Nierenersatztherapie –

Indikationen & Outcome

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tirol kliniken

MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Aufbau

1. Indikationen zur Nierenersatztherapie
2. Patienten Charakteristika & Outcome
3. Flüssigkeitsüberladung & optimaler Zeitpunkt des Beginns
4. Nieren-outcome bei Überlebenden

Einleitung

- Die kontinuierliche Nierenersatztherapie (CRRT) ist die bevorzugte Methode bei kritisch kranken Kindern auf der Pädiatrischen Intensivstation.

- Die Inzidenz der CRRT auf PICU's nimmt zu.

- Trotz technologischer Fortschritte der CRRT bleibt die Mortalität hoch (35-56%)

Indikationen - renale

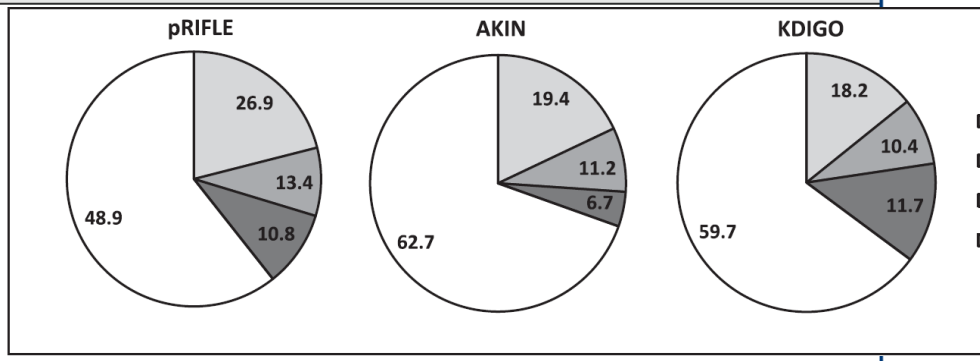
- Die akute Nierenschädigung (ANS, acute kidney injury = AKI) stellt ein Kontinuum mit unterschiedlichem Schädigungs-ausmaß der Niere dar
- Von Schädigung ohne Funktionsverlust bis zum Versagen des Organs mit Notwendigkeit der Nierenersatztherapie (CRRT)
- Die Inzidenz der ANS und die damit verbundene Morbidität und Mortalität nimmt weltweit zu.
- Neuere, standardisierte Klassifikationen erlauben eine bessere Definition + frühzeitigere Erkennung des ANS.

Definitionen

Table 1. Staged diagnostic criteria for AKI

Definition and Criteria for AKI Stages	Modifications
pRIFLE	
Stage 1 (Risk): eGFR decreased by 25%	
Stage 2 (Injury): eGFR decreased by 50%	
Stage 3 (Failure): eGFR decrease by 75%	
or	
eGFR <35 ml/min per 1.73 m^2	
AKIN	
Stage 1: Increase in creatinine of ≥50%	
or	
Absolute increase in creatinine of 0.3 mg/dl	
Stage 2: Increase in creatinine of ≥100%	
Stage 3: Increase in creatinine of ≥200%	
KDIGO	
Stage 1: Increase in creatinine of ≥50%	OR: Urine output <0,5mL/kg/hr for 6-12 hrs
or	**X 1,5-1,9 from baseline SCr**
Absolute increase in creatinine of 0.3 mg/dl	
Severe AKI Stage 2: Increase in creatinine of ≥100%	**X 2,0-2,9** Urine output <0,5mL/kg/hr for ≥12 hrs
Stage 3: Increase in creatinine of ≥200%	**X 3** Urine output <0,3mL/kg/hr for ≥24 hrs OR Anuria for ≥12 hrs
or	
eGFR ≤35 ml/min per 1.73 m^2 (if age <18 yr) or Increase to ≥ 4mg/dl or RRT initiation	

eGFR was estimated using the Schwartz method. pRIFLE, pediatric RIFLE; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Diseases Improving Global Outcomes.



Sutherland SM et al, CJASN 2015;10:554-561

Kidney Disease: Improving Global Outcomes ***(KDIGO)*** *Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2:1-138*

A Framework and Key Research Questions in AKI Diagnosis and Staging in Different Environments. Murray PT, Devarjan P, Levey AS, et al. CJASN 2008;3:864-868.

