AER 2019

25ème AER : 19 & 20 novembre 2020

ACTUALITES EN EPURATION EXTRA-RENALE

AER 2019

Session Réanimation Métabolique

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Quand débuter?

Quand arrêter?

Quelle technique utiliser?

EER

Quelle anticoagulation?

Quelle durée?

Quelle « dose » administrer?

Quand débuter?

Quand arrêter?

EER

Quelle technique utiliser?

Quelle durée?

Quelle « dose » administrer?

Quelle anticoagulation?

EER – Quand débuter?

EER – Quand débuter?

- **<u>Indications « consensuelles » = complications de l'IRA</u>**

  - OAP anurique
  - Hyperkaliémie menaçante (>7 mmol + signes ECG)
  - Acidose métabolique profonde (< 7,1 pH)
  - Urémie mal tolérée (> 30-40 mmol/l, troubles neuro)

  + Indications spécifiques = Epuration médicaments

EER – Quand débuter?

Uniquement sur des indications cliniques ?

(étude AKIKI)

Ou

Dès l’existence d’une Insuffisance Rénale Aigüe sévère ?

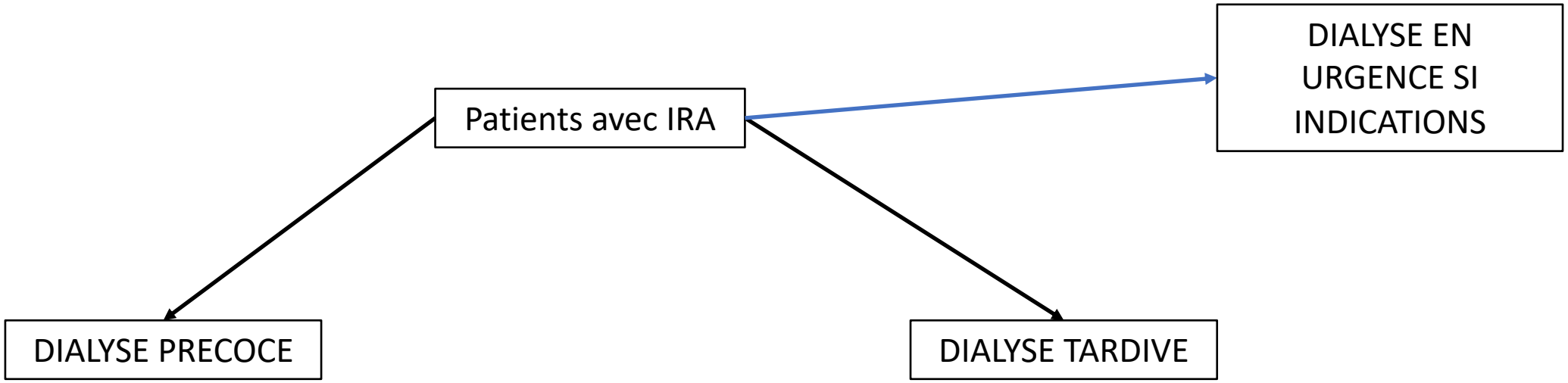
(étude ELAIN)

Classification KDIGO

Table 2 | Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR $\geqslant$0.3 mg/dl ($\geqslant$26.5 μmol/l) increase	$<$0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	$<$0.5 ml/kg/h for $\geqslant$12 hours
3	3.0 times baseline OR Increase in serum creatinine to $\geqslant$4.0 mg/dl ($\geqslant$353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients $<$18 years, decrease in eGFR to $<$35 ml/min per 1.73 m^2	$<$0.3 ml/kg/h for $\geqslant$24 hours OR Anuria for $\geqslant$12 hours

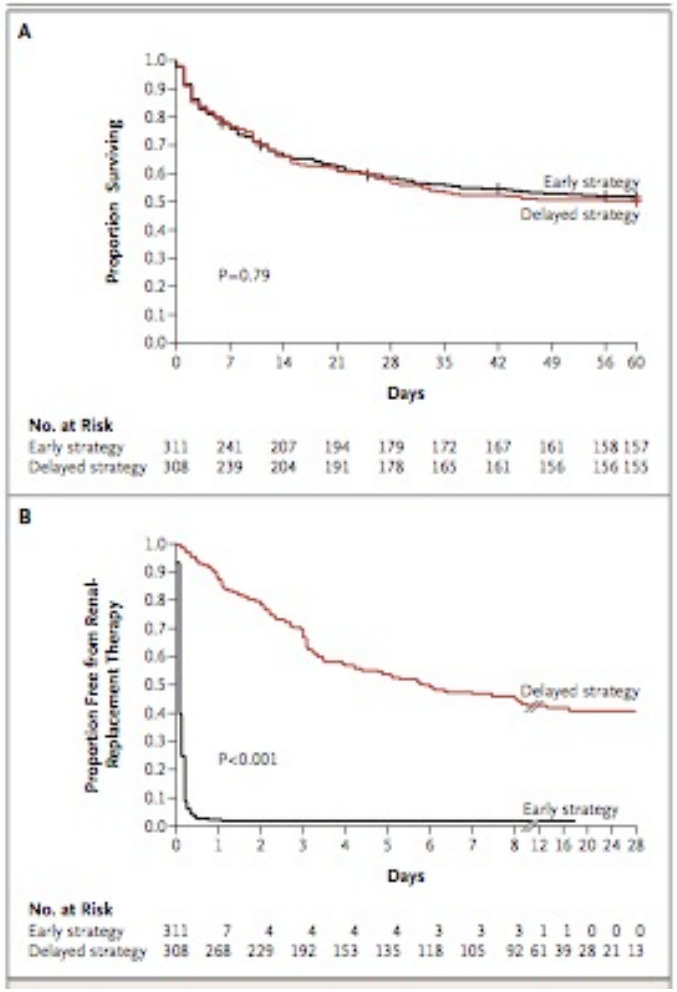
Etudes Randomisées



AKIKI

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit



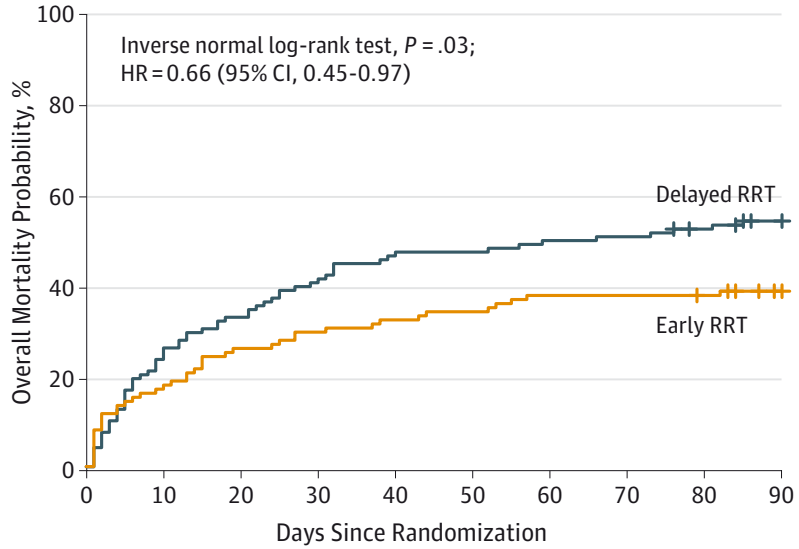
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury

The ELAIN Randomized Clinical Trial

ELAIN

Figure 2. Mortality Probability Within 90 Days After Study Enrollment for Patients Receiving Early and Delayed Initiation of Renal Replacement Therapy (RRT)



No. at risk

Early RRT	112	92	82	78	75	73	69	69	66	55
Delayed RRT	119	90	79	70	63	62	59	58	54	48

KDIGO indicates Kidney Disease: Improving Global Outcomes. In the delayed group, 18 patients had an absolute indication for RRT. The median (quartile 1 [Q1], quartile 3 [Q3]) duration of follow-up was 90 days (Q1, Q3: 90, 90) in the early group and 90 days (Q1, Q3: 90, 90) in the delayed group. The vertical ticks indicate censored cases.

