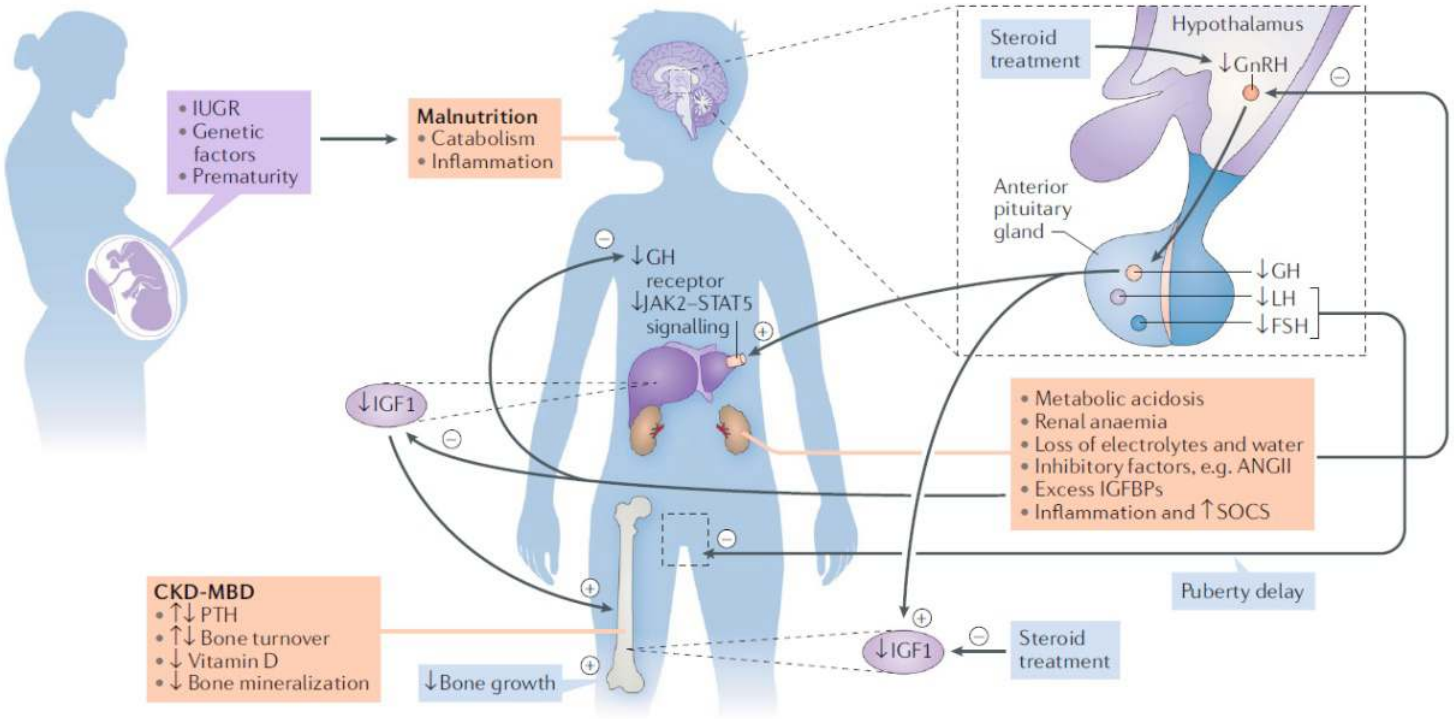
Abnormal GH/IGF-I axis

Mahan JD. *Ped Neph* 2006
Drube J. *Nat Rev Neph* 2018

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

THE OHIO STATE UNIVERSITY

The Many Factors that Contribute to Growth Failure in Children with CKD



Drube J. Nat Rev Neph 2018

Abnormal Birth History Impacts Growth in CKD

CKiD, 426 children
Detailed birth history

	Poor Growth	Good Growth	P value
Pre-term (%)	43.2	25.6	<0.001
SGA (%)	36.8	18.9	<0.001
LBW (%)	30.8	15.9	<0.001

Greenbaum L. *CJASN* 2011

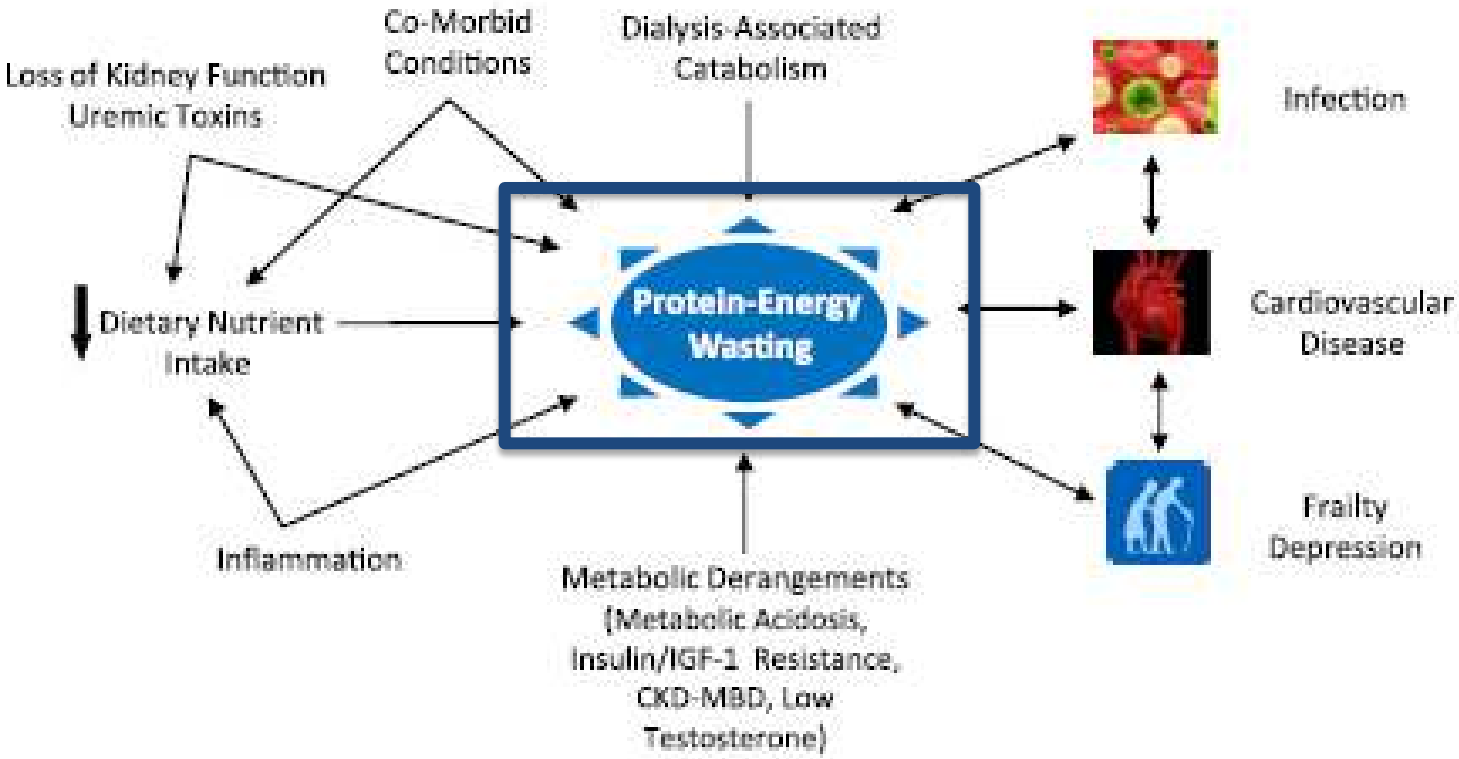
Malnutrition-Inflammation Cachexia Syndrome: Protein-Energy Wasting is Common in CKD

