ADVITOS
Bridging Life

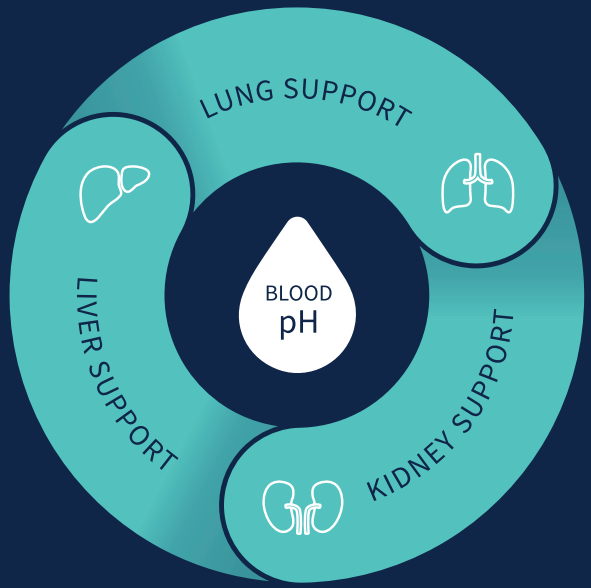
ADVOS Therapy

ADVanced **O**rgan **S**upport

The 4-in-1 Organ Support
for Treatment of
Multi-Organ Failure

ADVOS Therapy

Extracorporeal Blood Purification for Simultaneous Support of the Main Detoxification Organs



Liver

Removal of protein-bound toxins

Lungs

Fluid-based CO_2 removal in a low-invasive setting

Kidney

Removal of water-soluble and protein-bound nephrotoxins

Blood pH

Correction of metabolic and respiratory acidosis

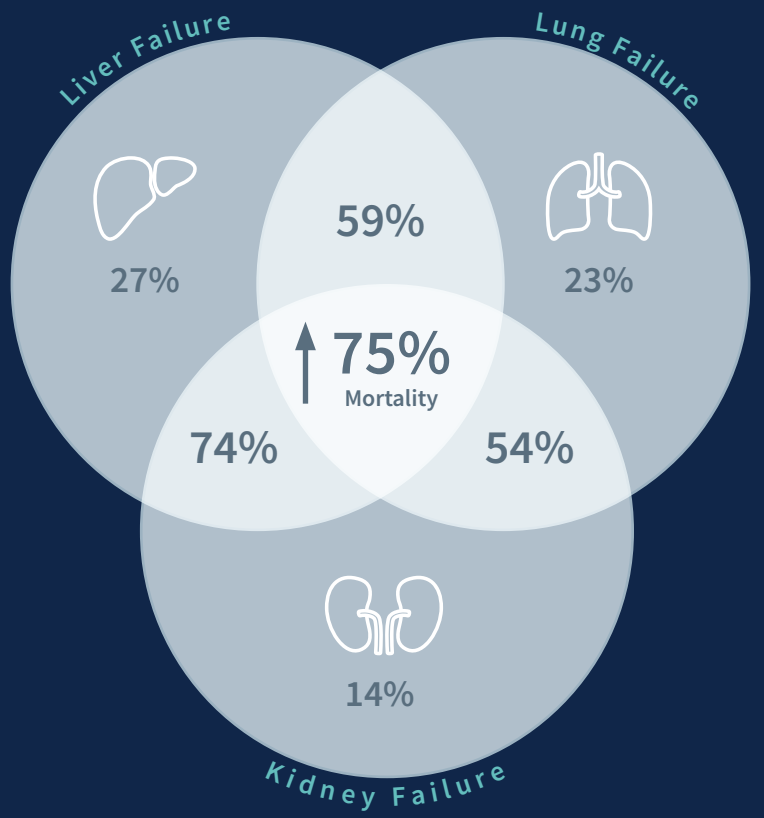
ADVOS Therapy: First Method Worldwide for Individualised Multi-Organ Support

The ADVOS (ADVanced Organ Support) procedure is designed to provide multi-organ support for liver, lung and kidney while also correcting acid-base imbalances. The ADVOS multi represents an evolution from conventional dialysis machines as it uses albumin-enriched instead of regular dialysate and allows targeted adjustment of the pH value of the dialysate. Within the device, the dialysate is permanently reprocessed and cleansed of toxins to maintain consistently high detoxification performance.