Table 1. A Comparison of the AKIKI and ELAIN Trials

	AKIKI	ELAIN
Principal hypothesis	Delayed RRT reduces 60-d mortality by 15%	Early RRT reduces 90-d mortality by 18%
Patients enrolled	620	231
Centers	31	1
Age, y	66	66
SOFA	11	16
CKD, %	10	41
Mechanical ventilation, %	86	88
Pressor requirement, %	85	88
Septic shock, %	67	32
Surgical, %	21	97
Criteria for early RRT	KDIGO stage 3 AKI	KDIGO stage 2 AKI
Criteria for delayed RRT	Clinical indications	KDIGO stage 3 AKI
Scr at RRT initiation in early group (SD), mg/dL	3.3 (1.4)	1.9 (0.6)
Scr at RRT initiation in delayed group (SD), mg/dL	5.3 (2.3)	2.4 (1.0)
Time to RRT initiation in early arm (IQR), h	2 (1-3)[a]	6 (4-7)[b]
Time to RRT initiation in delayed arm (IQR), h	57 (25-83)[a]	25.5 (18.8-40.3)[b]
RRT modality	IHD, SLED, or CRRT	CVVHDF only permitted modality for first 7 d
Received RRT in early arm, %	98	100
Received RRT in delayed arm, %	51	91

Abbreviations: AKI, acute kidney injury; AKIKI, Artificial Kidney Initiation in Kidney Injury; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; ELAIN, Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury; IHD, intermittent hemodialysis; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy; Scr, serum creatinine; SD, standard deviation; SLED, sustained low efficiency dialysis; SOFA, Sequential Organ Failure Assessment Score.

[a]Time to RRT expressed from randomization.

[b]Time to RRT expressed from meeting eligibility criteria.

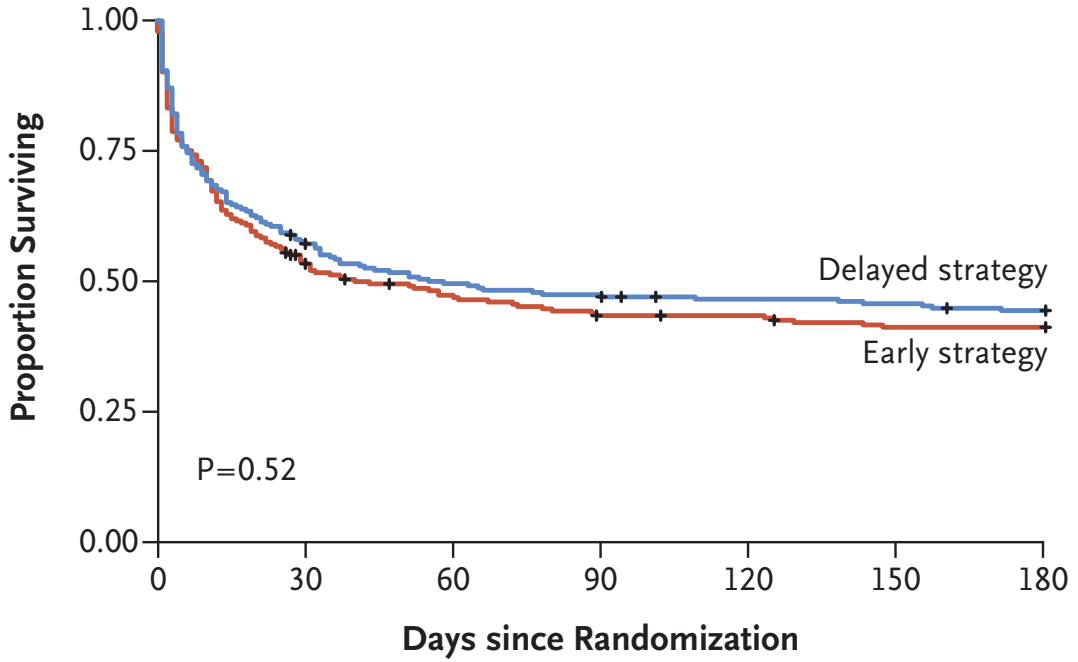
Table 1 | Design and primary results of the AKIKI and ELAIN trials

	AKIKI (n = 619)	ELAIN (n = 231)
Study site	Multicenter study (31 sites in France)	Single center (surgical ICU in Germany)
Enrollment criteria	• ICU patients age ≥ 18 yr • KDIGO stage 3 AKI presumed due to ATN • At least one of the following: Mechanical ventilation Catecholamine therapy **Major exclusion criteria** • Blood urea nitrogen > 112 mg/dl (40 mmol/l) • Potassium > 6 meq/l (> 5.5 with treatment) • pH < 7.15 due to metabolic or mixed acidosis • Severe pulmonary edema despite diuretics	• ICU patients age 18–90 yr • KDIGO Stage 2 AKI presumed due to ATN • Plasma NGAL > 150 ng/ml • At least one of the following: Severe sepsis Vasopressor/catecholamine therapy Nonrenal organ dysfunction (SOFA score ≥ 2) Fluid overload despite diuretics **Major exclusion criteria** • Prior CKD or RRT
Assignment	Randomized, unblinded	Randomized, unblinded Stratified by SOFA cardiovascular score & oliguria
Early RRT	Within 6 h of documented stage 3 AKI (Median 2 h after randomization)	Within 8 h of documented stage 2 AKI (Median 6 h after meeting entry criteria)
Indications for RRT in delayed arm	Any of the following: • Blood urea nitrogen > 112 mg/dl (40 mmol/l) • Potassium > 6 meq/l (> 5.5 with treatment) • pH < 7.15 due to metabolic or mixed acidosis • Severe pulmonary edema despite diuretics • Oliguria lasting > 72 h after randomization (Median 57 h after randomization)	• Documented stage 3 AKI or any of the following: • Blood urea nitrogen > 100 mg/dl (36 mmol/l) • Potassium > 6 meq/l (or ECG changes) • Magnesium > 8 meq/l (4 mmol/l) • Organ edema despite diuretics • Urine output < 200 ml/ 24 h (Median 26 h after meeting entry criteria)
Initial RRT modality	Discretion of the enrolling site (55% intermittent RRT, 45% continuous RRT)	Continuous venovenous hemodiafiltration
60-d mortality	49.1%	44.6%
Primary outcome	60-d mortality 48.5% versus 49.7% ($P = 0.79$)	90-d mortality 39.3% versus 54.7% ($P = 0.03$)
Receipt of RRT	98% versus 51% ($P < 0.001$) Catheter-related bacteremia: 10% versus 5% ($P = 0.03$)	100% versus 91% Median length of stay: 51 versus 82 d ($P < 0.001$) Mediation duration of mechanical ventilation: 126 versus 181 h ($P = 0.002$)

IDEAL ICU

ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis



No. at Risk

Delayed strategy	242	137	117	112	107	105	101
Early strategy	246	127	109	99	98	92	92

Quelle dose de Dialyse?