„Die Niere als Motor des MODS“

CRRT

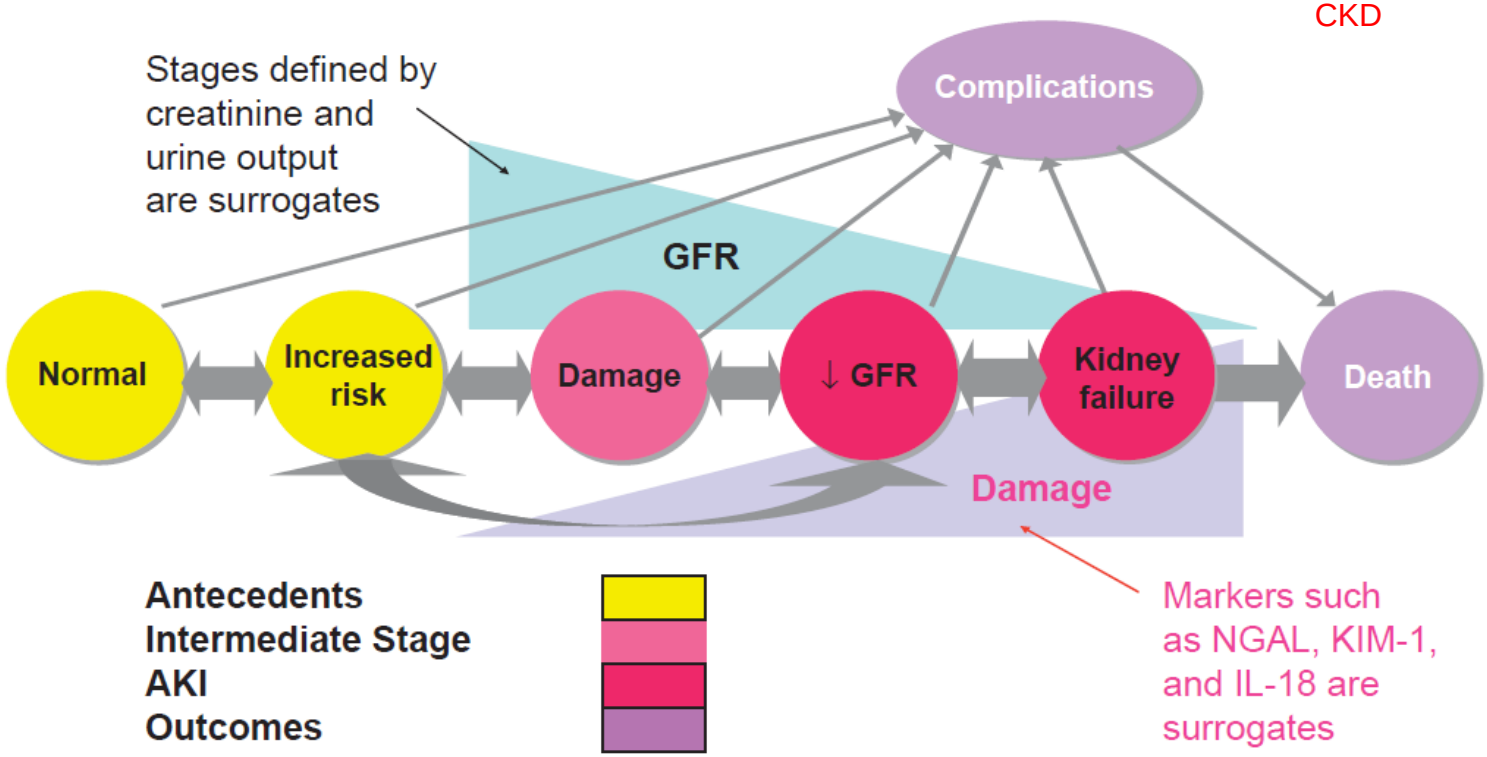
Ventilation ↑

ICU Stay ↑

Fluid overload

MODS

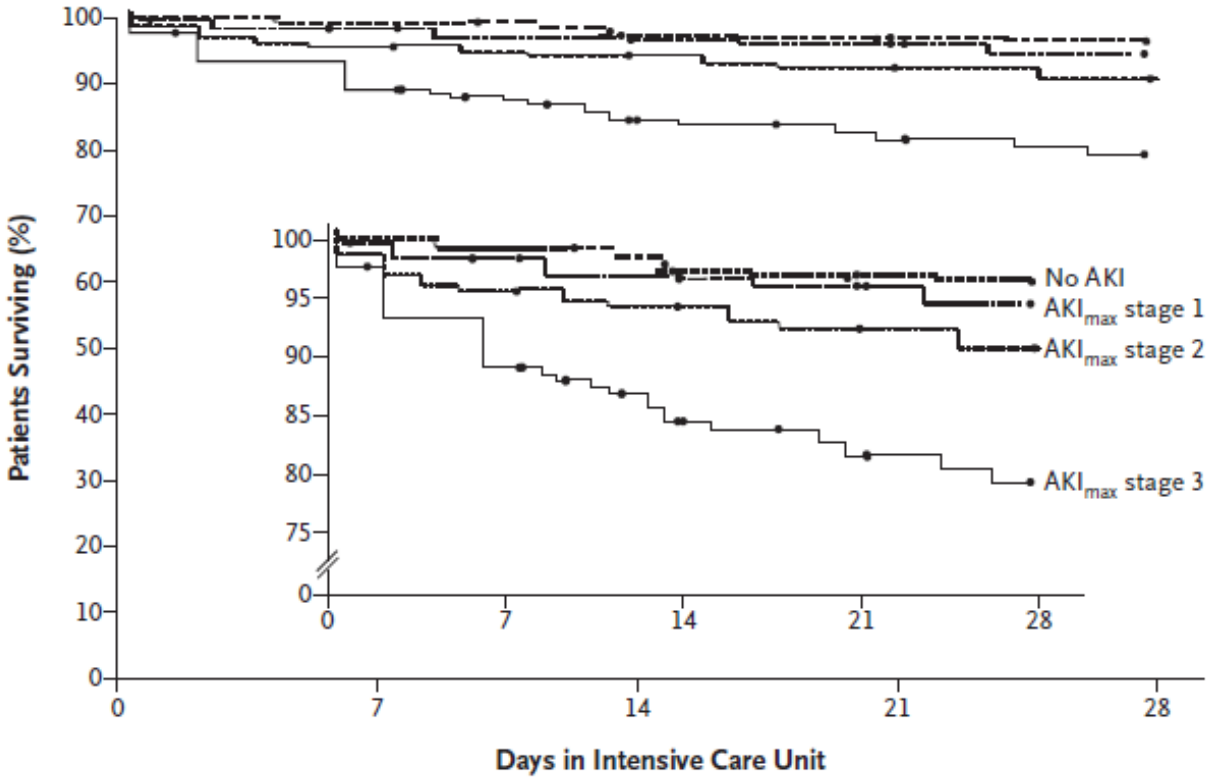
CKD



Subclinical AKI

The NEW ENGLAND JOURNAL of MEDICINE

Epidemiology of acute kidney injury in critically ill children and young adults. Kaddourhah A. Basu RK, Bagshaw SM, Goldstein SL; AWARE investigators. NEJM 2017; 376(1):1: 11-20



n = 4683
3 Mo – 25 J

- **26,9%** aller kritisch kranken Kindern hatten ANS und **11,6%** eine schwere ANS (Stage 2+3)
- Mortalität **11%** bei schweren ANS vs. **2,5%** ohne schweres ANS (Stage 1 oder keine ANS)
- Mit zunehmender Schwere der ANS steigt die Morbidität (Notwendigkeit einer CRRT, ICU Aufenthalt, Beatmungsdauer) und die Mortalität.

