Injuria renal aguda en el recién nacido

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Septiembre 2018

Introducción

- Avances en los últimos 20 años
- Neonatos críticamente enfermos tienen un alta probabilidad de presentar Injuria renal aguda (AKI)
- Asociación a peores outcomes
- Falta de definición estandarizada
- Reciente reconocimiento que pequeñas alzas en la creatinina sérica (CrS) incrementa la morbi-mortalidad
- Incremento del riesgo de enfermedad renal crónica

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)
Neonatal Acute Kidney Injury. Pediatrics 2015; 136;e463

Incidencia y población de riesgo

- Incidencia reportada varia ampliamente dependiendo de población estudiada y de definición
- En RN críticamente enfermos de 8 al 24% (54%)
- Mortalidad 10 al 61%
- Reconocimiento de grupos de riesgo
  - Hipoxia perinatal
  - Prematuros y MBPN
  - Cardiopatías congénitas (bypass cardiopulmonar)
  - RN que requieren ECMO
  - Sepsis
  - Malformaciones urinarias y renales

Acute kidney injury in critically ill newborns: What do we know? What do we need to learn? Pediatr Nephrol (2009)
Update on acute kidney injury in the neonate .Jetton and Askenazi. Curr Opin Pediatr 2012
Incidence, risk factors, and outcome of neonatal acute kidney injury: a prospective cohort study. PediatricNephrology. June 2018

Fisiología renal neonatal

- Nefrogénesis
  - Inicio 5ta semana EG hasta las 34-36 sem.
    - Prematuridad
    - RCIU
    - AKI
- Perfusión renal
  - 2,5 al 4% al nacer del debito cardiaco
  - 6% a las 24 horas de vida
  - 10% a los 7 días de vida
  - 18% a las 6 semanas

-Sistema renina angiotensina
-Prostaglandinas

Short-Term Gestation, Long-Term Risk: Prematurity and Chronic Kidney Disease. Pediatrics 2013;131:1168–1179

Fisiología renal neonatal

- Velocidad de filtración glomerular
  - 10 to 20 mL/min/1.73 m2 Durante los primeros dias de vida
  - Ajuste de fármacos

- Madures tubular
  - En RNPT disminuida
    - reabsorción de EL y proteínas
    - concentración de orina

Short-Term Gestation, Long-Term Risk: Prematurity and Chronic Kidney Disease. Pediatrics 2013;131:1168–1179

Definición y diagnostico AKI

- Repentina falla en la función renal afectando la adecuada homeostasis de fluidos, EL y productos de desecho
- Complejo y heterogéneo cuadro clínico de múltiples causas, fisiopatología y manifestaciones
- Clásicamente definida como
  - Incremento de creatinina sérica (CrS) y/o,
  - Disminución producción urinaria (diuresis < 0,5ml/kg/hr)

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

Clasificación

TABLE 1 Neonatal AKI KDIGO Classification

Stage	SCr	Urine Output
0	No change in SCr or rise <0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr rise ≥ 0.3 mg/dL within 48 h or SCr rise ≥1.5–1.9 × reference SCr[a] within 7 d	<0.5 mL/kg/h for 6 to 12 h
2	SCr rise ≥2.0–2.9 × reference SCr[a]	<0.5 mL/kg/h for ≥ 12 h
3	SCr rise ≥3 × reference SCr[a] or SCr ≥2.5 mg/dL[b] or Receipt of dialysis	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

Differences between the proposed neonatal AKI definition and KDIGO include the following:

[a] Reference SCr will be defined as the lowest previous SCr value.

[b] SCr value of 2.5 mg/dL represents <10 mL/min/1.73m^2.

Neonatal Acute Kidney Injury. Pediatrics 2015; 136;e463

Definición y diagnostico Limitaciones

- Limitaciones CrS
  - Refleja los niveles de CrS materna
    - Días a semanas dependiendo de EG
    - En RNPT pueden estar mas elevado que madre
    - Aumento de niveles por reabsorción y disminución fluido corporal total
  - Refleja función renal, no injuria
    - Tarda 24-48 hrs en aumentar post injuria
    - 25-50% perdida función renal
  - Influenciada por masa muscular, hidratación, genero, EG
  - No diferencia origen de injuria
    - Prerrenal
    - Medicación nefrotóxica
  - Falta de estandarización

Urine Biomarkers Predict Acute Kidney Injury in Newborns. J Pediatr 2012

Diuresis en el RN?