Dose de Dialyse

- Définition:

  = Quantité d'épuration

  Identique à une posologie de médicament: quelle dose administrer au patient pour:

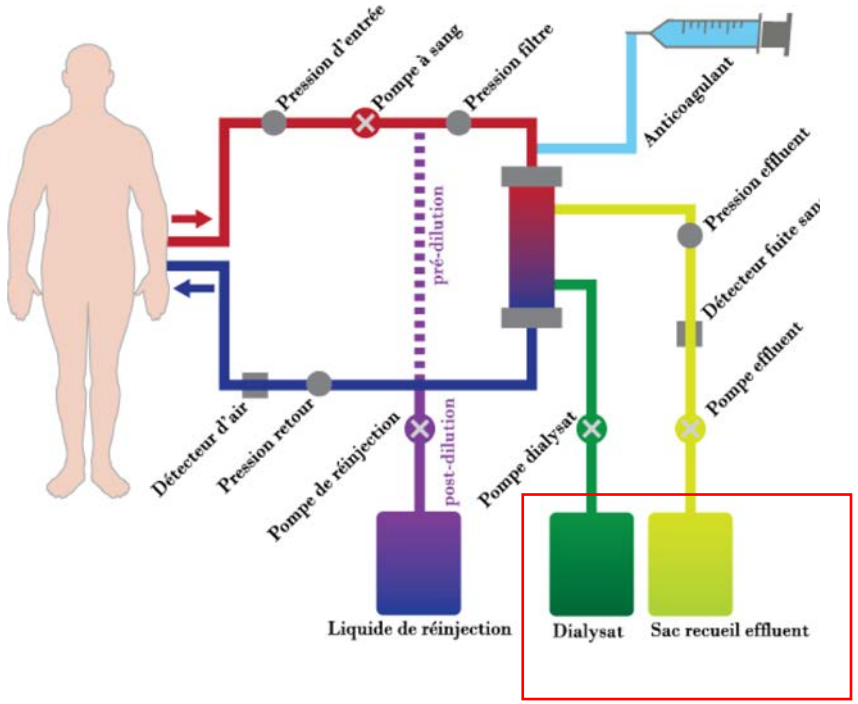
  - améliorer l'état du patient
  - éviter le surdosage responsable d'effets indésirables

  Mais comment évaluer la DOSE DE DIALYSE?

  ➔ Comme tous médicaments = **<u>en dose/Kg</u>**

Dose de Dialyse

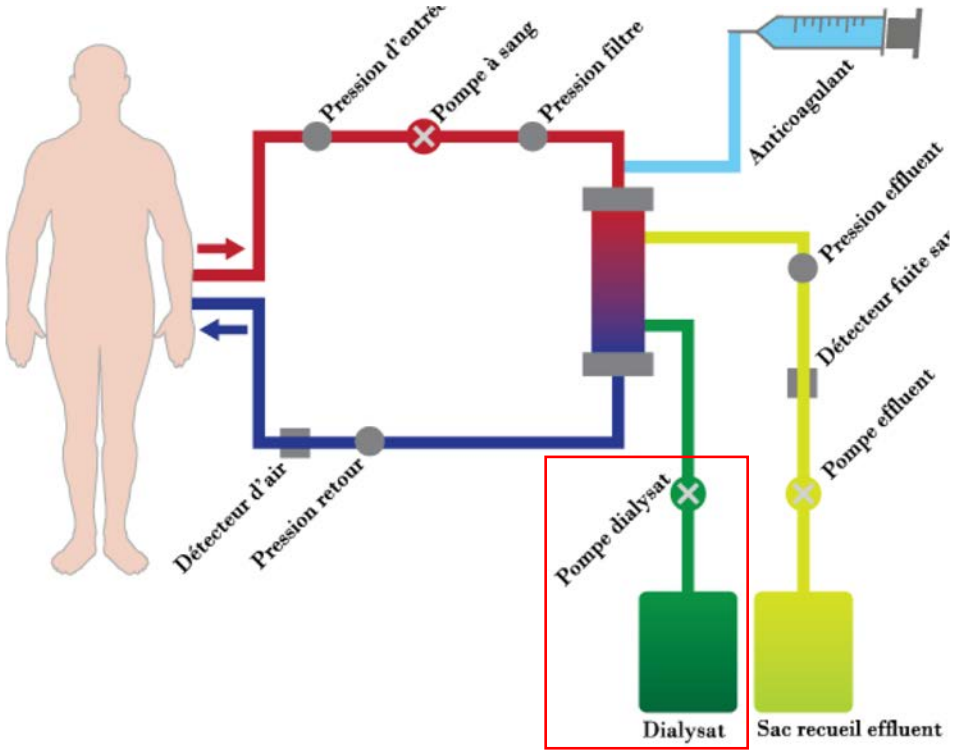
- En EER continue (CVVHF, CVVHD ou CVVHDF):
  - Quantité d'effluent par heure
    - Effluent = dialysat + ultrafiltrat
    - En ml/Kg/h
    - Recommandations= 20-25 ml/Kg/h
  - En pratique:
    - PRISMAFLEX/MULTIFILTRATE
      - Débit Dialysat = 2000 ml/h
      - Débit de Réinjection Post-Dilution = 1500 ml/h
        - Dose = 2000 + 1500 = **3500 ml/h**
        - Patients 85Kg: **40 ml/kg/h !**



Dose de Dialyse

- En EER Discontinue (HD intermittente):
  - Evaluation complexe
  - Basé sur ce qui se fait en HD chronique
  - Mesure d'un index = kT/V

  - En pratique:
    - Fresenius 5008 / Evosys
      - 3 séances/ semaine
      - À 500 ml/min de Débit Dialysat



Intérêt d’augmenter la Dose?

- Pourquoi:
  - Epurer des molécules toxiques (cytokines pro-inflammatoires dans le sepsis)

- Risques:
  - Métaboliques ++
    - Hypokaliémie, Hypomagnésémie, Hypophosphorémie
    - Hypoglycémie, Dénutrition

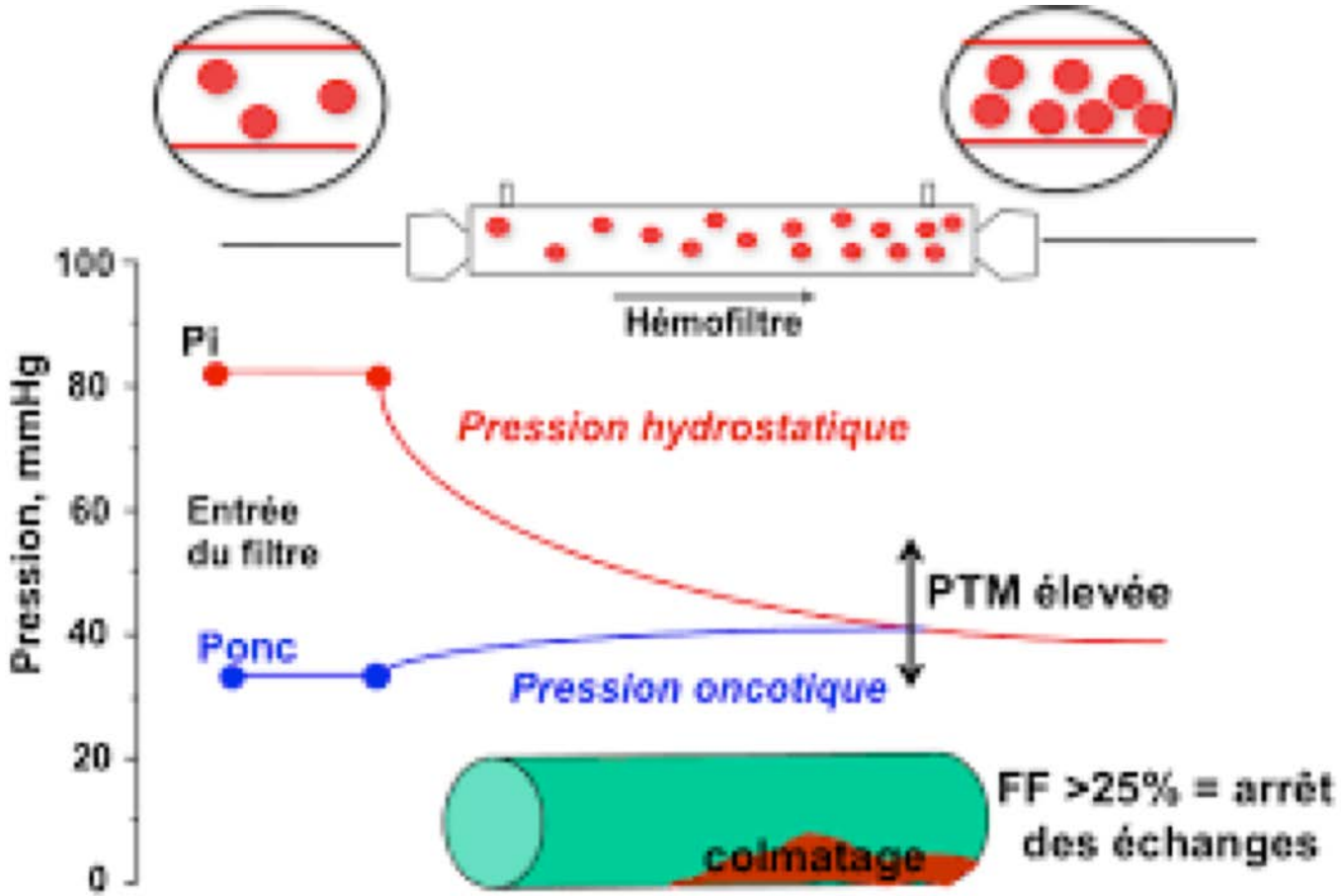
Table 7 Characters of ATN, RENAL and IVOIRE studies