'Cachexia in Slow Motion' – *Protein-energy malnutrition + inflammation*

Malnutrition	Protein Energy Wasting
Inadequate intake of nutrients	Inadequate intake of nutrients only partially responsible
Body fat is lost	Normal or even increase fat mass
Lean body mass initially preserved, later loss muscle mass and protein stores	Loss of lean body mass
Low resting energy expenditure	High resting energy expenditure
Can be reversed by dietary supplements	Inadequate response to dietary supplements

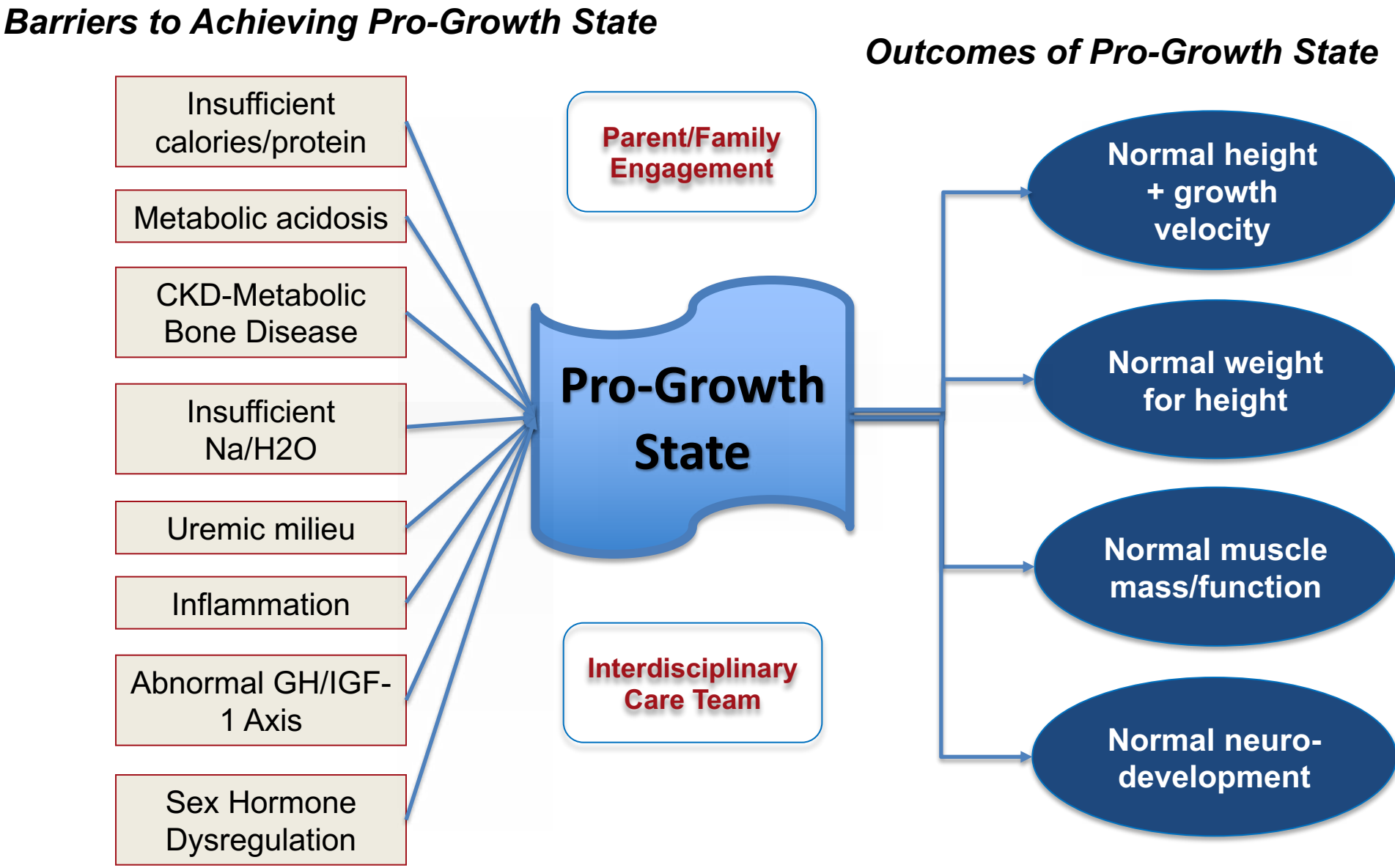
Fouque D. *KI* 2011

Protein Energy Wasting in CKD



Carrero JJ. *J Ren Nutr* 2013

Achieving Pro-Growth State in Childhood CKD



Pro-Growth Agenda in Childhood CKD – <u>It's Complicated!</u>

- Easy to ignore
  - Hard to overcome anorexia, dysgeusia, fatigue
- ***? Nutritional supplements/NG Tube-G Tubes – complicated!***
- Control of metabolic acidosis and CKD-MBD requires multiple meds, multiple times/day
- Lab monitoring complicated

Pro-Growth Agenda in Childhood CKD – It's Complicated!