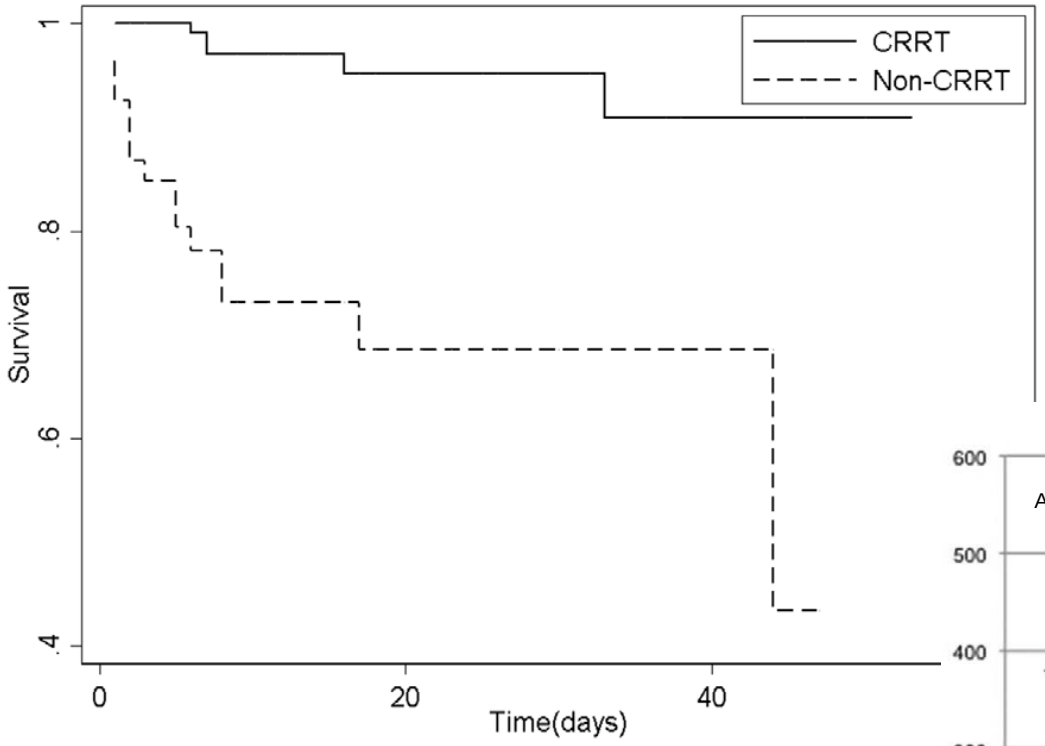
Indikationen – nicht-renale

- Flüssigkeitsüberladung (Fluid overload=FO) ohne AKI (Risikopatienten für FO: Z.n. Herz OP, ECMO, Sepsis)
- Störungen im Eletrolyt- und Säure Basen Haushalt (Hyper-kaliämie/naträmie, Laktatazidose,…)
- Elimination von Toxinen, z.b. bei angeborenen Stoffwechselerkranungen und akutem Leberversagen
- Elimination von Enztündungsmediatoren (Sepsis, ARDS,.. mit speziellen Filter wie Oxiris© oder evtl. in Kombination mit anderen extrakorporalen Verfahren (Plasmapherese, Cytosorb©,…)
- Rhabdomyolyse (crush injury) und Tumor Lyse Syndrom: Ausfallen von Myoglobin bzw. Harnsäurekristalle in Tubuli

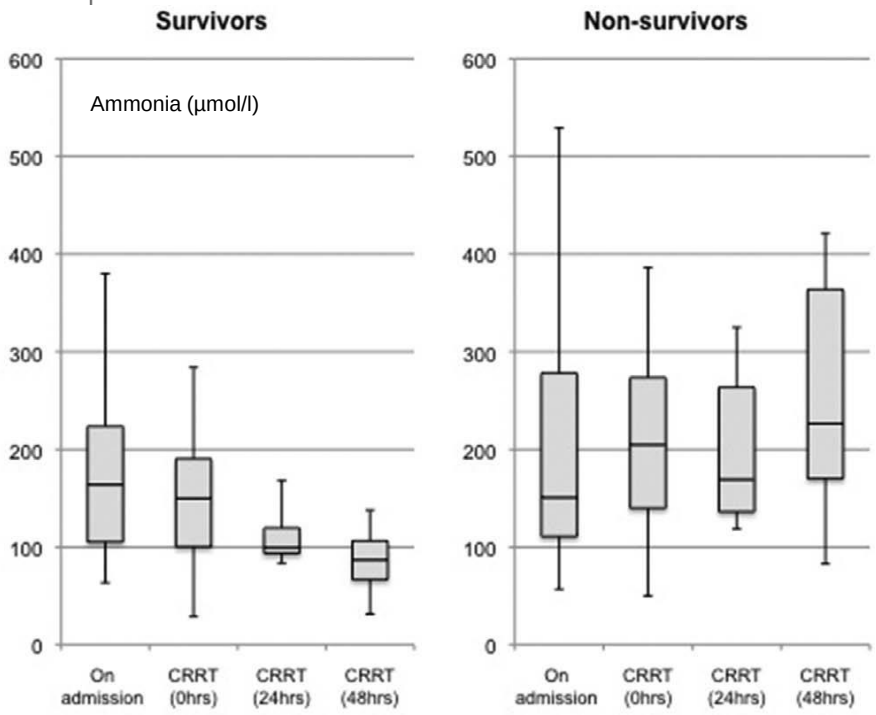
Critical Care Medicine

Society of Critical Care Medicine

Effect of contunuous renal replacement therapy on outcome in pediatric acute liver failure.
Deep A, Stewart CE, Dhawan A, Douiri A. Crit Care Med 2016; 44:1910-1919.



Continuous renal replacement therapy should be considered at an early stage to help prevent further deterioration and buy time for potential spontaneous recovery or bridge to liver transplantation.



Indikationen zur Nierenersatztherapie (CRRT) beim ALF:

- Ammoniak >150 µmol/l
- Enzephalopathie Grad III
- Oligurie/Anurie mit Flüssigkeitsüberladung >10%
- Therapierefraktäre Störungen im Elektrolyt- und Säure-Basen- Haushalt, insbesonders Hyponaträmie und Laktatanstieg

Extracorporeal organ support (ECOS)