- Valores extrapolados de clasificaciones de adulto y pediátricas

- AKI no oligúrica

Nephrol Dial Transplant (2013) 1–8
doi: 10.1093/ndt/gfs604

NDT
Nephrology Dialysis Transplantation

Original Article

Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification

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Table 1. Characteristics of patients according to hospital survival

	General population ($n=312$)	Non-survivors ($n=40$)	Survivors ($n=272$)	P
Pre-term neonates, *n* (%)	150 (48.1%)	21 (52.5%)	129 (47.4%)	0.649
5 min-APGAR < 7	74 (23.7%)	16 (40.0%)	58 (21.3%)	0.015
Low birth weight, *n* (%)	151 (48.3%)	20 (52.6%)	131 (49.6%)	0.729
Seizures, *n* (%)	55 (17.6%)	9 (30.0%)	46 (20.1%)	0.212
Neonatal infection, *n* (%)	278 (89.1%)	40 (100%)	238 (87.5%)	0.018
SNAPPE-II	14.9 ± 8.9	30.5 ± 21.7	12.6 ± 8.6	<0.0001
Umbilical catheter, *n* (%)	218 (69.9%)	31 (77.5%)	187 (68.8%)	0.260
Necrotizing enterocolitis, *n* (%)	07 (2.2%)	2 (5.0%)	5 (1.8%)	0.207
Septic shock, *n* (%)	65 (20.8%)	33 (86.8%)	32 (12.1%)	<0.0001
Perinatal asphyxia, *n* (%)	101 (30.4%)	20 (50.0%)	81 (29.8%)	0.011
Indomethacin use, *n* (%)	07 (2.2%)	1 (2.6%)	6 (2.2%)	0.891
Amphotericin, *n* (%)	09 (2.9%)	1 (2.5%)	8 (2.9%)	0.917
Amikacin, *n* (%)	249 (75.0%)	37 (92.5%)	212 (77.9%)	0.032
Parenteral nutrition time (days)	3.7 ± 2.4	4.6 ± 3.7	3.6 ± 2.6	0.264
Haematocrit (%)	40.3 ± 23.2	40.8 ± 18.8	39.9 ± 18.2	0.439
White blood cells ($\times 10^3$ cells/mm^3)	14.1 ± 6.7	16.3 ± 7.2	13.8 ± 6.9	0.295
Low platelets count, *n* (%)	75 (24.0%)	16 (40.0%)	59 (21.7%)	0.006
Maximum SCr (mg/dL)	0.92 ± 0.61	2.28 ± 1.26	0.73 ± 0.42	<0.0001
SBE (mEq/L)	−5.4 ± 4.8	−8.6 ± 4.3	−4.90 ± 4.3	<0.0001
Hyperkalaemia, *n* (%)	39 (12.5%)	17 (42.5%)	22 (8.1%)	<0.0001
Reduced UO, *n* (%)	64 (20.5%)	23 (57.5%)	41 (15.1%)	<0.0001
Mechanical ventilation time (days)	2.9 ± 1.9	7.2 ± 5.6	2,36 ± 2.0	<0.0001

Reduced UO, UO < 1.5 mL/kg/h.

RDS, respiratory distress syndrome; SNAPPE-II, scores for neonatal acute physiology-perinatal extension II; SCr, serum creatinine; SBE, standard base excess.

Table 3. Characteristics of patients according to UO

	Reduced UO < 1.5 mL/kg/h (n = 64)	Normal UO ≥ 1.5 mL/kg/h (n = 248)	P
Pre-term neonates, n (%)	13 (20.3%)	137 (55.2%)	<0.0001
5 min-APGAR < 7	20 (31.2%)	47 (18.9%)	0.049
Low birth weight, n (%)	16 (25.0%)	135 (54.4%)	<0.0001
Seizures, n (%)	21 (32.8%)	34 (13.7%)	0.001
Neonatal infection, n (%)	56 (87.5%)	222 (89.5%)	0.644
SNAPPE-II	20.6 ± 12.5	13.4 ± 7.7	0.002
Umbilical catheter, n (%)	50 (78.1%)	168 (67.7%)	0.107
Necrotizing enterocolitis, n (%)	1 (1.6%)	6 (2.4%)	0.680
Septic shock, n (%)	28 (43.7%)	37 (14.9%)	<0.0001
Perinatal asphyxia, n (%)	36 (56.2%)	65 (26.2%)	<0.0001
Indomethacin use, n (%)	1 (1.6%)	6 (2.4%)	0.688
Amphotericin, n(%)	2 (3.1%)	7 (2.8%)	0.872
Amikacin, n (%)	54 (84.4%)	195 (78.6%)	0.307
Diuretic use, n (%)	08 (12.5%)	19 (7.7%)	0.328
Parenteral nutrition time (days)	3.6 ± 2.6	3.8 ± 2.5	0.767
Haematocrit (%)	44.5 ± 8.3	43.6 ± 7.8	0.473
White blood cells ($\times 10^3$ cells/mm^3)	16.3 ± 5.3	13.5 ± 4.9	0.170
Low platelets count, n (%)	18 (28.1%)	57 (23.0%)	0.295
Maximum SCr (mg/dL)	1.50 ± 0.82	0.78 ± 0.41	<0.0001
SBE (mEq/L)	−7.50 ± 5.01	−4.91 ± 4.60	<0.0001
Hyperkalaemia, n (%)	15 (23.4%)	24 (9.7)	0.003
Mechanical ventilation time (days)	4.4 ± 2.7	2.6 ± 1.6	0.007
Mortality	23 (35.9%)	17 (6.9%)	<0.0001