	ATN (2008)	**RENAL** (2009)	**IVOIRE** (2013)
Design	Multicenter RCT	Multicenter RCT	Multicenter RCT
Country	USA	Australia and New Zealand	France, Belgium and Netherlands
Patients	AKI	AKI	AKI with septic shock
No. of patients	1124	1508	140
Modality	CVVHDF, SLED, IHD	CVVHDF	CVVH
Prescribed dose	CVVHDF: 21.5 versus 36.2 ml/kg/h SLED and IHD: 3 versus 6/wk	25 versus 40 ml/kg/h	35 versus 70 ml/kg/h
Delivered dose	CVVHDF: 22 versus 35.8 ml/kg/h SLED: 2.9 versus 6.2/wk IHD: 3 versus 5.4/wk	22 versus 33.4 ml/kg/h	33.2 versus 65.6 ml/kg/h
Mortality	60 days 51.5 versus 53.6%	90 days 44.7 versus 44.7%	90 days 50.7 versus 56.1%

AKI acute kidney injury, *CVVH* continuous venous–venous hemofiltration, *CVVHDF* continuous venous–venous hemodiafiltration, *SLED* sustained low-efficiency dialysis, *IHD* intermittent hemodialysis

PAS D'INTERÊT D'AUGEMNTER LA DOSE AU DELA DE 20-25 ml/Kg/h

Fraction de Filtration



Fraction de Filtration (FF) =
« Quantité d'eau plasmatique hémofiltrée »

< 20-25% sinon risque de colmatage du filtre

= Q Hémofiltration / Q Sang

Augmentation Dose de dialyse = Augmentation de l'Hémofiltration = Risque de colmatage si pas d'augmentation du Q sang

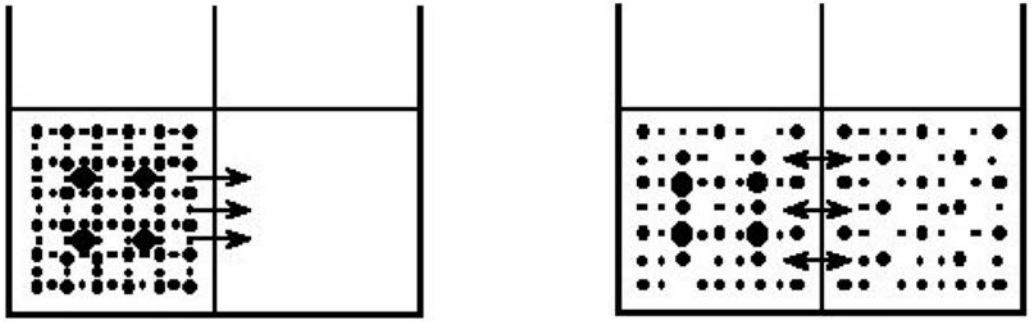
Type de Dialyse

Principes

DIFFUSION

Transfert de solutés

Force motrice : différence de concentration

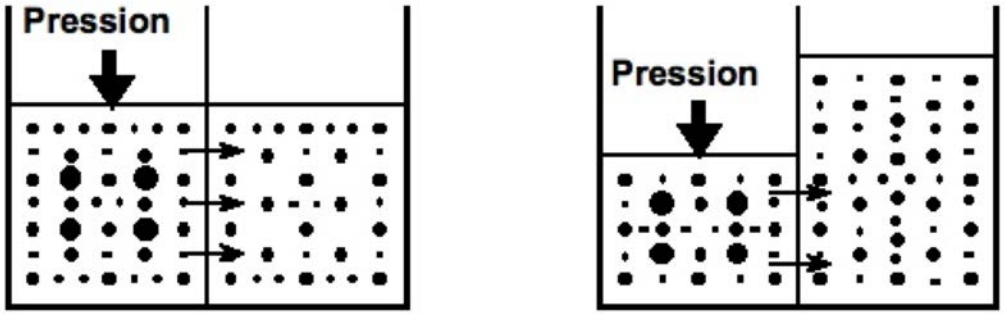


Etat initial **Etat d'équilibre**

CONVECTION

Transfert simultané d'eau et de solutés

Force motrice : différence de pression



Etat initial **Etat final**

HEMODIALYSE

Echange des **PETITES MOLECULES**
Pas de transfert d'eau = pas de perte de poids

HEMOFILTRATION

Echange des **MOYENNE MOLECULES**
Transfert **D'EAU** + molécules = permet perte de poids

Type de DIALYSE

CONTINUE (24H/24)	**INTERMITTENT (4-6H)**
CVV HD = ÉCHANGES DIFFUSIFS	HDI = ÉCHANGES DIFFUSIFS
CVVHF = ECHANGES CONVECTIFS	HFI = ECHANGES CONVECTIFS
CVV HDF = ECHANGES DIFFUSIFS + CONVECTIFS	HDFI = ECHANGES DIFFUSIFS + CONVECTIFS

CONVECTION SYSTEMATIQUE POUR PERTE DE POIDS (ULTRAFILTRATION)

Type de DIALYSE

CONTINUE (24H/24)	**INTERMITTENT (4-6H)**
CVV HD = ÉCHANGES DIFFUSIFS	**HDI = ÉCHANGES DIFFUSIFS**
CVVHF = ECHANGES CONVECTIFS	HFI = ECHANGES CONVECTIFS
CVV HDF = ECHANGES DIFFUSIFS + CONVECTIFS	HDFI = ECHANGES DIFFUSIFS + CONVECTIFS

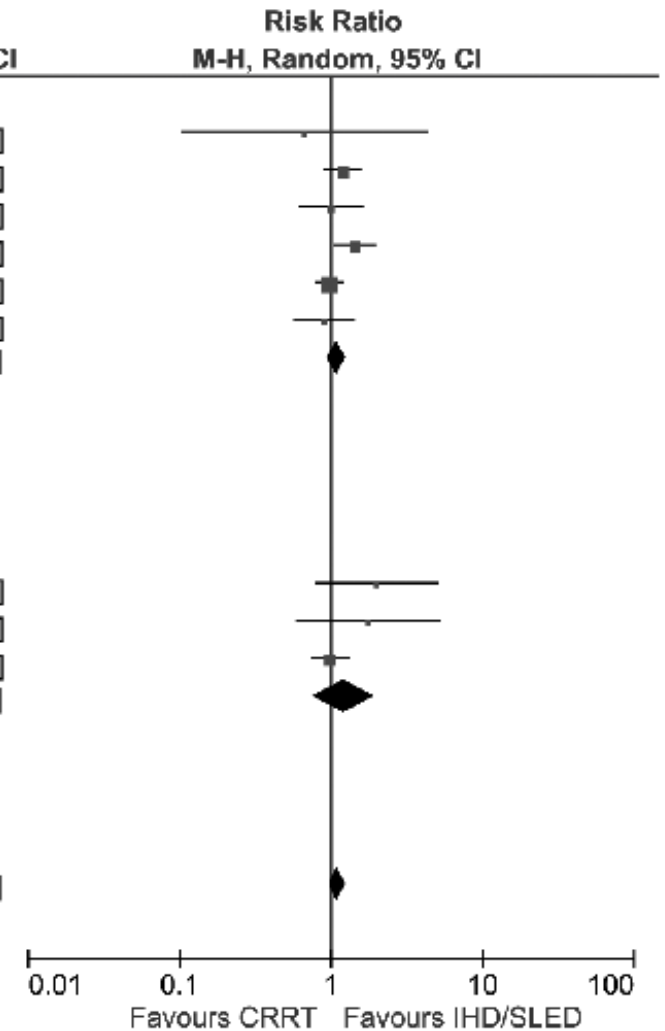
CONVECTION SYSTEMATIQUE POUR PERTE DE POIDS (ULTRAFILTRATION)