Despite the progress made in intensive care, the mortality rate of patients with multi-organ failure is still very high. Although dysfunction of the individual detoxification organs liver, lung and kidney can clearly be delineated, the failure of one organ can affect several others. Examples include renocardiac, cardiopulmonary and hepatorenal syndromes, where the severity of the pathology correlates directly with the number of decompensated organs.

Compromised functionality of the main detoxification organs causes life-threatening toxins to accumulate in the body, resulting in progressive organ failure and death within a few days.

Conventional extracorporeal procedures merely support the function of one or two organs. The innovative approach of the ADVOS therapy, on the other hand, is based on a multi-organ concept, supports all three main detoxification organs simultaneously and is unique in acid-base balancing.



Correlation between mortality and the number of organ failures[1]

Indications for Organ Support Therapy[2]

Level of organ support needed in different patient indications

\+ important
++ very important
+++ highest priority




		Liver Support	Kidney Support	Lung Support	Blood pH
MULTI-ORGAN FAILURE	Postoperative (e.g. after liver surgery)	+++	+	+	++
	Postoperative (e.g. after cardiac surgery)	+	++	+++	+++
	Cardiogenic shock	+	++	+++	+++
	Septic shock	+	++	+++	+++
	Hypoxic liver failure	+++	+	+	++
	LIVER TRANSPLANT (waiting list & postoperative)	+++	++	+	+
	ACUTE LIVER FAILURE	+++	++	+	+++
	ACUTE-ON-CHRONIC LIVER FAILURE	+++	+	+	++
	RESPIRATORY FAILURE	+	++	+++	+++

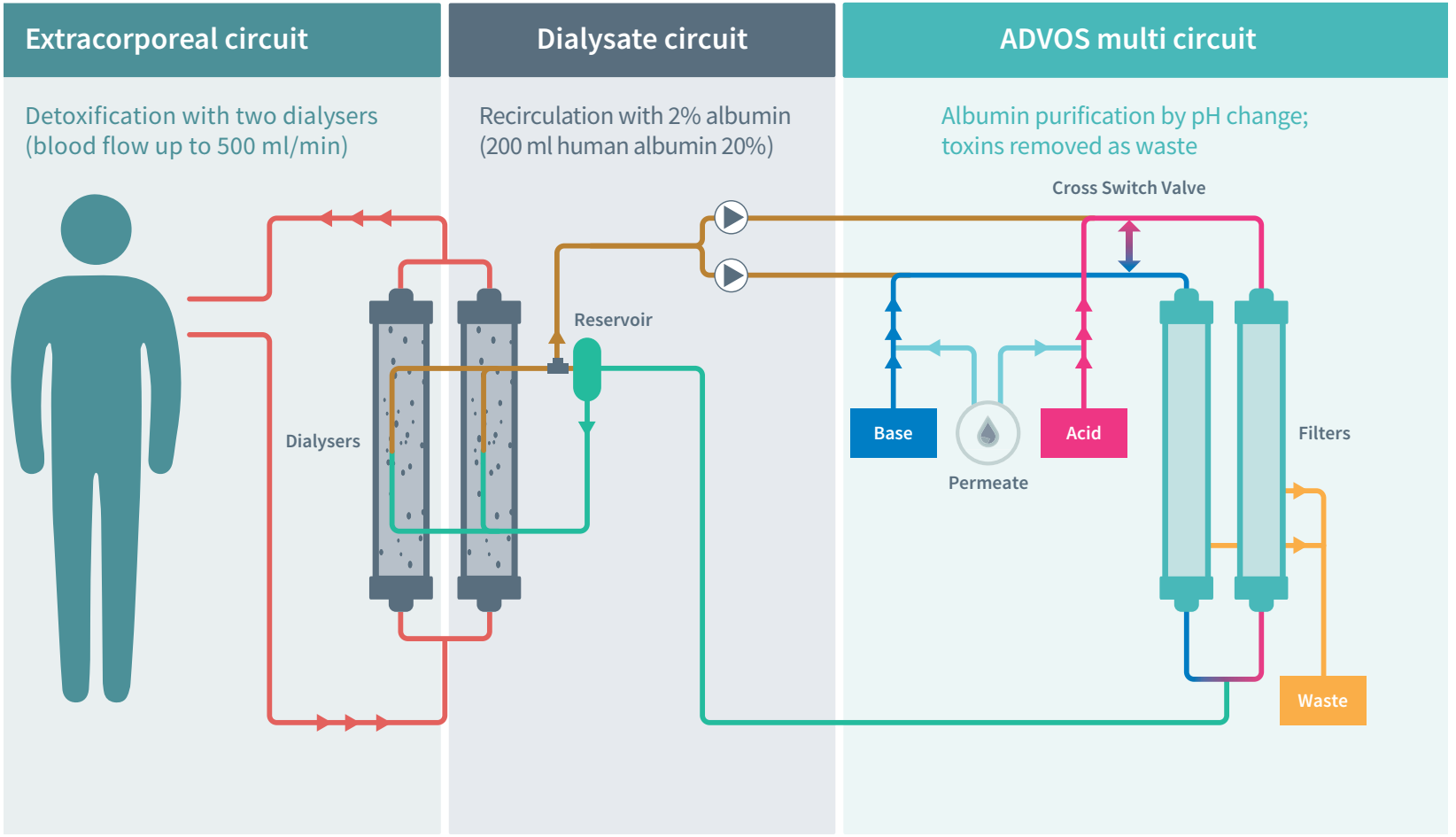
ADVOS Therapy Might Improve Survival Chances Through Unique Multi-Organ Support[4,5,7,8]