RDS, respiratory distress syndrome; SNAPPE-II, scores for neonatal acute physiology-perinatal extension II; SBE, standard base excess; SCr, serum creatinine.

Hospital mortality according to UO ranges

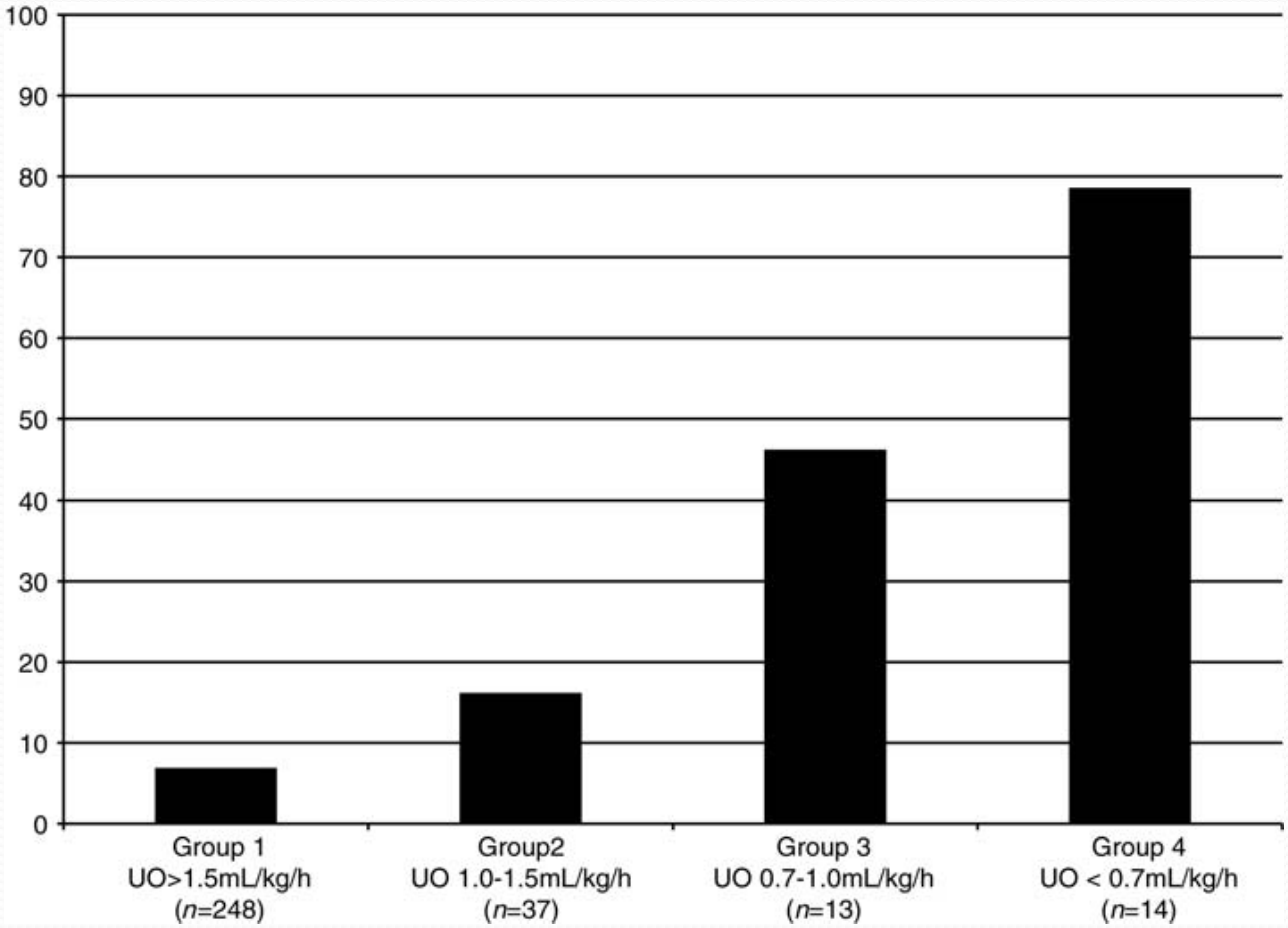

Table 1: Comparison between AKI classification system in adults, older children, and newborns.