Table 3 Characteristics of CRRT, SLED and IHD

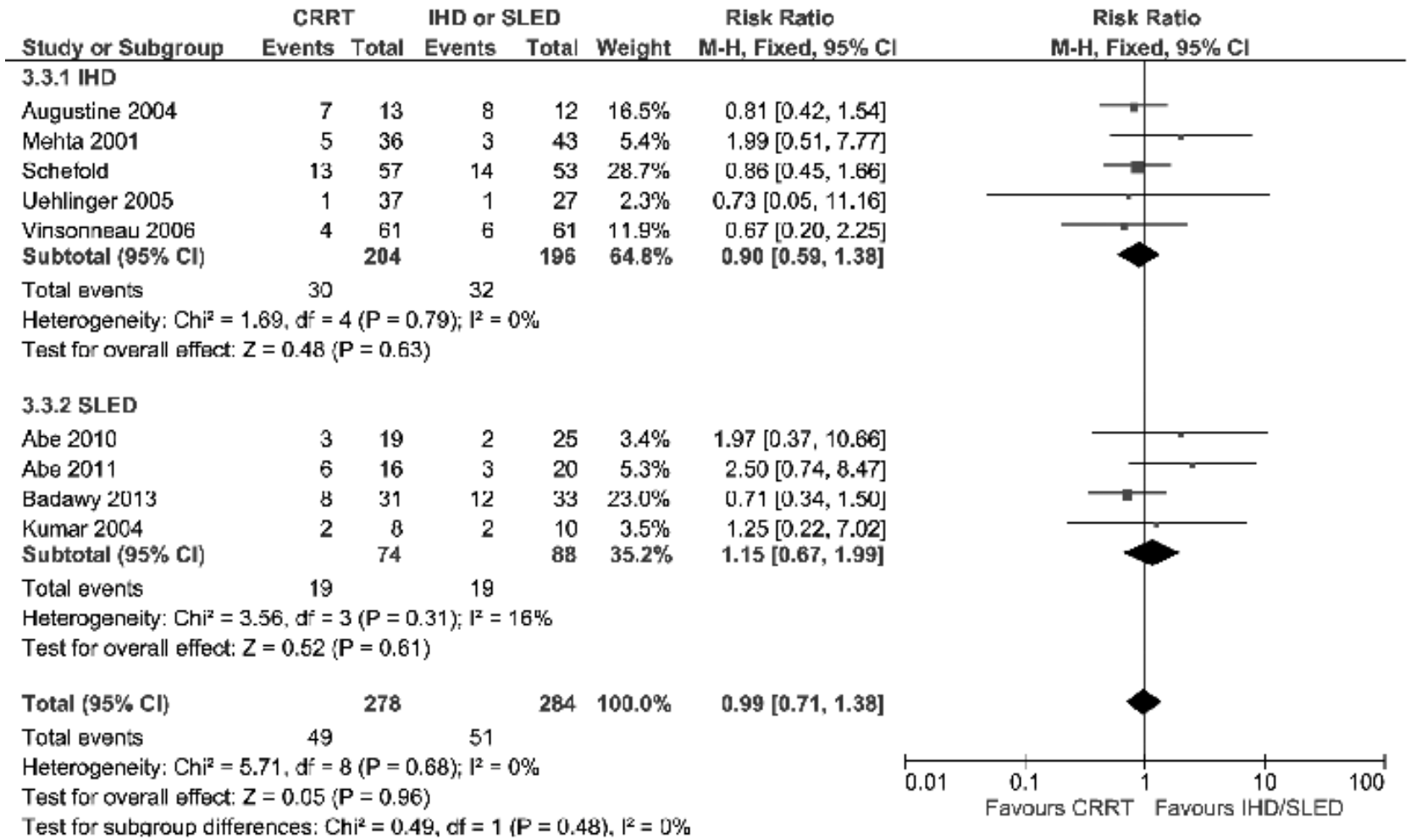
	CRRT	SLED	IHD
Modality	CVVH/CVVHDF/CVVHD	SLED/SLED-f	IHD/IHD-f
Duration per session	24 h	6–12 h	4 h
Frequency	24 h/day	3–6/week	3/week
Blood flow (ml/min)	100–200	100–200	250–350
Dialysate dose	20–25 ml/kg/h	100–300 ml/min	500–800 ml/min
Hemodynamic status	Stable	Possible stable	Unstable
Volume control	+++	++	+
Heparin dose	High	Moderate	Low

Mortalité

Study or Subgroup	CRRT Events	CRRT Total	IHD or SLED Events	IHD or SLED Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 IHD						
Davenport 1989	1	3	2	4	0.5%	0.67 [0.10, 4.35]
Gasparovic 2003	37	52	31	52	19.3%	1.19 [0.90, 1.58]
John 2001	14	20	7	10	6.5%	1.00 [0.61, 1.64]
Mehta 2001	50	84	34	82	16.0%	1.44 [1.05, 1.96]
Noble 2006	46	64	39	53	30.1%	0.98 [0.78, 1.22]
Uehlinger 2005	24	70	21	55	7.3%	0.90 [0.56, 1.43]
Subtotal (95% CI)		**293**		**256**	**79.7%**	**1.10 [0.95, 1.28]**
Total events	172		134			
Heterogeneity: Tau² = 0.00; Chi² = 5.43, df = 5 (P = 0.37); I² = 8%						
Test for overall effect: Z = 1.25 (P = 0.21)						
3.2.2 SLED						
Abe 2010	10	30	5	30	1.8%	2.00 [0.78, 5.15]
Abe 2011	7	25	4	25	1.4%	1.75 [0.58, 5.24]
Schwenger	49	117	49	115	17.1%	0.98 [0.73, 1.33]
Subtotal (95% CI)		**172**		**170**	**20.3%**	**1.23 [0.77, 1.95]**
Total events	66		58			
Heterogeneity: Tau² = 0.06; Chi² = 2.81, df = 2 (P = 0.25); I² = 29%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**465**		**426**	**100.0%**	**1.10 [0.97, 1.25]**
Total events	238		192			
Heterogeneity: Tau² = 0.00; Chi² = 8.24, df = 8 (P = 0.41); I² = 3%						
Test for overall effect: Z = 1.42 (P = 0.16)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%						