- **Inflammation** often insidious, challenging
- **Uremia control – *complicated!***
- GH Rx to overcome GH/IGF-1 resistance state – ***complicated!***
- Never too soon to start additional efforts to promote – do not wait for significant growth failure!
- Best way to achieve normal adult height and good quality of life/satisfaction = ***good growth!***

Always Start with Aggressive Nutrition in CKD: Strong Evidence for Good Outcomes

Prevention of growth disturbances in CKD as major goal nutrition Rx

- Initiation of **enteral feedings** (NG/GT) before important height deficits provides superior height outcomes [Parekh]
- Infants show significant increases in growth velocity after provision of **adequate calories** NG/GT [Parekh, Kari, Ledermann]
- **Extra calories** in childhood CKD often result in BMI gains > Ht gains – improved albumin may be critical marker for good growth [Rees]
- **GT associated with better growth than NG** [Rees] – may have less oral aversion with GT; neither associated with more obesity

CKD Management to Promote Growth

	Barrier	Treatment
1.	**Insufficient calories/protein**	100% RDA calories/protein for ideal weight
2.	**Metabolic acidosis**	Alkali as needed to maintain HCO3 >22
3.	**CKD-Mineral Bone Disease**	P restriction; maintain normal 25D, Ca and P; maintain PTH in CKD appropriate range
4.	**Insufficient Na/H2O**	Na/H2O supplements as needed
5.	**Uremic milieu**	CKD5 – dialysis for adequacy + more
6.	**Inflammation**	Prevent/treat infections
7.	**Abnormal GH/IGF-1 Axis**	GH in pharmacologic doses if needed
8.	**Sex Hormone Dysregulation**	Typically not treated; evaluate significant delays

Q3: How Does GH Work to Improve Growth in CKD?

Uremia is State of GH/IGF-1 Resistance [Altered GH/IGF-1 Axis]

GH Resistance

- ❑ GH receptor density diminished in target organs
- ❑ GH signal transduction impaired (JAK/STAT)
- ❑ Diminished IGF-1 release