	Creatinine criteria		Urine output criteria		
	RIFLE	pRIFLE and nRIFLE	RIFLE	pRIFLE	nRIFLE
Risk	Increased creatinine x1.5 or GFR decreases >25%	Increased creatinine x1.5 or GFR decreases >25%	UO ≤0.5 mL/kg/h × 6 h	UO ≤0.5 mL/kg/h × 8 h	UO <1.5 mL/kg/h for 24 h
Injury	Increased creatinine x2 or GFR decreases >50%	Increased creatinine x2 or GFR decreases >50%	UO ≤0.5 mL/kg/h × 12 h	UO ≤0.5 mL/kg/h × 16 h	UO <1.0 mL/kg/h for 24 h
Failure	Increased creatinine x3 or GFR decreases >75% or creatinine >4 mg/dL (acute rise of >4 mg/dL)	Increased creatinine x3 or GFR decreases >75% or GFR <35 mL/min/1.73 m^2	UO ≤0.3 mL/kg/h × 24 h or anuria × 12 h	UO ≤0.3 mL/kg/h × 24 h or anuria × 12 h	UO <0.7 mL/kg/h for 24 h or anuria for 12 h

Acute Kidney Injury in Neonates: From Urine Output to New Biomarkers. BioMed Research International. Volume 2014

Causas de IRA

- **HIPOPERFUSION RENAL**
  - Aumento de perdidas insensibles
    - Cuna radiante
    - Fototerapia
    - fiebre
  - Perdida de fluidos
    - Drenajes pleurales, abdominales
    - Aspiración por SNG
  - Diuréticos
  - Enfermedad renal congénita
  - Falla cardiaca congestiva
  - Elevada presión media de la vía aérea
  - Perdidas sanguíneas
  - Medicamentos
    - AINE
    - IECA

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

Table 1
Parenchymal (intrinsic) kidney injury

Ischemic injury/ATN	Any of the prerenal causes if prolonged Patient is at risk for further kidney injury throughout the injury and recovery phases, so avoid additional insults as much as possible Perinatal asphyxia/hypoxic-ischemic injury Endothelial and tubular cell damage may trigger a systemic inflammatory response that causes distant organ dysfunction[14,48,49]
Nephrotoxic medications	
Direct tubular injury	Aminoglycosides, amphotericin, intravenous contrast Aminoglycosides: primarily proximal tubular cell damage;[50] use with caution in any patient with preexisting AKI, concomitant nephrotoxic medication use, or poor renal perfusion. Usually nonoliguric AKI Amphotericin B: causes renal tubular acidosis and increased urinary potassium excretion. Reported levels of toxicity vary widely[51,52]
Decreased renal perfusion	ACE inhibitors, NSAIDs (indomethacin), diuretics Indomethacin: commonly associated with increased SCr concentrations, decreased urine output, hyponatremia. Usually reversible[47,53]

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

Causas de IRA

Tubular obstruction	Acyclovir
Sepsis and other infections	Decreased renal blood flow and subsequent ATN from shock/hypotension Sepsis-associated AKI Microvascular dysfunction associated with normal or increased renal blood flow that manifests with decreased GFR and tubular dysfunction; histologically distinct from ATN[54] Pyelonephritis Congenital infections
Vascular lesions	Renal vein and artery thrombosis Perinatal event; risk factors include perinatal asphyxia, dehydration, infection, prematurity, maternal diabetes, and underlying hypercoagulable state[55]

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

Causas de IRA

- OBSTRUCCION DE LA VIA URINARIA
  - Valvas uretra posterior
  - Vejiga neurogénica
  - Mal posición catéter urinario
  - Medicamentos
  - Litiasis renal
  - Bolas fúngicas

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

FARMACOS

Drug	Mechanism
Acyclovir	Urinary precipitation, especially with low flow and hypovolemia, with renal tubular obstruction and damage and decreased GFR. May cause direct tubular toxicity (metabolites).
Angiotensin-converting enzyme inhibitors	Decreased angiotensin II production inhibiting compensatory constriction of the efferent arteriole to maintain GFR.
Aminoglycosides	Toxic to the proximal tubules (transport in the tubule, accumulate in lysosome, intracellular rise in reactive oxygen species and phospholipidosis, cell death); intrarenal vasoconstriction and local glomerular/mesangial cell contraction.
Amphotericin B	Distal tubular toxicity, vasoconstriction, and decreased GFR.
Nonsteroidal antiinflammatory drugs	Decreased afferent arteriole dilatation as a result of inhibiting prostaglandin production resulting in reduced GFR.
Radiocontrast agents	Renal tubular toxicity secondary to increase in reactive oxygen species; intrarenal vasoconstriction may play a role.
Vancomycin	Mechanism of AKI unclear, possible mechanism includes proximal tubular injury with generation of reactive oxygen species.