User Benefits

- Worldwide only 4-in-1 device to provide multi-organ support for liver, lung, kidney and acid-base balance
- Reduced user effort and lower risk of human error
- Integrated container with 85-litre dialysate volume for reduced workload in the ICU ward

Clinical Outcome

- Correction of acid-base imbalances by direct removal of acids; treatment of severe metabolic and respiratory acidosis (fluid-based CO_2 removal);
  blood pH is physiologically balanced as in the kidney
- High and long-lasting efficacy of detoxification of all main organs
- Low-invasive and safe method: no large-lumen catheter necessary, low blood flow and volume needed



Highest possible detoxification performance:

- **Blood pH management** (H^+, HCO_3^-)
- **Kidney** (water-soluble and protein-bound toxins)
- **Liver** (protein-bound toxins)
- **Lung** (CO_2)

Principle of the ADVOS Procedure

The ADVOS procedure is based on the principle of albumin dialysis with the advantages of high dialysate flow, low albumin consumption and enhanced toxin removal.

The core procedures are the recycling of toxin-loaded albumin dialysate by pH and temperature regulation in the purification circuit (ADVOS multi circuit) and its subsequent reuse.

Acid circuit

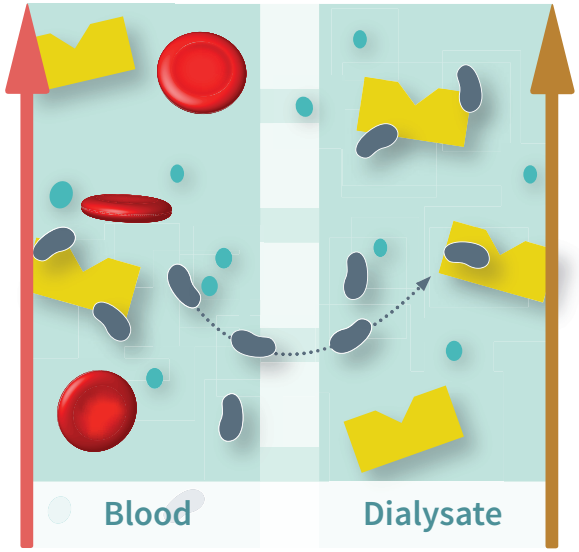
Reduction of pH eliminates positively charged toxins (e.g. copper and CO_2) from the albumin dialysate

Base circuit

Increase of pH eliminates negatively charged toxins (e.g. bilirubin and bile acids) from the albumin dialysate