Increased IGFBPs

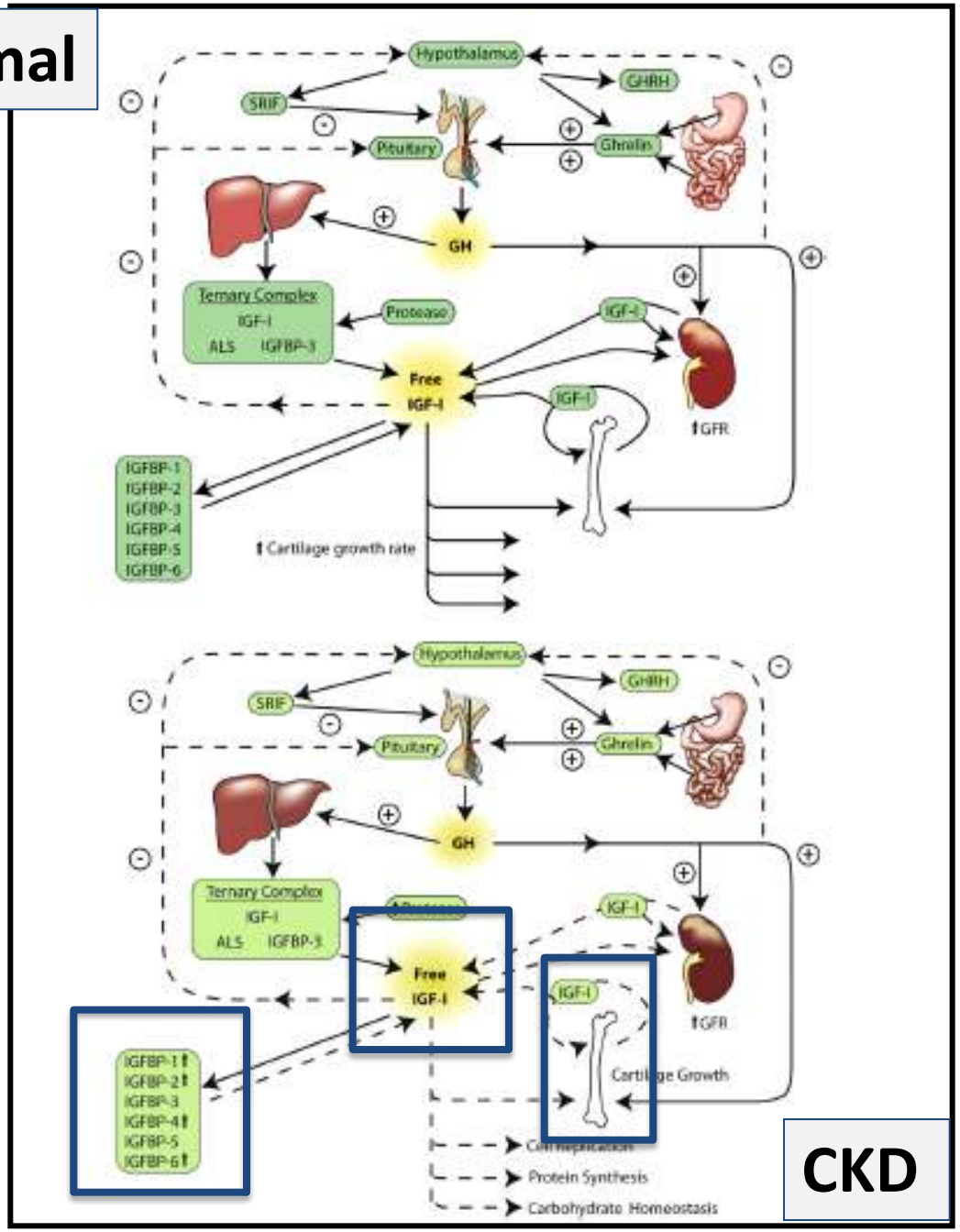
- ❑ Decreased bioactive IGF-1

Altered GH Signaling

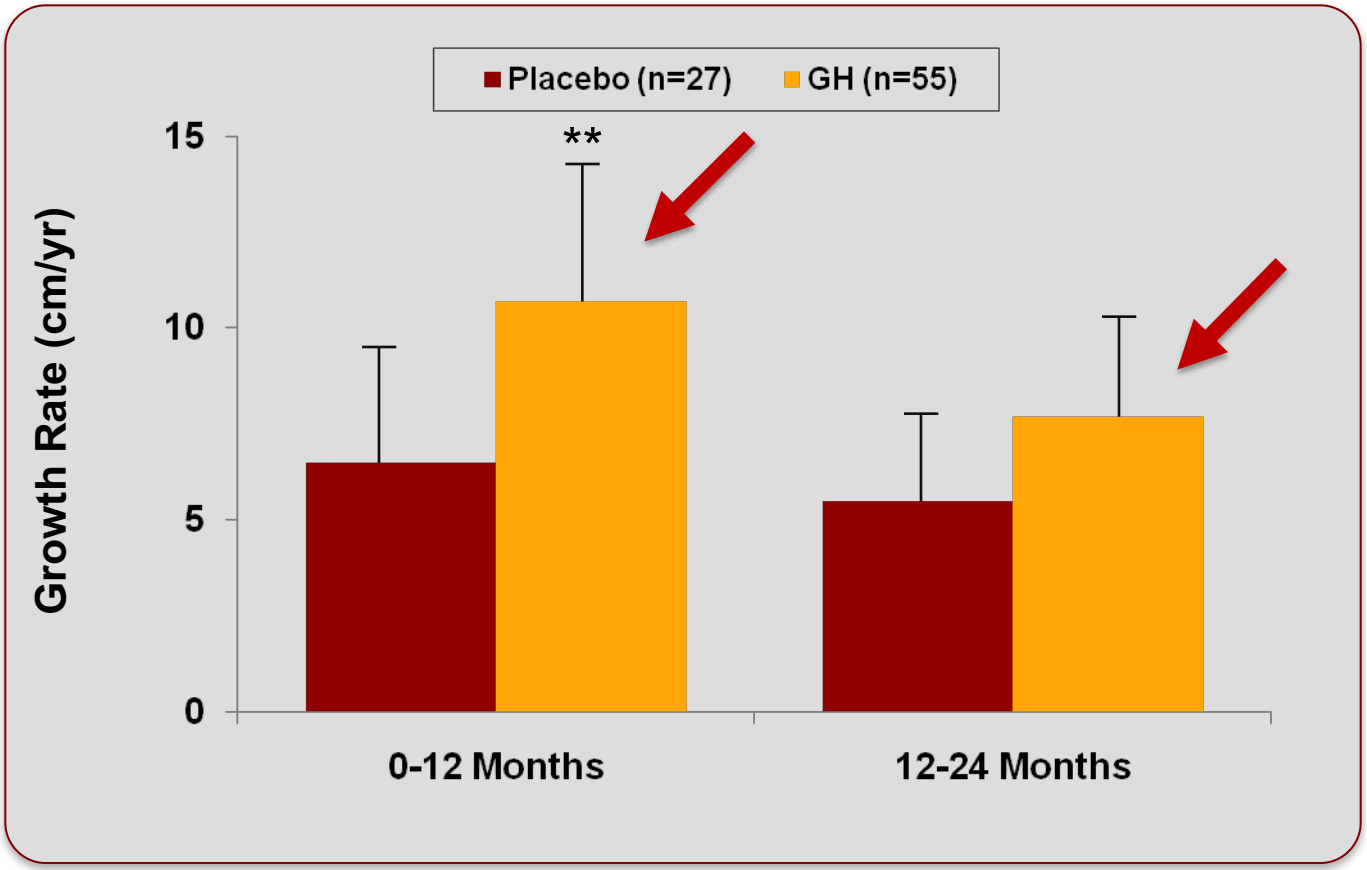
- ❑ Inflammatory cytokines activate ***Suppressor of Cytokine Signaling 2 (SOCS2)*** pathway that suppresses GH release

Uremia is a State of GH/IGF-1 Resistance

[Altered GH/IGF-1 Axis]



rhGH Treatment Improves Growth in Children with CKD

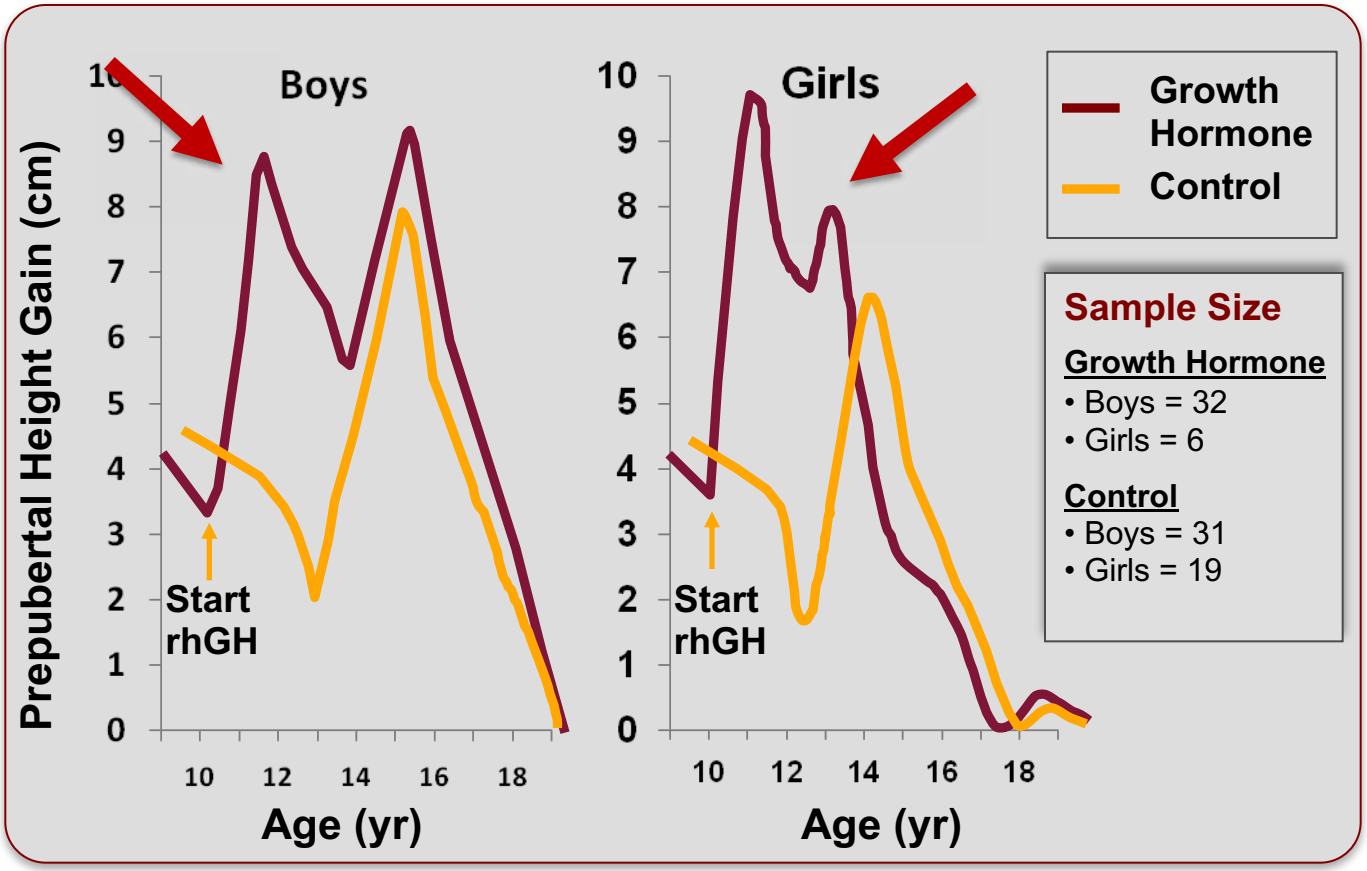


**P<0.00005 compared to placebo.

Children with CKD who receive rhGH therapy have better growth rates than placebo-treated children.