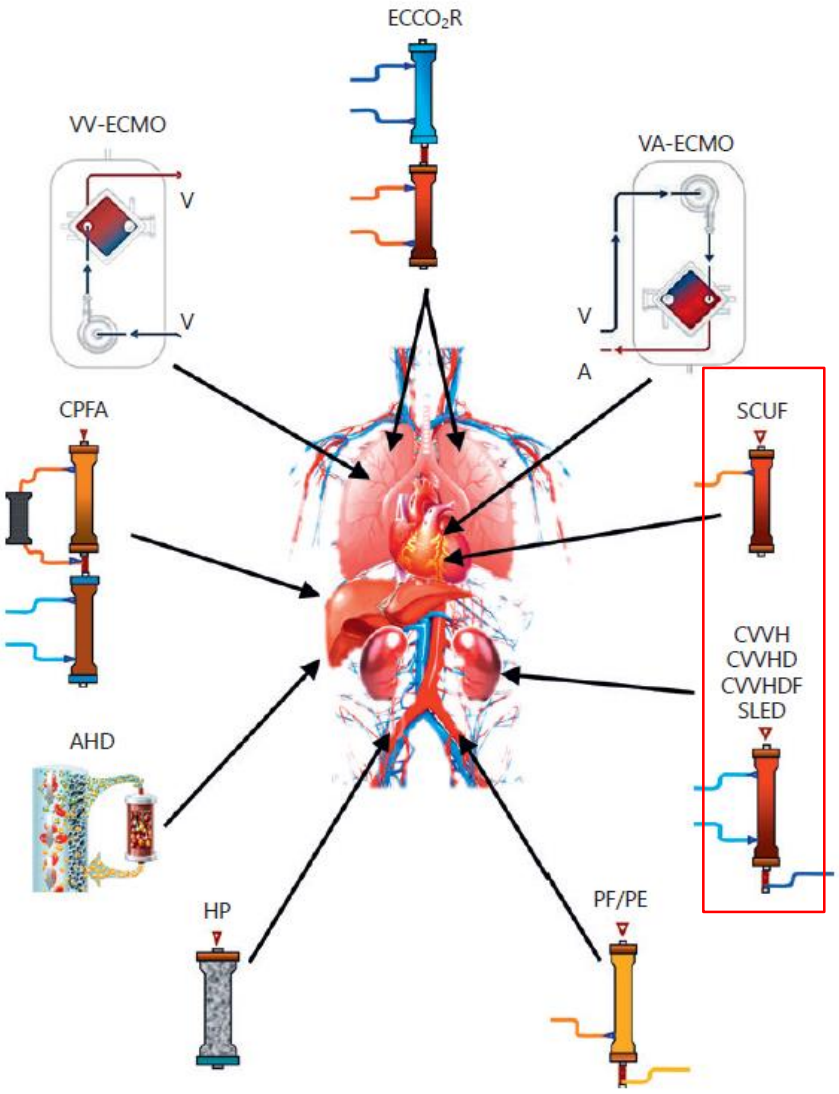
From Multipile Organ Support to Extracorporeal Organ Support in Critically Ill Patients. Ronco C, Zaccaria R, Husain-Syed F.

Blood Purif 2019; 48: 99-105

ECCO2R: extracorporeal CO2 removal
VA-ECMO: veno-arterial extracorporeal membrane oxygenation
VV-ECMO: veno-venuos extracorporeal membrane oxygenation
SCUF: slow continuous ultrafiltration
CVVH: continuous veno-venuous haemofiltration
CVVHD: continuous veno-venuous haemodialysis
CVVHDF: continuous veno-venuous haemodiafiltration
PF: plasmapheresis/ PE: plasmaexchange
HP: hemoperfusion
AHD: albumin hemodialysis
CFPA: continuous plasma filtration absorption

CRRT

Organ crosstalk: - cardiorenal syndrome
- hepatorenal syndrome
- hepatopulmonary syndrome
- cardiopulmonary interactions …



Comparision of mortality in studies of critically ill patients on CRRT

Author	Year	Country	Nb of Patients	Mortality	Main findings
Foland	2004	USA single centre	113	39%	Higher mortality in MODS (57%)
Pichler	2007	Austria single centre	115	43%	Mortality decreased from 45% (1985-1994) to 39% (1995-2004)
Symons	2007	USA multicentre	344	42%	Higher mortality in infants (56% vs 38%)
Santiago	2010	Spain single centre	174	35%	Mortality higher in infants (44.7%) and in sepsis (44.1%)
Sutherland	2010	USA multicentre	297	43%	Mortality increased with %FO at CRRT initiation
Selewski*	2011	USA single centre	113	56%	Mortality higher in patients on ECMO (68% vs 46%)
Modem	2014	USA single centre	190	47%	Survivors started earlier on CRRT than non-survivors (2.0 vs 3.4d)
De Galasso	2015	Italy single centre	131	54%	Mortality higher in patients with MODS and onco-haematological disease
Riley	2018	USA single centre	273	47%	No significant difference in mortality between eras (2004-2008 vs 2009-2013)
Choi	2017	Republic of Korea single centre	123	41%	Mortality increases with higher VIS and need for mechanical ventilation
Cortina*	2019	Australia single centre	161	36%	Mortality higher in patients on ECMO (47 vs 28%)

Diagnosen & Outcome

Demographic Characteristics of Pediatric Continuous Renal Replacement Therapy: A Report of the Prospective Pediatric Continuous Renal Replacement Therapy Registry.
Symons J. et al. CJASN 2007,2; 732-738

Parameter	*n*	Survivors	% Survival
Sepsis	81	48	59
Bone marrow transplant	55	25	45
Cardiac disease/ transplant	41	21	51
Renal disease	32	27	84
Liver disease/ transplant	29	9	31
Malignancy (no tumor lysis syndrome)	29	14	48
Ischemia/shock	19	13	68
Inborn error of metabolism	15	11	73
Drug intoxication	13	13	100
Tumor lysis syndrome	12	10	83
Pulmonary disease/ transplant	11	5	45
Other	7	5	71

n = 344, 13 centers

Overall Mortality 42%

Mortality higher in infants

(56% vs 38%, p=0.007)

and in children < 10kg

(57% vs 37%, p=0.001)

Pediatric Critical Care Medicine

Mortality of critically ill children requiring continuous renal replacement therapy: the effect of fluid overload, underlying disease and timing of initiation.
Cortina G, Mc Rae R, Hoq S, et al. *Pediatr Crit Care Med 2019;20(4):314-322.*

Admission Diagnosis	*n* (%)	Survivors (%)	Fluid Overload Percent, Median (IQR)
Sepsis	31 (19)	21 (67.7)	12 (6.3–15.4)
Cardiac surgery	23 (14)	15 (65.2)	7 (2.5–18.3)
Cardiac arrest[a]	22 (14)	6 (27.3)	9.6 (5.7–21.0)
Metabolic disease	19 (12)	17 (89.5)	1 (0.0–4.1)
Onco-hematologic disease[b]	18 (11)	4 (22.2)	6.9 (4.0–12.7)
Renal disease	18 (11)	17 (94.4)	1.9 (1.4–5.0)
Liver failure/liver transplant	10 (6)	5 (50)	13.2 (8.4–20.5)
Rhabdomyolysis	10 (6)	9 (90)	5.5 (3.0–8.5)
Cardiopathies[c]	4 (3)	3 (75)	5.2 (5.0–11.4)
Other[d]	6 (4)	6 (100)	13.4 (7.8–18.5)

IQR = interquartile range.
[a]Out-of-hospital cardiac arrest, $n = 5$; in-hospital cardiac arrest outside of ICU, $n = 17$.
[b]Acute lymphoblastic leukemia, $n = 6$; acute myeloid leukemia, $n = 3$; bone marrow transplant, $n = 7$; neuroblastoma, $n = 1$; non-Hodgkin lymphoma, $n = 1$.
[c]Myocarditis, $n = 3$; dilative cardiomyopathy, $n = 1$.