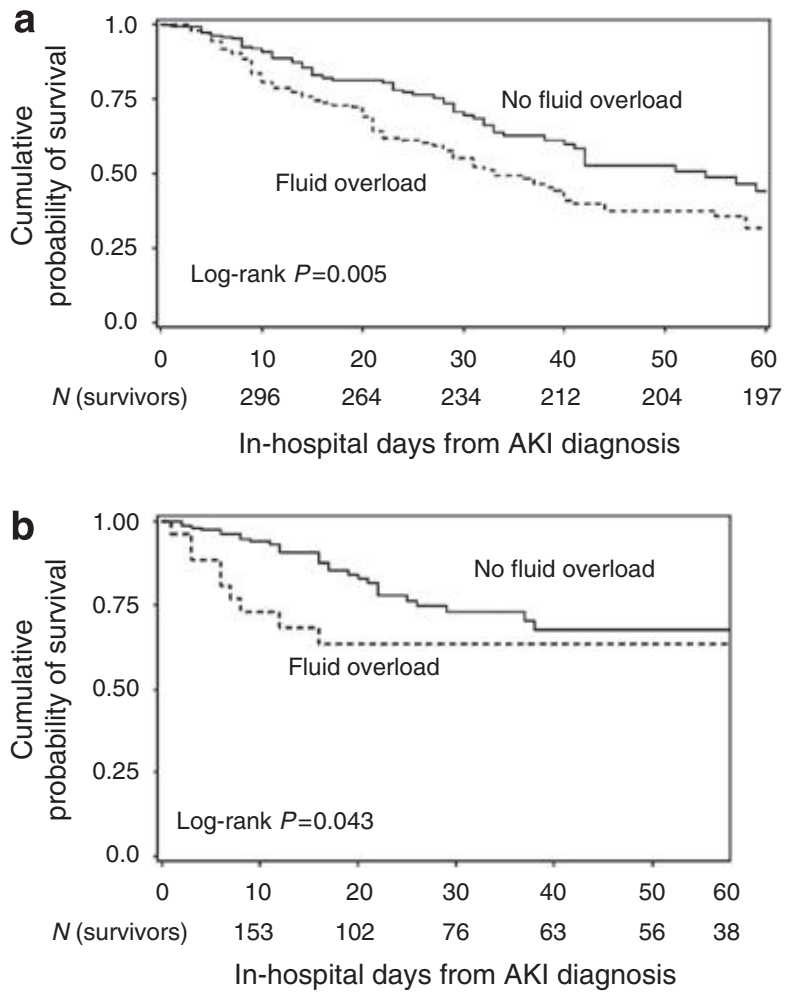


Récupération Rénale



Dialyse et Fluid Overload

Fluid Overload



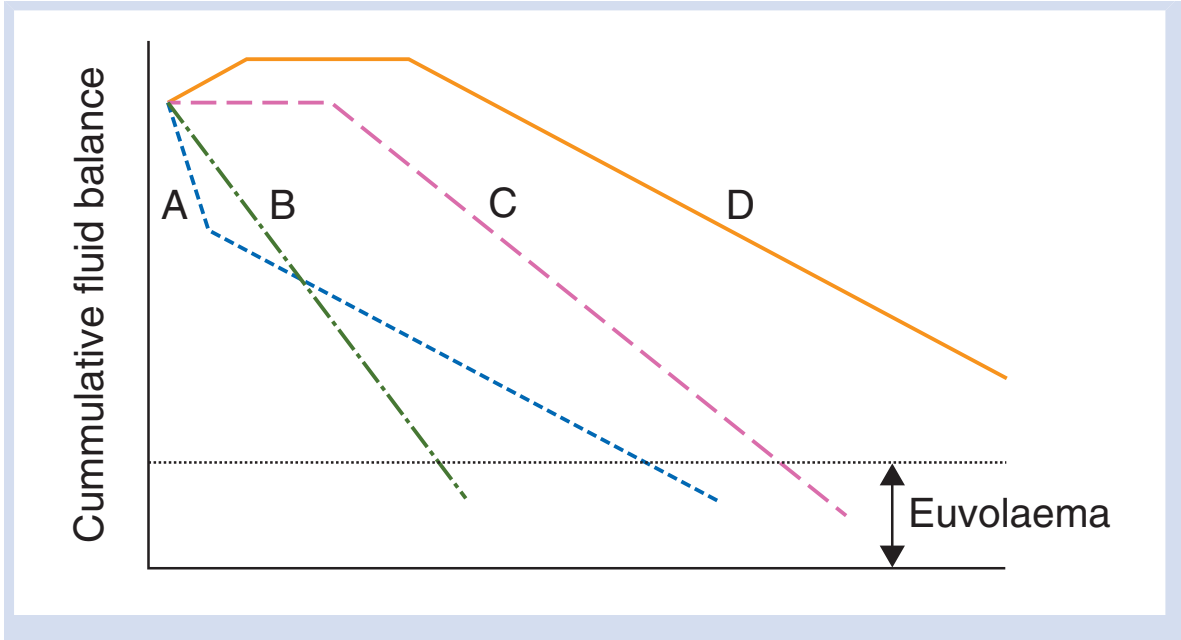


Table 3 Mechanical fluid removal techniques. SCUF, slow continuous ultrafiltration; CVVH, continuous veno-venous haemofiltration

Modality	Blood flow rates (ml min^{-1})	Fluid removal rates (ml h^{-1})	Anti-coagulation	Advantages	Disadvantages
Intermittent ultrafiltration	250–400	0–2000	Desirable	Widely available	Less effective in reaching fluid balance goals Can lead to haemodynamic instability Requires venous access
Continuous ultrafiltration	50–100	0–300	Desirable	Can be performed as either SCUF or CVVH Haemodynamically better tolerated CVVH allows for a replacement solution and dissociation of sodium and water clearance	Requires venous access Not as widely available
Peritoneal dialysis	Not applicable	0–500	Not required	Modality of choice for paediatrics No venous access Haemodynamically more stable	Cannot be used in patients with abdominal surgery or trauma Not available at all sites Requires technical expertise to place catheters
Haemodialysis (intermittent)	250–400	0–2000	Desirable	Widely available Adds clearance of solutes	Less effective in reaching daily fluid balance goals Can lead to haemodynamic instability Requires venous access
Haemodialysis (continuous)	50–100	0–300	Desirable	Adds clearance of solutes Haemodynamically more stable	Requires venous access Not as widely available

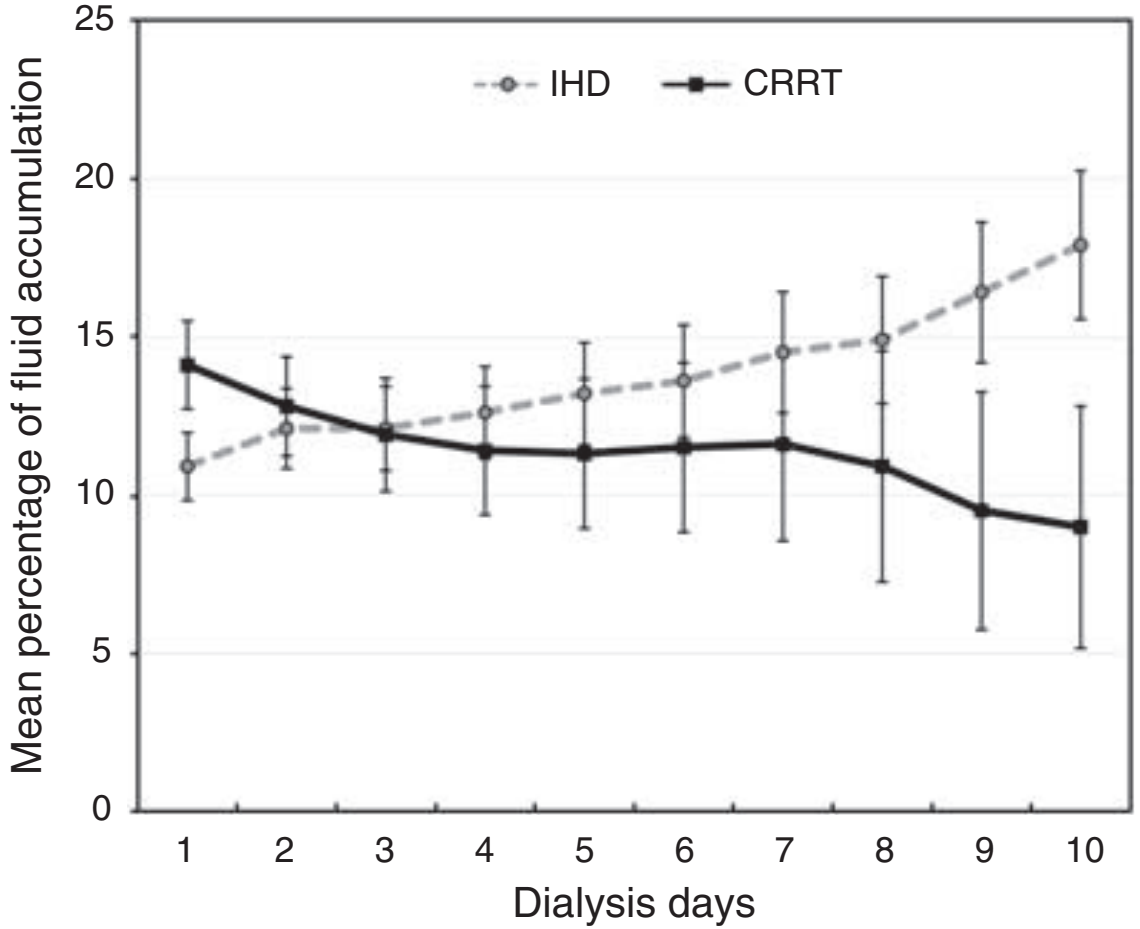


Figure 4 | Fluid accumulation over time in patients on continuous renal replacement therapy and on intermittent hemodialysis.