Evaluación diagnostica

- Historia y factores de riesgo
  - Antecedentes prenatales
    - Ecografía
      - Anormalidades del tracto urinario
      - Oligohidramnios
    - Uso de medicamentos
      - IECA, AINE, drogas ilegales
  - Antecedentes recientes
    - EG, peso
    - Hipo perfusión
      - Resucitación
    - Patologías
    - Medicamentos nefrotóxicos
      - Niveles plasmáticos de aminoglicosidos

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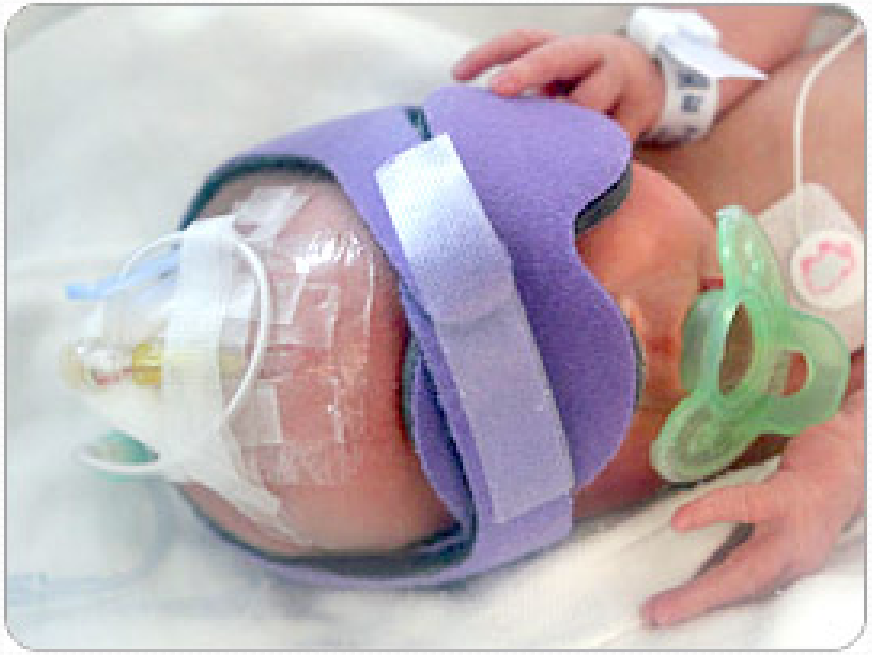
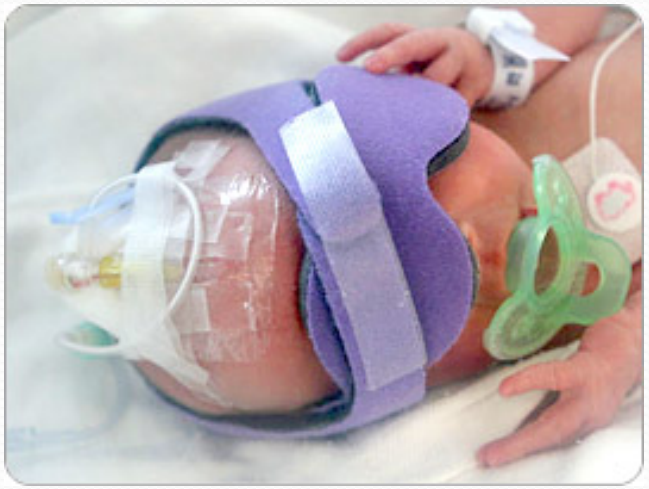
Evaluación inicial

- Examen físico y signos vitales
- Balance hídrico
- Peso
- ELP



Evaluación diagnostica

- Examen físico
  - Deshidratación
    - Mucosas secas
    - Taquicardia
    - Hipotensión
    - Fontanelas hundidas
    - Ojos hundidos
  - Sobre hidratación
    - Taquipnea
    - Edema
    - Hipertensión
    - Mala evolución respiratoria, aumento parámetros ventilatorios



Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

Evaluación diagnostica

- Laboratorio
  - Creatinina ,Ca, P, Mg, Bic Na, BUN, glucosa, albumina, GSA, Hemograma completo, uronalisis, y URC
  - Na y cretinina urinaria
    - FENa
- Imagenología
  - Ecografía renal y vesical
  - Eco doppler de vasos renales
  - Rx de tórax

Acute Kidney Injury in the Neonate. Clin Perinatol - (2014)

Prevención

- Ajustar fármacos con potencial nefrotóxico (evitar)
- Evitar la hipervolemia e hipovolemia
- Restricción de volumen cuidadosa cuando sea necesario

Drug-induced acute kidney injury in neonates.. Hanna MH, Askenazi DJ, Selewski . Curr Opin Pediatr. 2016;28(2):180.

Manejo especifico

- Hipovolemia
  - Bolo de sol isotónica 10 ml/kg
  - Según tipo de perdida modificar composición de electrolitos
  - Reevaluación frecuente
- Cardiopatías con reducción de perfusión renal
- Sepsis
- Uropatía obstructiva
- Trombosis vascular renal

Neonatal Acute Kidney Injury. Pediatrics 2015; 136;e463

Manejo nutricional

- Proporcionar mínimo 100 Kcal/kg/día.
- Enteral
  - LME
  - Formula láctea baja carga de solutos y fosfatos
  - Adicionar hidratos de carbono o lípidos
  - No fortificar
- Parenteral
  - AA hasta 1,5 g/kg/día
  - Lípidos max 2 g/kg/día
  - EL según exámenes
  - Evitar al inicio K y P

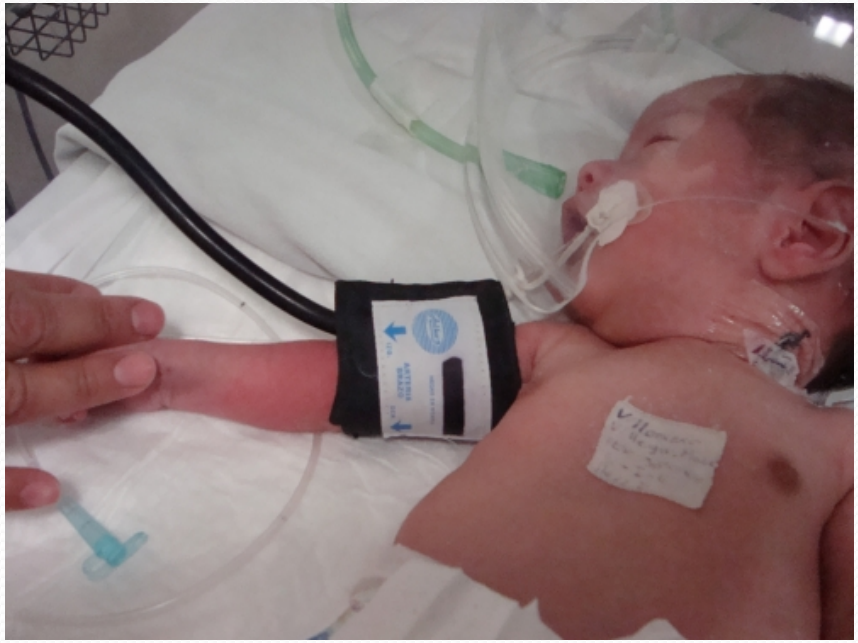
Manejo Trastornos HE

- Hiperkalemia
- Acidosis metabólica
  - Tratamiento de la causa
  - Bic de Na??
- Hipocalcemia
- Hiperfosfatemia
- Hiponatremia

Sodium bicarbonate: basically useless therapy. Pediatrics. 2008;122(4):831.

Manejo hipertensión arterial

- 10-20%
- Por sobrecarga de volumen
- Restricción de volumen
- Diuréticos
- Fármacos



Fármacos usados en AKI

Table 2 Therapeutics	
Dopamine	Widely used for support of systemic blood pressure in preterm and term infants,[66–68] although no survival benefit or decreased length of hospital stay has been shown in adult patients[69–72]
Diuretics	Used to augment urine output in oliguric patients; useful in small patients for whom placing dialysis access presents technical challenges. No evidence to suggest that diuretics prevent or reverse AKI once it has occurred.[69,73] Long-term furosemide therapy has several potential side effects: ototoxicity, interstitial nephritis, osteopenia, nephrocalcinosis, hypotension, and persistence of patent ductus arteriosus[74]
Fenoldopam	Selective dopamine-1 receptor agonist; causes vasodilation of renal and splanchnic vasculature, increased renal blood flow, and increased GFR. Not clinically approved for the treatment of AKI. Use in augmenting urine output in neonates with AKI has been explored in several single-center analyses.[75,76] Used in 2 prospective studies of infants undergoing cardiopulmonary bypass; some modest benefit seen with high-dose fenoldopam (1 μg/kg/min)[77,78]
Theophylline	Recent meta-analysis including 4 randomized trials on full-term asphyxiated infants suggests that prophylactic theophylline significantly reduces the incidence of severe renal dysfunction.[79] However, there is little evidence on the long-term renal and neurodevelopmental outcomes or adverse effects at various measured levels, so prudence with clinical use of prophylactic theophylline is required. In addition, the trials were before the therapeutic hypothermia era