The Royal Children's Hospital Melbourne

n = 161
Mortalität 36%

Patienten ohne ECMO vs. mit ECMO: 28% vs. 48%, p < 0.001

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Factor	Unadjusted		Adjusted	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Timing of initiation	1.007 (1.00–1.01)	0.004	1.01 (1.00–1.01)	**0.040**
Fluid overload				
10%–20%	4.54 (2.03–10.15)	< 0.001	3.83 (1.33–11.07)	**0.013**
> 20%	13.11 (4.34–39.66)	< 0.001	15.03 (4.03–56.05)	**< 0.001**
Pediatric Index of Mortality 2 score at admission	1.37 (1.50–1.64)	< 0.001	1.49 (1.18–1.89)	**< 0.001**
Presence of onco-hematologic disease	7.87 (2.45–25.28)	< 0.001	17.10 (4.10–72.17)	**< 0.001**
Presence of sepsis	0.81 (0.35–1.87)	0.627	0.50 (0.16–1.52)	0.219
Presence of extracorporeal membrane oxygenation	2.17 (1.11–4.22)	0.023	2.26 (0.84–6.09)	0.107
Diuretic exposure	2.99 (1.50–5.93)	0.002	1.69 (0.66–4.34)	0.279

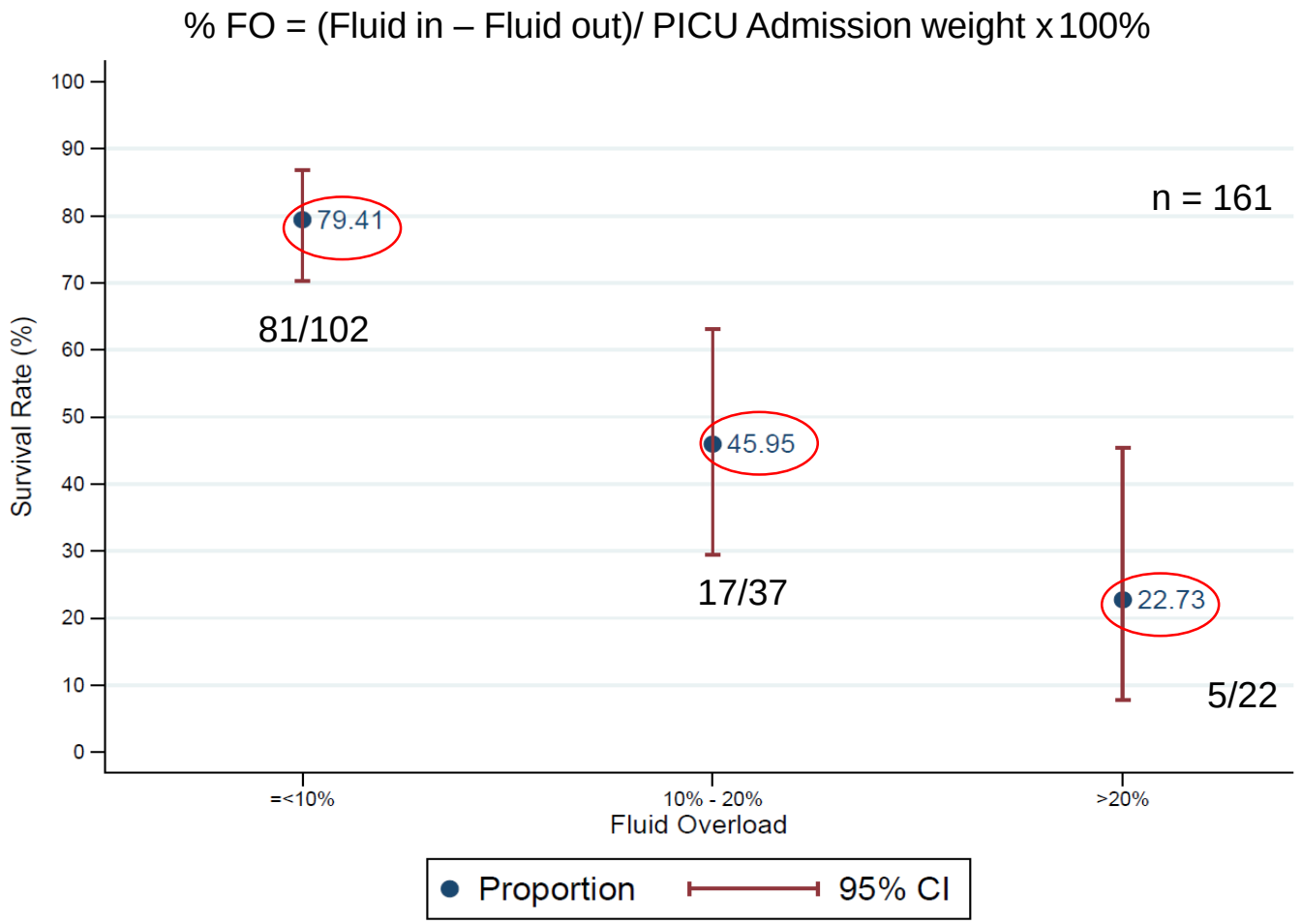
OR = odds ratio.

Unabhängige Risikofaktoren für erhöhte Mortalität:

- ✓ Onkologische Grunderkrankung
- ✓ Schwere der Erkrankung
- ✓ FO >10%
- ✓ Beginn der CRRT: **mit jeder Stunde Verzögerung steigt Mortalität steigt um 1%**