- Albumin dialysate flows at a rate of up to 96 l/h due to rapid recycling in both purification circuits
- High detoxification capacity due to simultaneous removal of toxins in both sub circuits
- H^+ and CO_2 removal for treatment of metabolic and respiratory acidosis through individualised pH adjustment of the albumin dialysate
- Protein-bound uraemic toxin removal (e.g. indoxyl sulphate)
- Cytokine removal (e.g. interleukin-6)
- Reduction of ammonia levels
- Unique recirculation circuit of the dialysate allows a steady state detoxification in contrast to a complete removal of substances through absorption or single pass dialysis

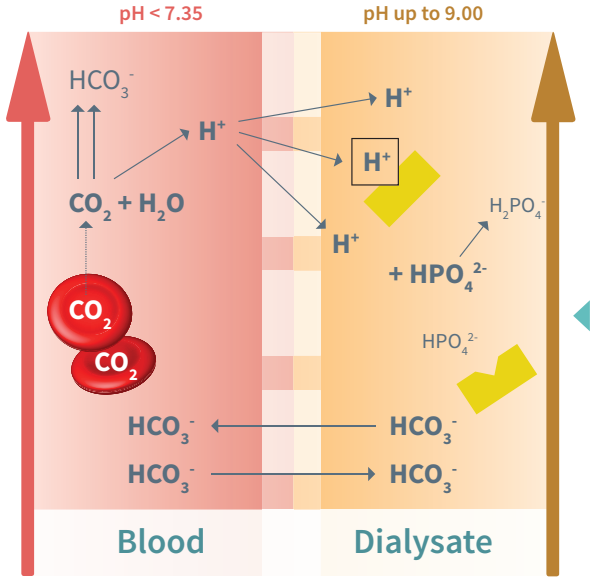
Dialyser Cross-Section



Membrane

- Erythrocyte
- Albumin
- Protein-bound Toxins
- Water-soluble Toxins

Renal Acid-Base Compensation



Membrane

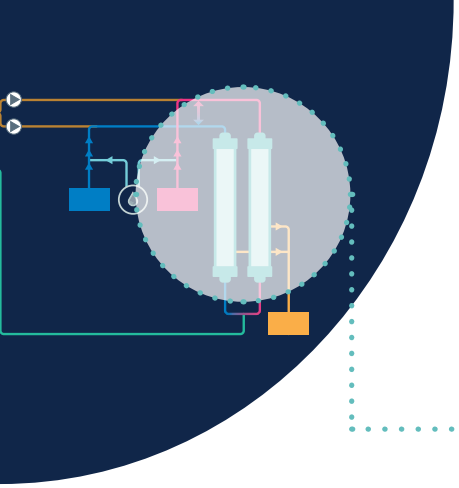
$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$

Diffusionsgradient Blut ➡ Dialysat

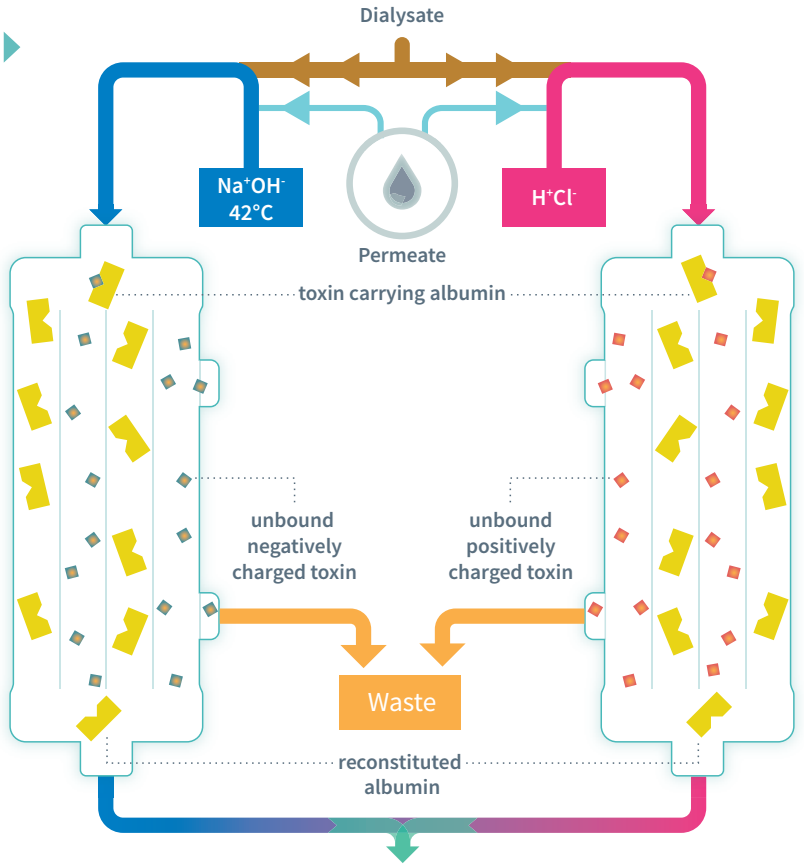
1. Direct diffusion of H^+ ions
   blood pH <7.35 ° dialysate pH up to 9.0
2. H+ binding to albumin and phosphate
3. Erythrocytes excrete CO_2