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Terapia de reemplazo renal

- Se recomienda no esperar una disfunción renal severa para terapia de reemplazo renal
- Pacientes sobrehidratados tienen peor respuesta a terapia de remplazo renal → menor sobrevida
- Prevenir la sobrecarga de volumen e inicio temprano de TRR → mejor sobrevida

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Terapia de reemplazo renal

- Indicaciones
  - Acidosis severa (Bic < 12 mEq/L)
  - Hiperkalemia (> 8 mEq/L) refractaria a tto
  - Hiponatremia (< 120 mEq/L)
  - Sobrecarga de volumen
    - IC
    - Edema pulmonar
  - Asegurar nutrición en pac oligo-anuricos.

Nuevos biomarcadores de IRA

- Nueva investigación enfocada a marcadores capaces de anticiparse al ascenso creatinemia y disminución de diuresis
- Estudios limitados
  - RN MBPN
  - Asfixia neonatal
  - RN sometidos a bypass cardiopulmonar
- Nuevos biomarcadores comparados con creatinina sérica
- Varían por EG y peso de nacimiento

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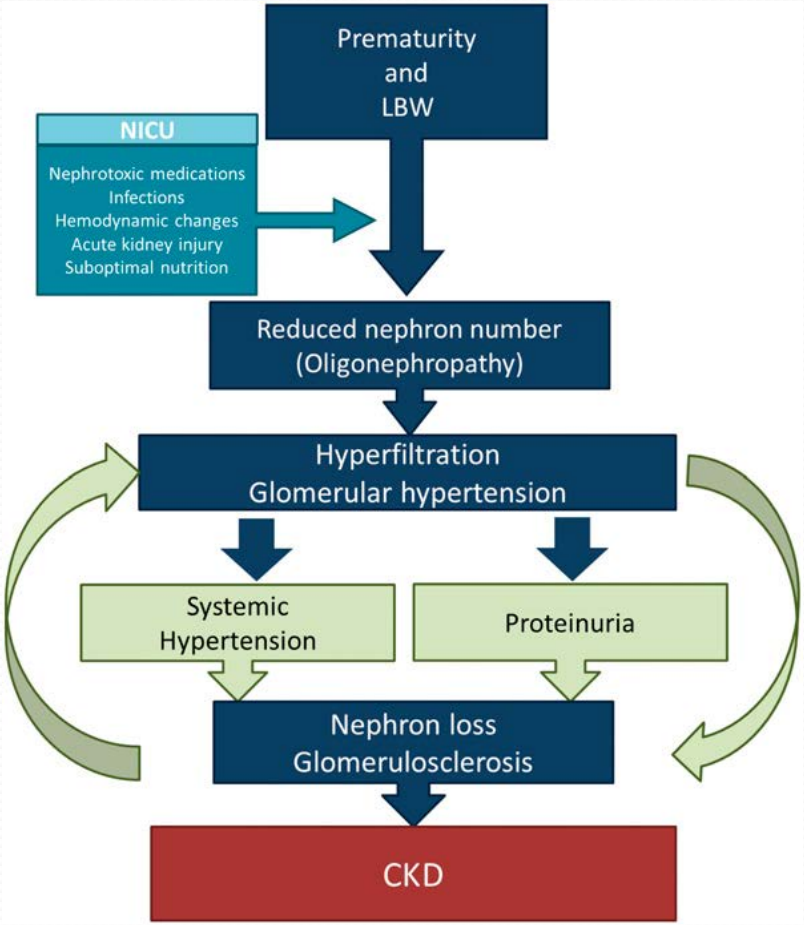
Enfermedad renal crónica