The Royal Children's Hospital Melbourne

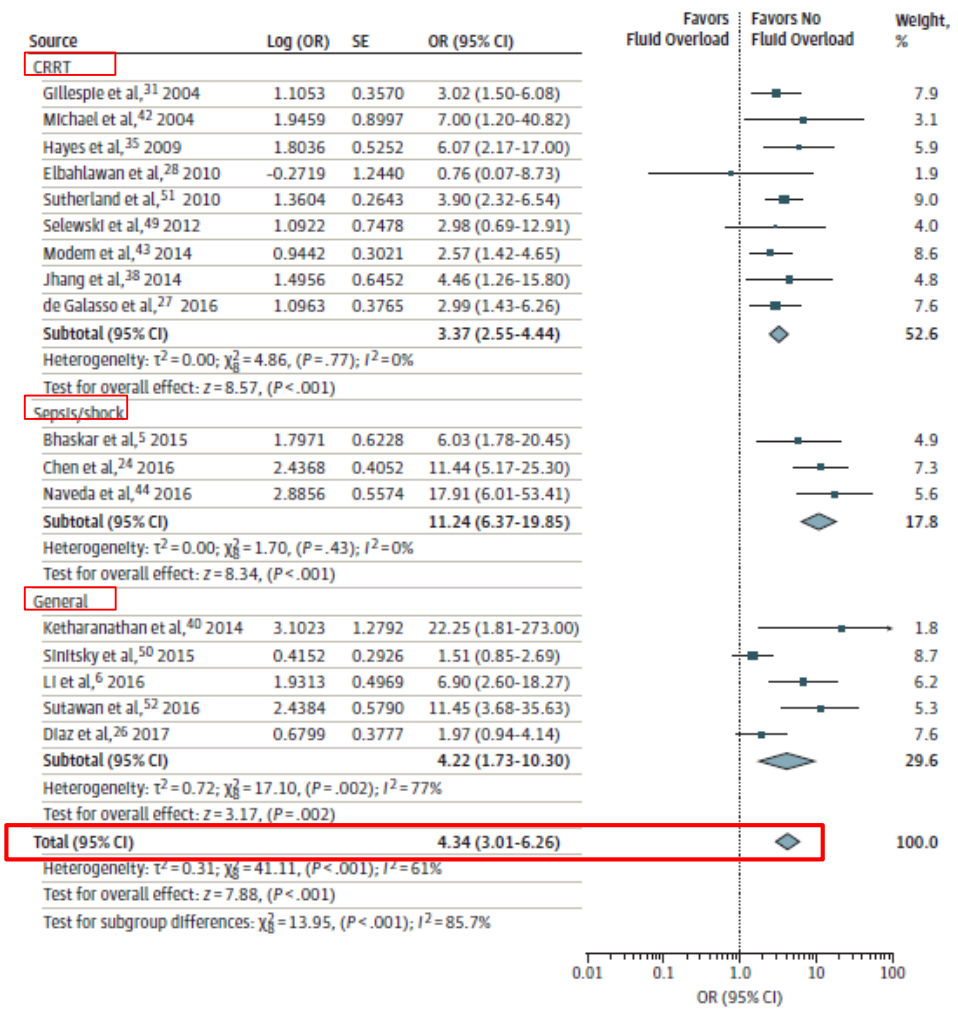
FO und Überleben



Mortality of critically ill children requiring continuous renal replacement therapy: the effect of fluid overload, underlying disease and timing of initiation. Cortina G, Mc Rae R, Hoq S, et al. Pediatric Critical Care Medicine *2019;20(4):314-322*

Association between fluid balance and outcomes in critically ill children: a systematic review and meta-analysis. Alobaidi R, Morgan C, Basu RK, et al. JAMA Pediatrics 2018;172(3):257-268.

Figure 1. Random-Effects Meta-analysis of Fluid Overload (Categorical Exposure) and Mortality Stratified by Case Mix



Source	Log (OR)	SE	OR (95% CI)	Weight, %
CRRT				
Gillespie et al,[31] 2004	1.1053	0.3570	3.02 (1.50-6.08)	7.9
Michael et al,[42] 2004	1.9459	0.8997	7.00 (1.20-40.82)	3.1
Hayes et al,[35] 2009	1.8036	0.5252	6.07 (2.17-17.00)	5.9
Elbahlawan et al,[28] 2010	-0.2719	1.2440	0.76 (0.07-8.73)	1.9
Sutherland et al,[51] 2010	1.3604	0.2643	3.90 (2.32-6.54)	9.0
Selewski et al,[49] 2012	1.0922	0.7478	2.98 (0.69-12.91)	4.0
Modem et al,[43] 2014	0.9442	0.3021	2.57 (1.42-4.65)	8.6
Jhang et al,[38] 2014	1.4956	0.6452	4.46 (1.26-15.80)	4.8
de Galasso et al,[27] 2016	1.0963	0.3765	2.99 (1.43-6.26)	7.6
Subtotal (95% CI)			**3.37 (2.55-4.44)**	**52.6**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 4.86$, ($P = .77$); $I^2 = 0\%$				
Test for overall effect: $z = 8.57$, ($P < .001$)				
Sepsis/shock				
Bhaskar et al,[5] 2015	1.7971	0.6228	6.03 (1.78-20.45)	4.9
Chen et al,[24] 2016	2.4368	0.4052	11.44 (5.17-25.30)	7.3
Naveda et al,[44] 2016	2.8856	0.5574	17.91 (6.01-53.41)	5.6
Subtotal (95% CI)			**11.24 (6.37-19.85)**	**17.8**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 1.70$, ($P = .43$); $I^2 = 0\%$				
Test for overall effect: $z = 8.34$, ($P < .001$)				
General				
Ketharanathan et al,[40] 2014	3.1023	1.2792	22.25 (1.81-273.00)	1.8
Sinitsky et al,[50] 2015	0.4152	0.2926	1.51 (0.85-2.69)	8.7
Li et al,[6] 2016	1.9313	0.4969	6.90 (2.60-18.27)	6.2
Sutawan et al,[52] 2016	2.4384	0.5790	11.45 (3.68-35.63)	5.3
Diaz et al,[26] 2017	0.6799	0.3777	1.97 (0.94-4.14)	7.6
Subtotal (95% CI)			**4.22 (1.73-10.30)**	**29.6**
Heterogeneity: $\tau^2 = 0.72$; $\chi^2_8 = 17.10$, ($P = .002$); $I^2 = 77\%$				
Test for overall effect: $z = 3.17$, ($P = .002$)				
Total (95% CI)			**4.34 (3.01-6.26)**	**100.0**
Heterogeneity: $\tau^2 = 0.31$; $\chi^2_8 = 41.11$, ($P < .001$); $I^2 = 61\%$				
Test for overall effect: $z = 7.88$, ($P < .001$)				
Test for subgroup differences: $\chi^2_8 = 13.95$, ($P < .001$); $I^2 = 85.7\%$				

JAMA Pediatrics

Fluid overload, was associated with increased in-hospital mortality (17 studies [n = 2853]; odds ratio [OR] 4.34 [95%CI, 3.01-6.26]).

After adjustment for illness severity, there was a **6% increase in odds of mortality for every 1% increase in percentage fluid overload** (11 studies [n = 3200]; adjusted OR 1.06 [95%CI, 1.03-1.10]).