Fine R. *J Pediatr* 1994

GH Treatment Provides Significant Height Gains in Children with CKD During Puberty



It is important to initiate GH therapy early in children with CKD

Adapted from Haffner *NEJM*. 2004;343:923-930.

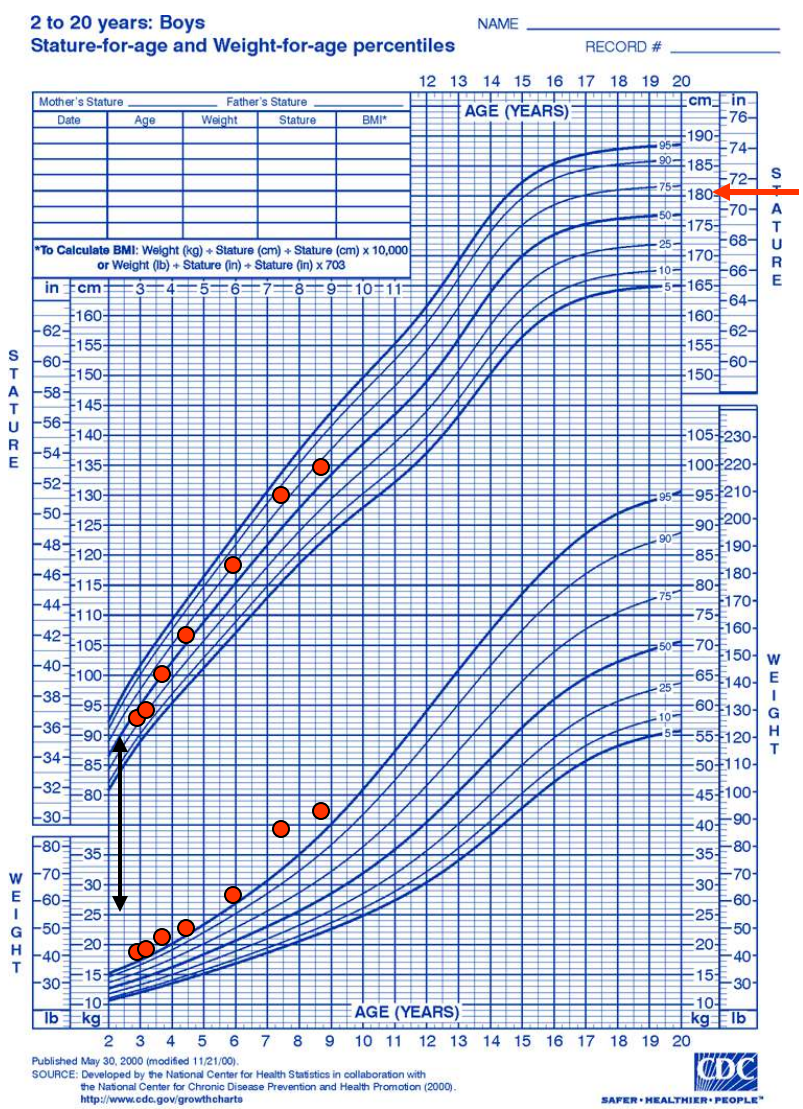
RCTs Show rhGH Rx Improves Height in Children with CKD

Analysis 1.1. Comparison 1 28 IU/m²/wk versus placebo/no treatment, Outcome 1 HSDS after 1 year of rhGH.

Study or subgroup	rhGH N	rhGH Mean(SD)	Placebo/no treatment N	Placebo/no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Change in HSDS after 1 year of rhGH							
Broyer 1996 (TP)	41	0.3 (1.1)	44	0 (1.3)		14.33%	0.3[-0.21,0.81]
Fine 1994 (preD)	55	1 (0.9)	27	-0.1 (1)		16.89%	1.09[0.65,1.53]
Maxwell 1998a (TP)	4	0.5 (1.4)	3	-0.1 (0.4)		3.02%	0.6[-0.81,2.01]
Maxwell 1998b (TP)	9	0.6 (1)	6	-0.3 (0.9)		5.79%	0.9[-0.07,1.87]
Powell 1997 (preD)	30	0.8 (0.5)	14	0 (0.3)		25.85%	0.8[0.56,1.04]
Santos 2010 (preD/Dial)	7	1.4 (0.8)	7	-0.1 (0.8)		7.49%	1.5[0.67,2.33]
Subtotal ***	**146**		**101**			**73.36%**	**0.84[0.55,1.13]**
Heterogeneity: Tau²=0.05; Chi²=8.14, df=5(P=0.15); I²=38.58%							
Test for overall effect: Z=5.63(P<0.0001)							
1.1.2 HSDS after 1 year of rhGH							
Fine 2002 (TP)	30	-2.6 (1)	22	-3 (0.8)		14.73%	0.41[-0.09,0.91]
Kuizon 1998 (Dial)	6	-1.4 (0.6)	8	-2.2 (1.1)		6.96%	0.82[-0.05,1.69]
Sanchez 2002 (TP)	9	-1.1 (1.1)	9	-2.8 (1.2)		4.94%	1.67[0.6,2.74]
Subtotal ***	**45**		**39**			**26.64%**	**0.84[0.16,1.52]**
Heterogeneity: Tau²=0.2; Chi²=4.51, df=2(P=0.1); I²=55.7%							
Test for overall effect: Z=2.41(P=0.02)							
Total ***	**191**		**140**			**100%**	**0.82[0.56,1.07]**
Heterogeneity: Tau²=0.05; Chi²=13.07, df=8(P=0.11); I²=38.8%							
Test for overall effect: Z=6.22(P<0.0001)							
Test for subgroup differences: Chi²=0, df=1 (P=1), I²=0%							

Placebo/no treatment -4 0 2 4 rhGH

Success - Patient AC: Growth Chart 2-9 yrs



Midparental height

Patient AC: Growth and Renal Status

	Age (yr)	Wt (kg)	Wt SDS	Ht (cm)	Ht SDS	Wt/Ht %tile	Cr (mg)	GFR (mL/min/1.73 m^2)
	Birth	3.03	–0.87	47	–1.11	74	1.9	11.1
	0.5	5.4	–3.57	58.5	–4.26	42	1.5	17.5
	0.9	8.84	–1.27	71	–1.42	53	1.0	31.9
	1.9	11.2	–0.99	82	–1.16	43	1.0	45
GH Started	2.9	12.9	–0.92	87.1	–2.06	60	1.1	43.5
	3.7	15	–0.36	94.6	–1.38	73	1.3	40
	4.5	16.9	–0.13	100.5	–1.09	79	1.4	39.5

Q4: How is GH Used in Children with CKD?