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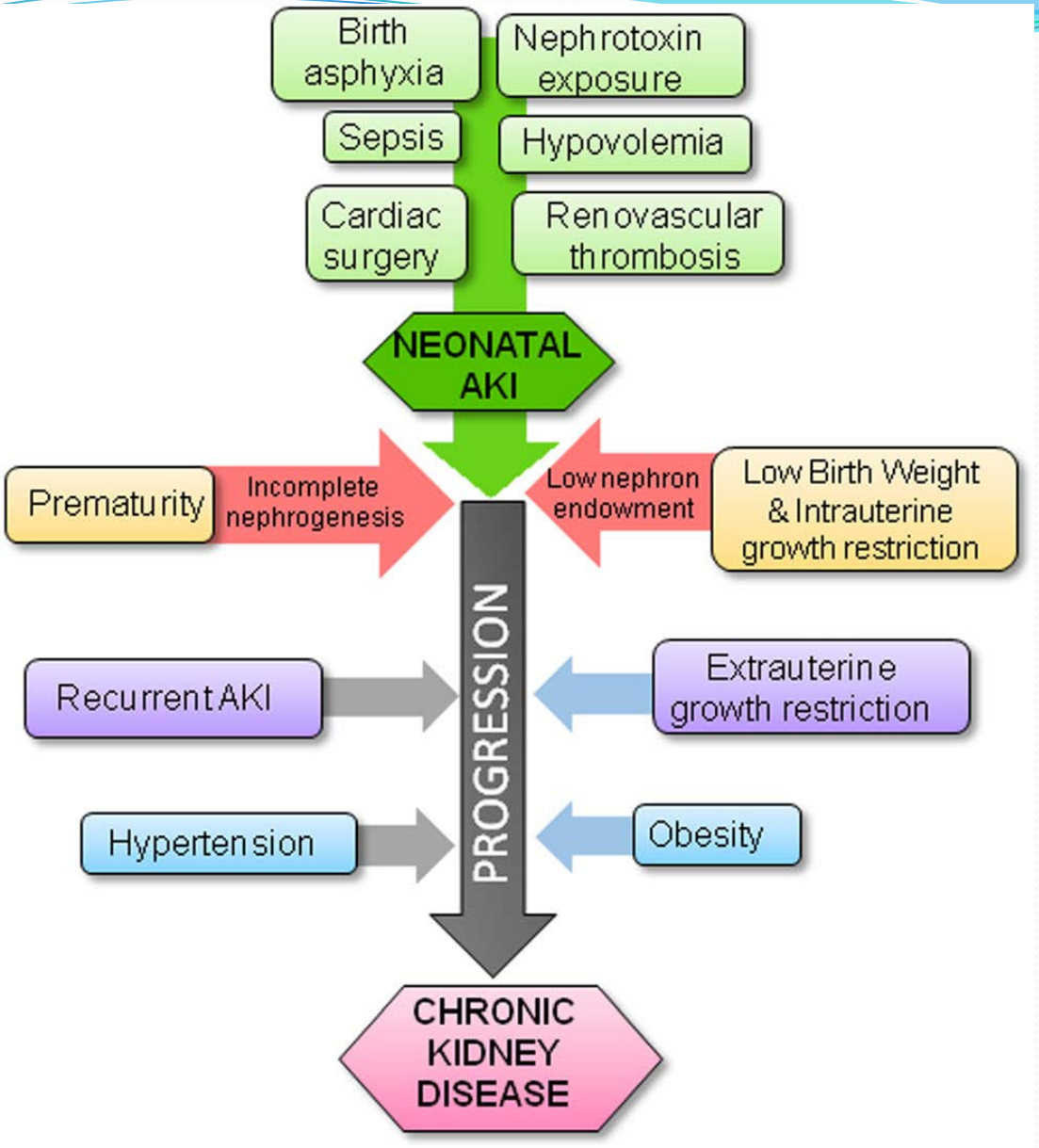

The path to chronic kidney disease following acute kidney injury: a neonatal perspective. Pediatr Nephrol 2016

Enfermedad renal crónica

- La nefrogenesis es interrumpida en el RNPT
  - Hipertrofia compensatoria de los nefrones
  - Evolucionaría a glomeruloesclerosis
    - Retención de Na
    - HTA
    - Proteinuria
    - ERC
- IRA asociada aumentaría aun mas riesgo de ERC
  - Afectando el desarrollo del nefron
- Este impacto recién se está conociendo

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Conclusiones

- Falta de consenso en la definición de Injuria Renal Aguda
- Incidencia en aumento
- Alza significativa de creat mayor o igual 0,3 mg/dl
- Oliguria
  - < 0,5 ml/kg/h?
  - < 1,5 ml/kg/h?
- Necesidad de nuevos biomarcadores
- Énfasis en población de riesgo
- Mayor entendimiento de la progresión a ERC
- Lograr disminuir incidencia y severidad de IRA