FO in survivors

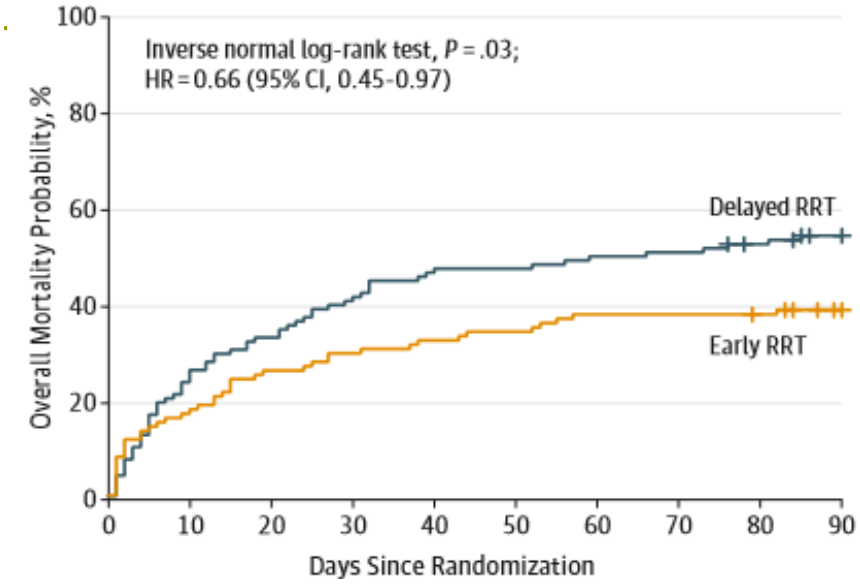
Characteristic	FO ≥ 10% (*n* = 23)	FO < 10% (*n* = 80)	95% CI	*p*
Ventilation time (hr)	300 (174.0–951.0)	133.3 (51.5–276.2)	−161.5 (−319.3 to −187.6)	**0.010**
ICU stay (d)	16 (8.0–28.0)	8 (4–16.5)	−8 (−15.3 to −0.6)	**0.034**
Total duration of CRRT (hr)	114.5 (47.0–173.5)	63.0 (28.6–160.5)	−50.5 (−92.8 to −8.2)	**0.012**
Characteristic	**FO ≥ 20% (*n* = 5)**	**FO < 20% (*n* = 98)**	**95% CI**	***p***
Ventilation time (hr)	951 (377–1,265)	159 (58.5–300)	788 (188–1,388)	**0.011**
ICU stay (d)	22 (19–55)	9 (5–17)	13 (−16.3 to 42.3)	0.382
Total duration of CRRT (hr)	105.8 (105–120)	65.9 (29.3–161.5)	39.7 (−40 to 120.4)	0.331

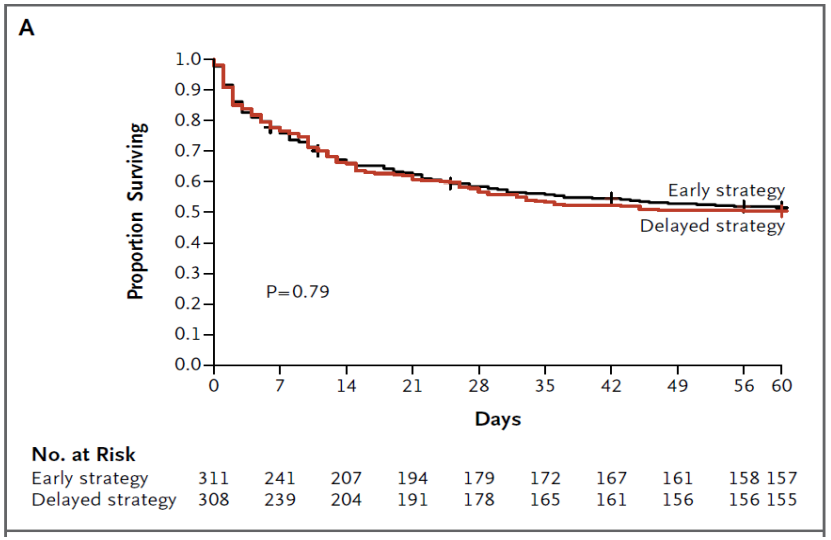
CRRT = continuous renal replacement therapy, FO = fluid overload.
Data are presented as median (interquartile range).

- 6 mal längere Beatmungsdauer bei Überlebenden mit FO >20%

Mortality of critically ill children requiring continuous renal replacement therapy: the effect of fluid overload, underlying disease and timing of initiation. Cortina G, Mc Rae R, Hoq S, et al. Pediatric Critical Care Medicine 2019;20(4):314-322

Wann beginnen?





- Prospektive randomisiert Single-center Studie in Erwachsenen (n=231)
- Signifikante Reduktion der Mortalität bei „early" (39,3%) vs „late" (54,7%) initiation

- Prospektive randomisiert Multicenter Studie bei Erwachsenen (n= 620)
- Kein Unterschied zwischen „early" (48,5%) vs. „late" (49,7%)

Effect of Early vs Delayes Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury. The ELAIN Randomized Clinical Trial **Zarbock A et al. JAMA 2016:315.2190-2199**.

Initiation Straegies for Renal-Replacement Therapy in the Intensive Care Unit. **Gaudry S et al. For the AKIKI Study Group. NEJM 2016:315: 122-33.**