Membrane HCO et Sepsis

Membrane HCO et Sepsis

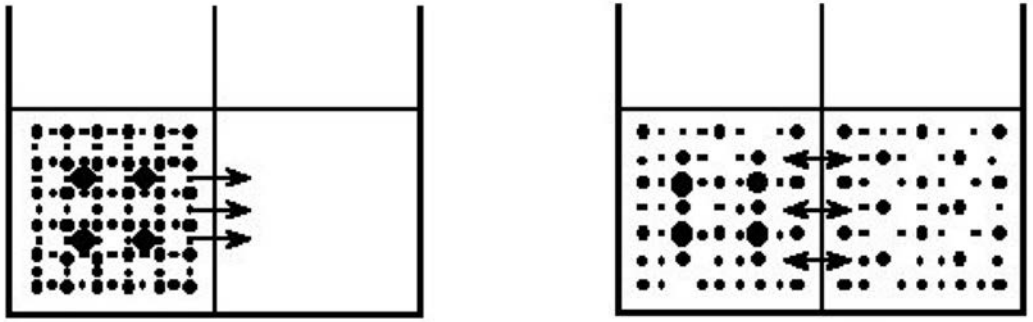
- Objectifs d'une EER:
  - Correction des troubles hydro-electrolytiques (K+, Ph...) et acido-basiques (Gestion de l'acidose métabolique=pH)
  - Ultrafiltration (fluid overload)

  - **ELIMINER TOXINES**
    - **Endogènes = toxines urémiques (urée = représentant de ces toxines)**
    - **Exogènes = médicaments**

    - **CYTOKINES pro-inflammatoires = sécrétées en grande quantité dans le sepsis avec des effets délétères ➔ Intérêt de les épurer?**

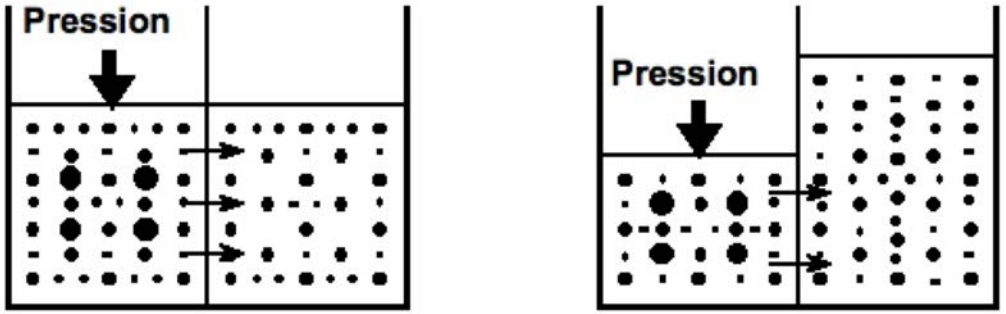
Principes

DIFFUSION
Transfert de solutés
Force motrice : différence de concentration



Etat initial | Etat d'équilibre

CONVECTION
Transfert simultané d'eau et de solutés
Force motrice : différence de pression



Etat initial | Etat final

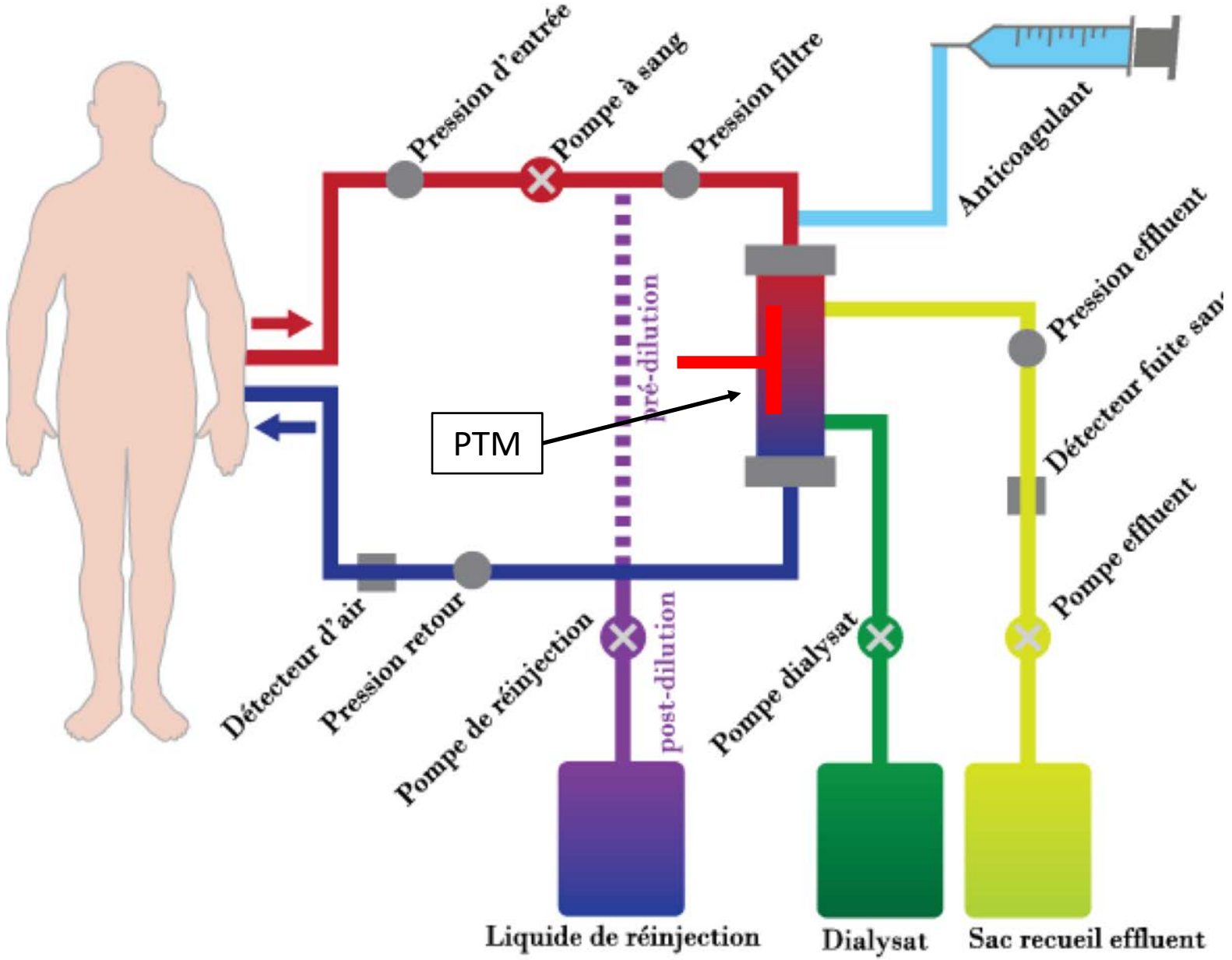
HEMODIALYSE

Echange des petites molécules
Pas de transfert d'eau = pas de perte de poids

HEMOFILTRATION

Echange des moyenne molécules
Transfert d'eau + molécules = permet perte de poids