Adapted from Mahan JD. *Ped Neph* 2006

GH Evaluation
Determine pubertal stage
Analyze bone age; Hip & knee X-Rays
Hip and knee X-rays
Baseline funduscopic exam
Labs: Baseline chemistries; PTH; T4/TSH

Treatment

- Evaluation
- Insurance approval
- GH Dose: 0.35 mg/kg/wk; divided into daily SC injections
- Patient education

GH Considerations
Typically administered in evening
HD patients receive injections at bedtime or 3-4 hrs post HD
CCPD receive injections AM after dialysis
CAPD receive injections in evening, at overnight exchange

Monitoring Growth Hormone Therapy in CKD

Monitor growth response/safety - every 3-4 months

- Height, weight, height velocity; OFC* (until 3 years of age)
- Pubertal stage
- Nutritional intake
- Funduscopic exam
- Labs (chemistries, PTH)
- Bone age, hip and knee X-rays (every year)

Adjust GH doses as needed

Encourage compliance/measure IGF-1 levels

Consider pubertal dosing if growth response lagging during puberty

- 125-200 % of standard dose
- If limited time until epiphyseal closure
- If IGF-1 response is not large (large = > 3-4 times normal)

Adapted from Mahan JD. *Ped Neph* 2006

The Many Obstacles to Growth Hormone Therapy in Children with CKD

Lack of urgency

- rhGH treatment can be delayed
- Short stature as a cosmetic issue

Evaluation and documentation

- Uncertainty - evaluation, rhGH dosing, monitoring
- Reimbursement worries – lack of support for reimbursement

Patient compliance

Table 2 Reasons why children below the 5th percentile for height did not receive recombinant human growth hormone

Reason	Number of patients (n=56)
No reason identified	14 (25%)
Family refusal	10 (18%)
Severe hyperparathyroidism	9 (16%)
Non-compliance	5 (9%)
Too young	4 (7%)
Poor nutrition	3 (5%)
Neurologically impaired	3 (5%)
Maintaining growth curve[a]	2 (3%)
Overwhelmed family	2 (3%)
Transplantation scheduled	2 (3%)
Concurrent or recent malignancy	2 (3%)

[a] SD score was below −1.88, but growth velocity was normal

Greenbaum L. *Ped Neph* 2008

Growth Hormone is Safe in Childhood CKD

Targeted Events by Indication

Results	NCGS	CRI
Number	54,996	1778
Adverse Events	6.2	10.9
Serious AE	2.4	6.5
Deaths	0.3	1.2
Malignancy*	0.1	0.0
IC Tumor Recurrence	0.3	0.1
Leukemia*†	0.0	0.0
2nd Neoplasm	0.1	0.1
Adrenal Insufficiency†	0.0	0.0
Diabetes Mellitus	0.1	0.2
Intracranial Hypertension	0.1	0.3
SCFE	0.1	0.3
Scoliosis	0.4	0.1
Pancreatitis	0.0	0.0

Data are expressed as percentage. *New onset, no risk factors.
†Based on fewer than 15 reports.

PTLD: 3/300 post-renal Tx
1/17 post-liver Tx
All 4 - immunosuppressives

Adapted from Bell et al. *J Clin Endocrinol Metab*. 2010

Tidbits

Adult with CKD Experience Several Benefits to Therapies Directed to GH/IGF-1 Axis

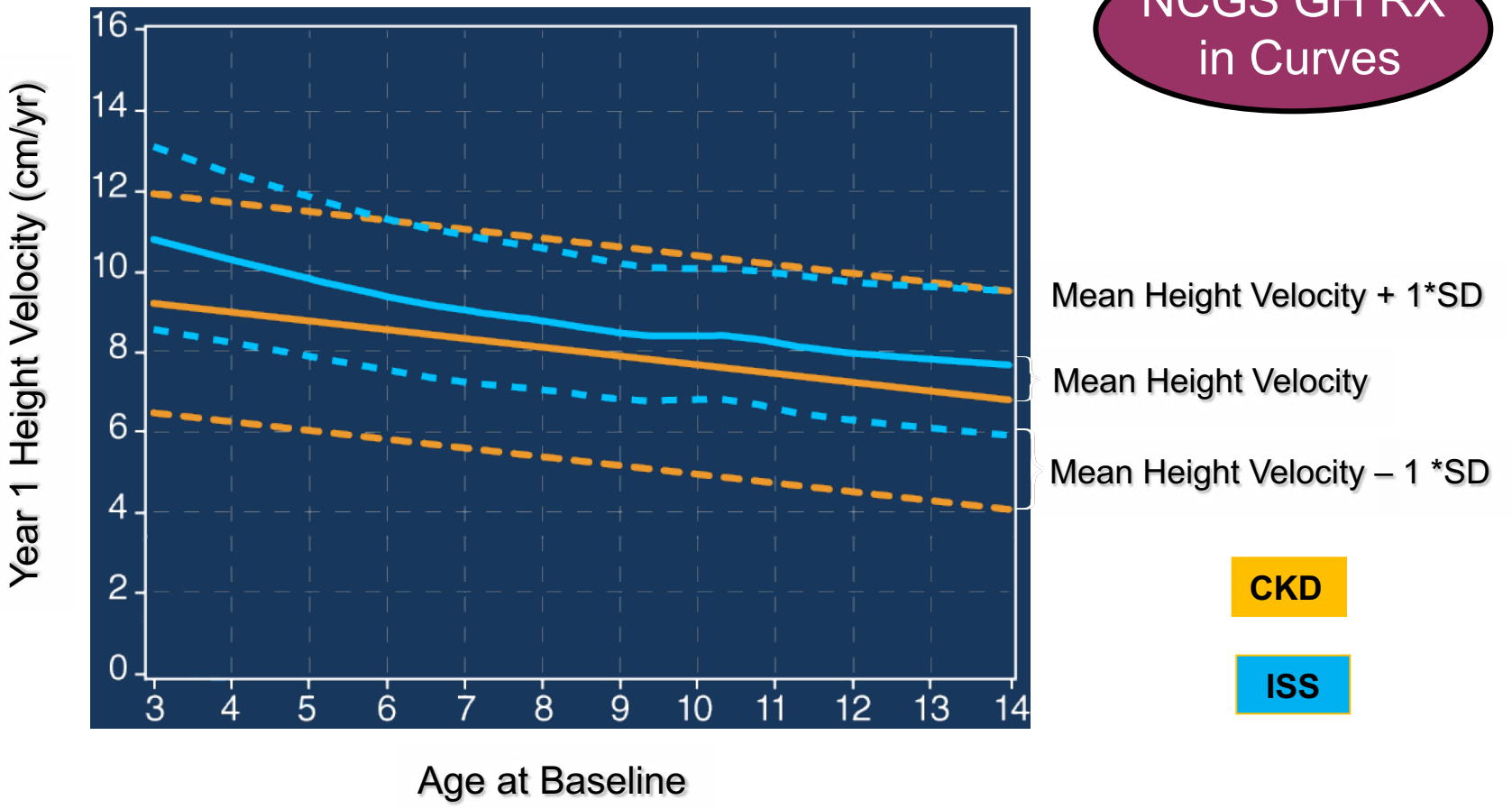
Adult CKD = GH/IGF-1 axis derangement
Less IGF-1 receptor activation at cellular level