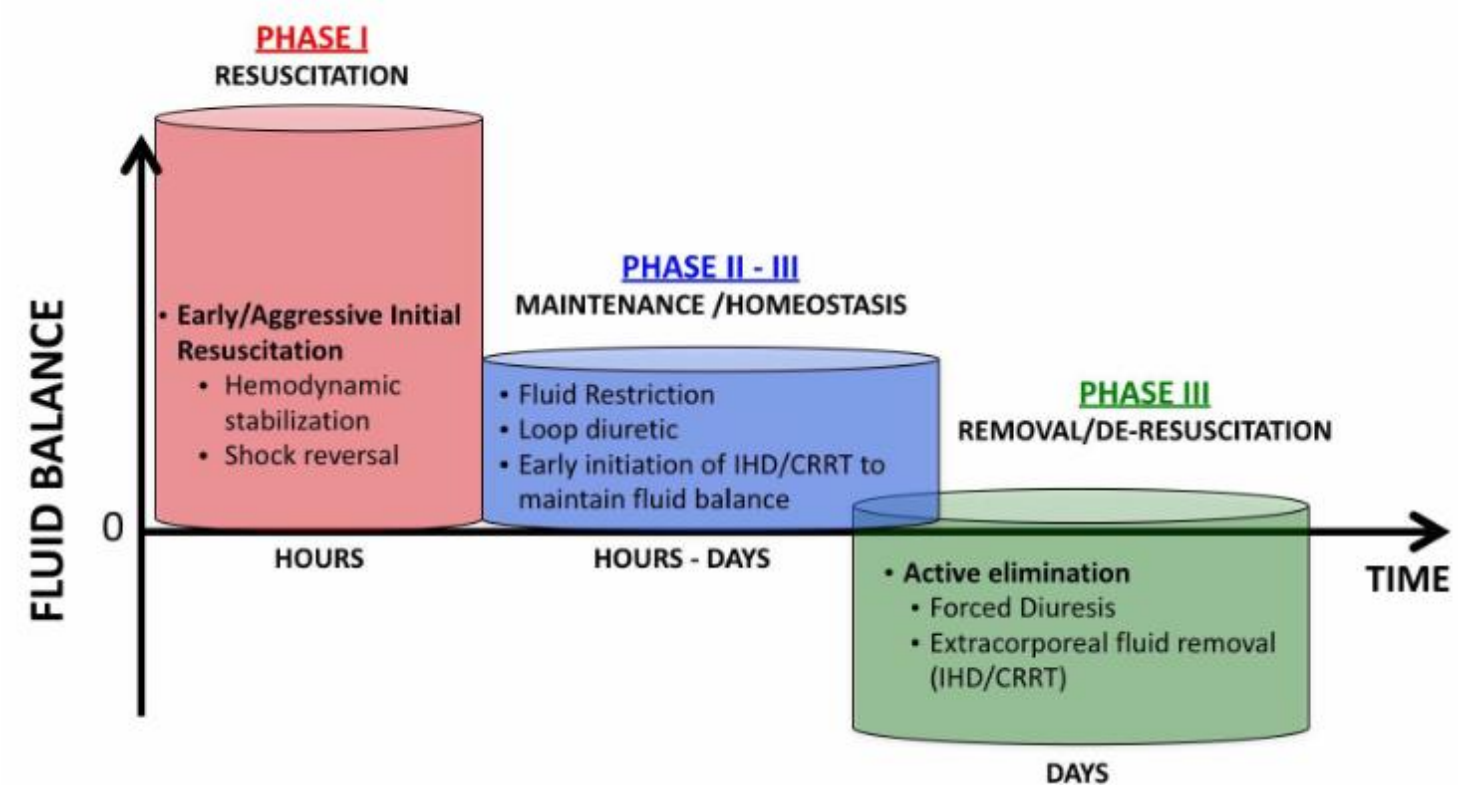
Timing of initiation

SURVIVING SEPSIS RECOMMENDATIONS

Use diuretics to reverse fluid overload when shock has resolved and if unsuccessful then CVVH or intermittent HD to prevent >10% total body weight fluid overload (grade 2C)

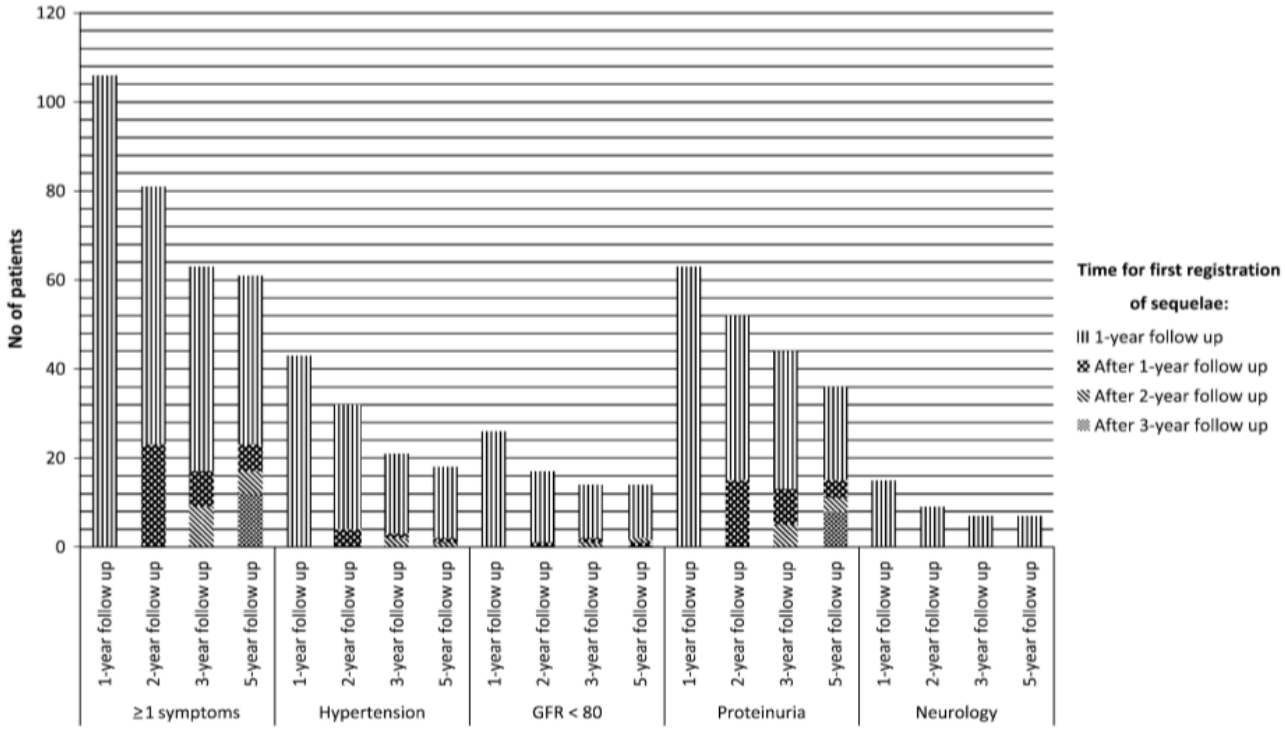
Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive* Care Med 2020; 46 (Suppl 1): S10-S67.

Timing of initiation



Nierenüberleben nach AKI & CRRT?

Need for Long-term Follow-up in Enterohemorrhagic Escherichia coli–Associated Hemolytic Uremic Syndrome Due to Late-Emerging Sequelae. Rosales A et al for the Austrian-German HUS Study Group. Clin Inf Dis 2012;54:1413-1421



- 619 Patienten mit klassischem HUS; 65% erhielten Nierenersatztherapie, 7 verstarben (1,4%)
- Nach 5 Jahren follow-up: 70% komplett erholt, 18% Proteinurie (>150mg/gCreatinine), 9% Hypertension, 8% eine eingeschränkte Nierenfunktion (GFR < 80 mL/min/1.73 m²)

Zusammenfassung

- Indikationen zur CRRT umfassen renale (ANS) & nicht-renale (FO,...)
- Die Mortalität von Patienten an der CRRT hängt von der Grunderkrankung, dem Grad der FO und dem Beginn der CRRT ab.
- Bei Patienten mit hohem Risiko für ANS und FO, könnte ein früherer Beginn der CRRT die Mortalität weiter senken.
- Patienten nach ANS & CRRT sollten nephrologisch nachkontrolliert werden.

Vielen Dank für die Aufmerksamkeit

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