HémoDiaFiltration (HDF)



= Dialysat + Ultrafiltrat

HémoDiaFiltration (HDF) :

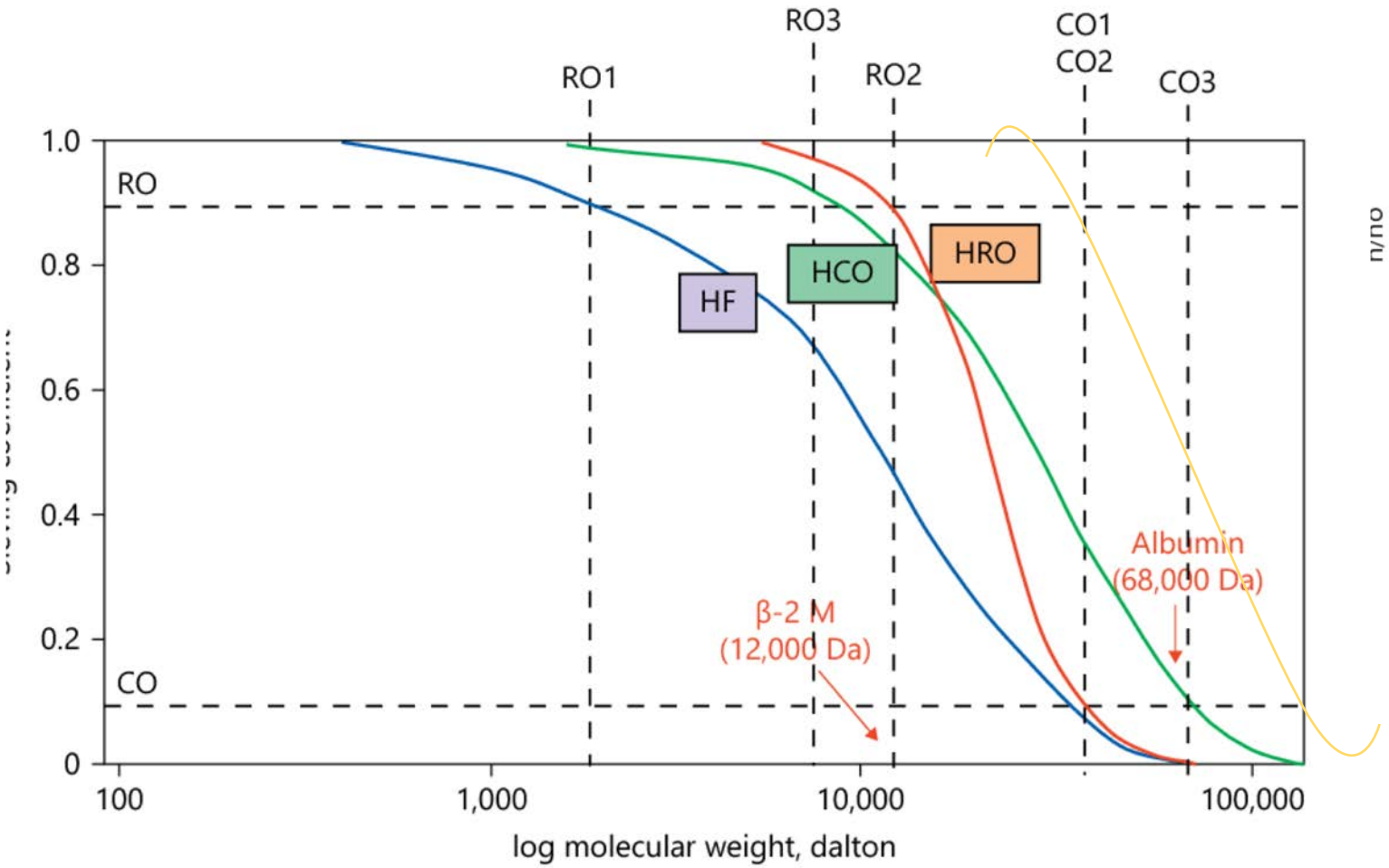
Hémodialyse = diffusion = échanges des petites molécules (K+, Urée...)

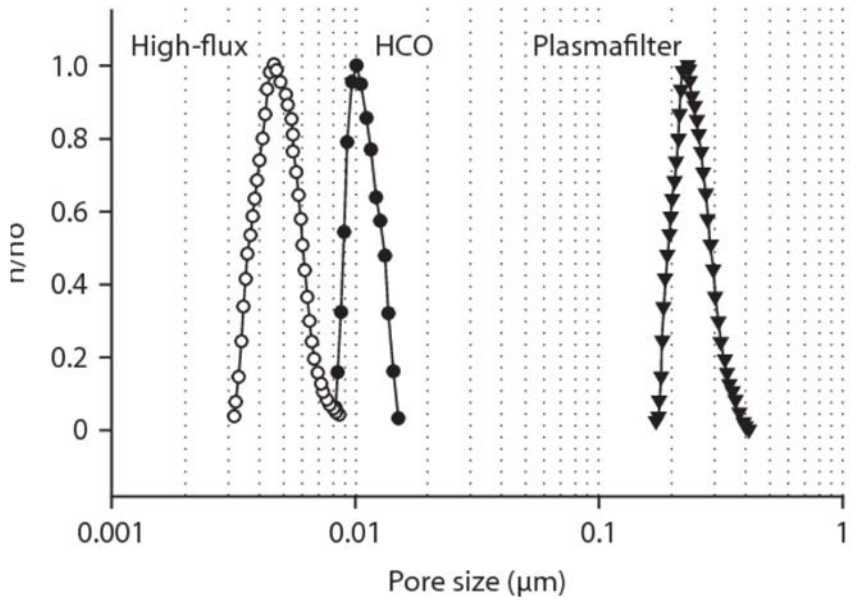
Hémofiltration = convection =
- Perte de poids (UF)
- Echange moyenne molécules (cytokines, médicaments)

Hémofiltration

DIALYSE

PLASMAPHERESE





Membrane HCO et Sepsis

- Sepsis/Choc Septique → synthèse de molécules (Cytokines) Pro-inflammatoires

- Cytokines = effet délétère potentiel

- Pour éliminer ces Cytokines → membrane à « large pores » = membrane HCO = High Cut-Off (60-100 Kdalton)

Comparaison membrane HCO versus membrane standard

Table 4 Cytokine clearance, albumin clearance and clinical effects of renal replacement therapy using high cutoff membranes

First author, year	*N*	RRT modality	Qf or Qd (l/h)	Cutoff[a] (kDa)	Cytokine clearance	Albumin clearance	Clinical effects
Morgera et al. [103]	24	CVVH versus CVVHD	Qf 1 versus 2.5 Qd 1 versus 2.5	60	Greater IL-1ra clearance with CVVH. Increased Qf or Qd increased IL-6 and IL-1ra clearance	Highest with CVVH 2.5 l/h	Overall decrease in APACHE II and MODS scores. No difference between groups
Morgera [235]	30	CVVH	Qf 2.5	30 versus 60	Greater IL-6 and IL-1ra clearance with 60 kDa-filter	Plasma albumin levels not affected by filter cutoff	Reduced noradrenaline requirements with 60 kDa-filter
Haase et al. [104]	10	IHD	Qd 18	20 versus 60	Greater IL-6, IL-8 and IL-10 clearance with 60 kDa-filter	Plasma albumin levels not affected by filter cutoff	Trend toward increased mean arterial pressure and reduced vasopressor requirements with 60 kDa-filter

RRT renal replacement therapy, *Qf* ultrafiltration rate, *Qd* dialysate flow rate, *CVVH* continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *IHD* intermittent hemodialysis, *APACHE* acute physiology and chronic health evaluation, *MODS* multiorgan dysfunction syndrome

[a] Estimated in vivo membrane cutoff