Studies of rhGH Rx in Adult CKD

- **Doses 2–4 IU/m2/day (0.67–1.33mg/ m2/day)**
- **No major side effects in these short-term studies**
- **Improves net protein anabolism**
- **Improved nPCR, limited by inflammation**
- **Serum IGF-1 rises significantly after 3 months rhGH**
- **Impressive increases in bone turnover/PTH (inconsistent effects on BMD)**

Chu LW. *JCEM* 2001; Hansen TB *Clin Neph* 2000
Jensen PB. *Clin Neph* 2005; Feldt-Rasmussen B. *JASN* 2007

CKD Responses to GH Rx Mirrors That Seen in Idiopathic Short Stature and CKD



rhGH Rx Year 1 Height Mean Velocity ± 1 SD in ISS Males and CKD

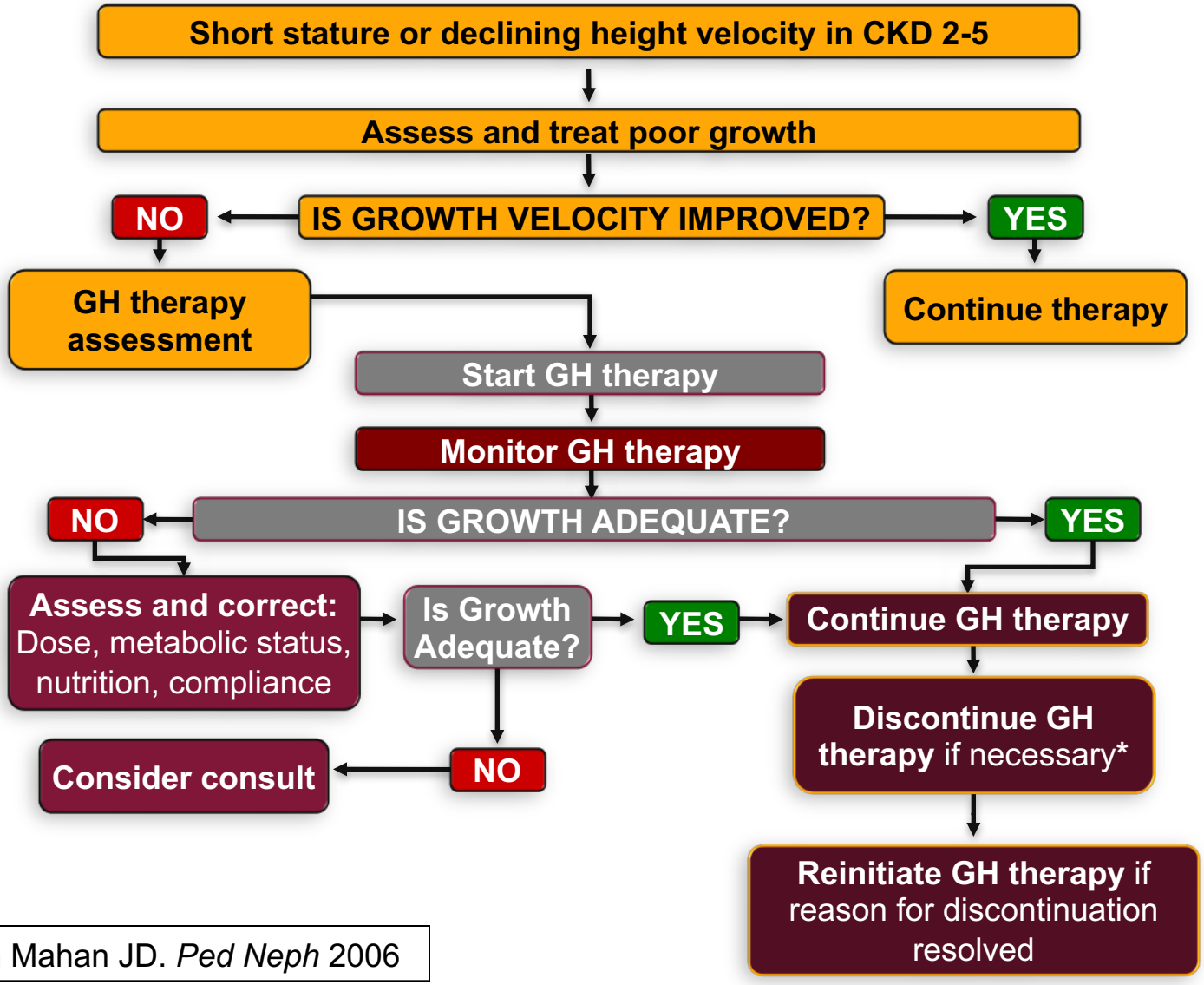
Other Potential Benefits of GH/IGF-1 Therapies in Childhood Diseases

1. Growth Failure in other chronic conditions of childhood:

   Cyanotic Heart Disease; Cystic Fibrosis; GI Malabsorption/IBD; Rheumatologic Disorders

   Answer may not always be nutrition!
2. Improving anabolism and muscle mass in variety of childhood disorders
3. Oral GH agonists; IGF-1 Displacers

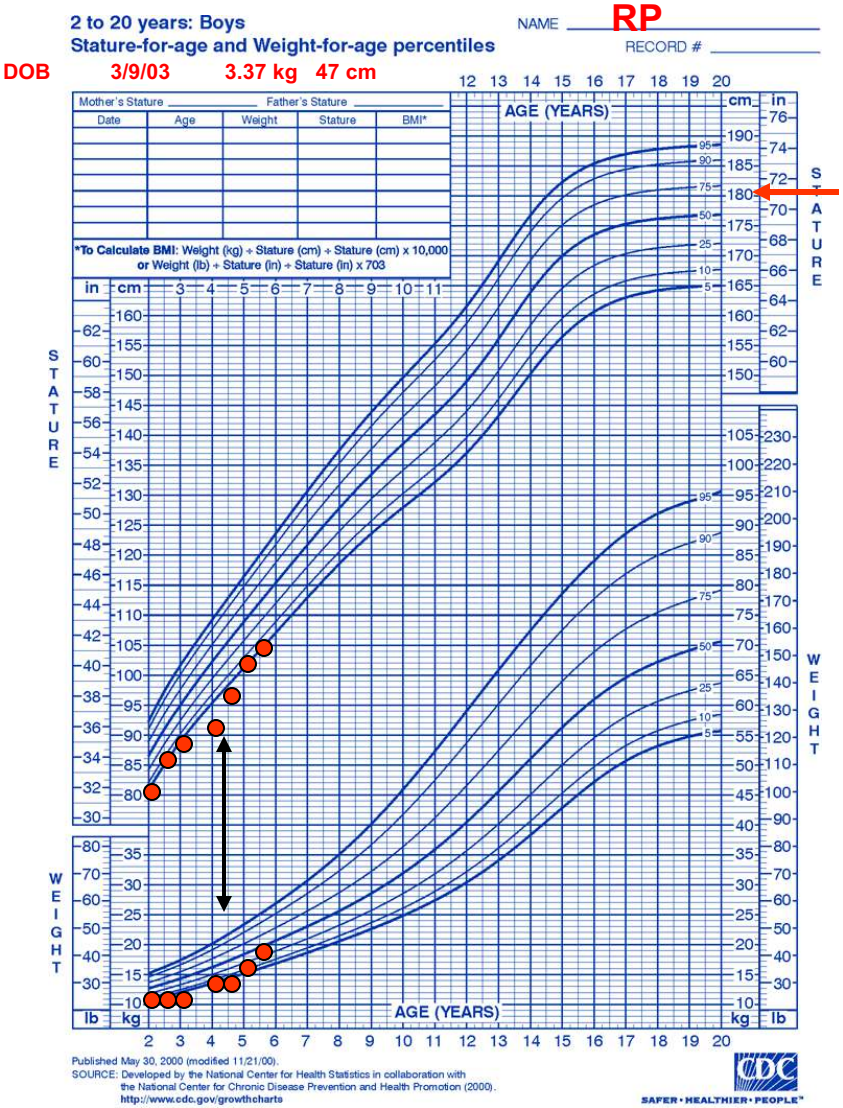
Algorithm for Evaluation and Treatment of Growth Retardation in Children with CKD: Overview



Adapted from Mahan JD. *Ped Neph* 2006

Patient RP: Growth Chart 2-20 yrs

3 Years

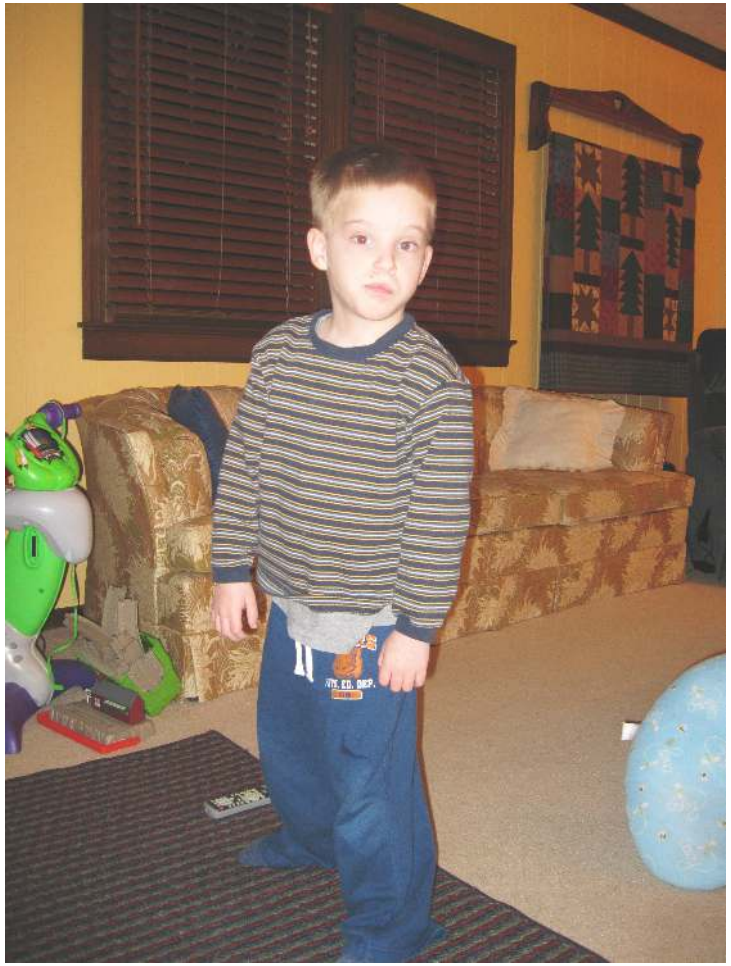


Midparental height

3 Years/4 Months

On GH Rx

5 Years/7 Months



5 Years/11 Months

Plea: Growth is a Beautiful Thing……
And You Should Regard Your Patient's Growth as Your Paramount Responsibility!

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Take Home Points

1. Growth is one of the MOST important medical issues for children with CKD & is important to patients and families
2. We are doing better in promoting growth in children with CKD – but have a long way to go to see 100% of children with CKD growing well and in normal range for height and weight
3. Barriers to promoting growth in children with CKD are surmountable with vigilance and attention to detail
4. There are promising prospects for therapies directed to the GH-IGF-1 Axis in CKD in adults and in a variety of children with growth delay