Dialysate

4. Setting dialysate HCO_3^-
   - during metabolic acidosis - increasing HCO_3^- ↑
   - during respiratory acidosis - lowering HCO_3^- ↓



ADVOS multi Circuit - Filter Operation



BASE CIRCUIT

- Removal of anionic protein-bound substances, e.g. bilirubin
- Removal of water-soluble substances
- Removal or addition of HCO_3^- (bicarbonate)
- H^+ removal

ACID CIRCUIT

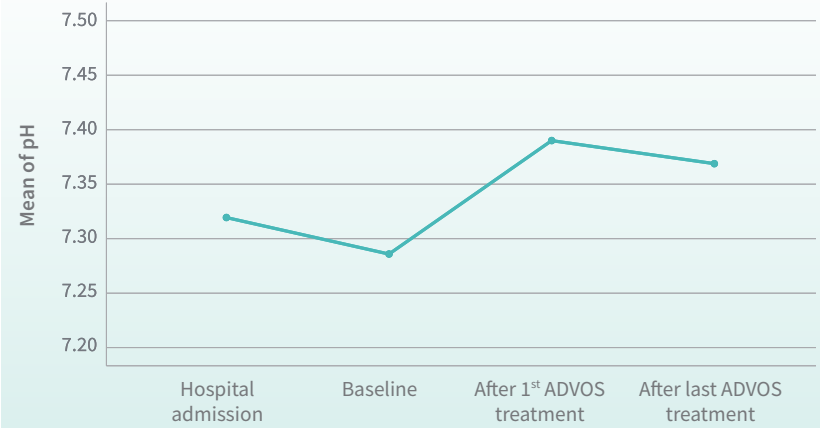
- Removal of cationic protein-bound substances, e.g. copper
- Removal of water-soluble substances
- Removal of CO_2 and HCO_3^-

Clinical Results

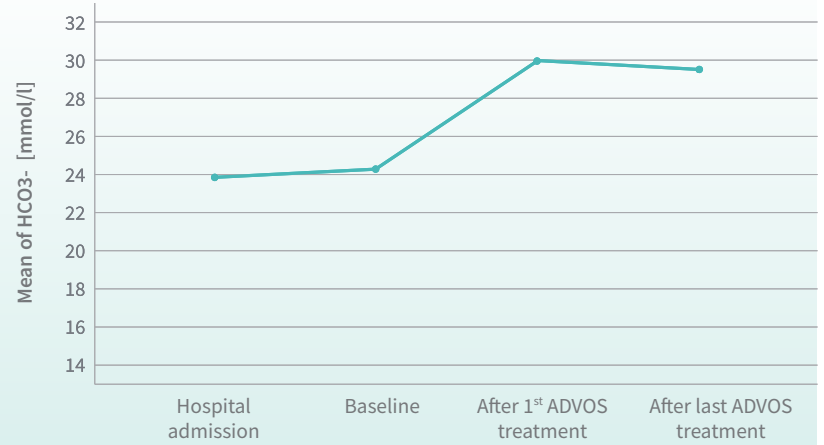
Blood pH Management and Lung Support

Rapid pH and CO_2 correction during **respiratory acidosis**[3]

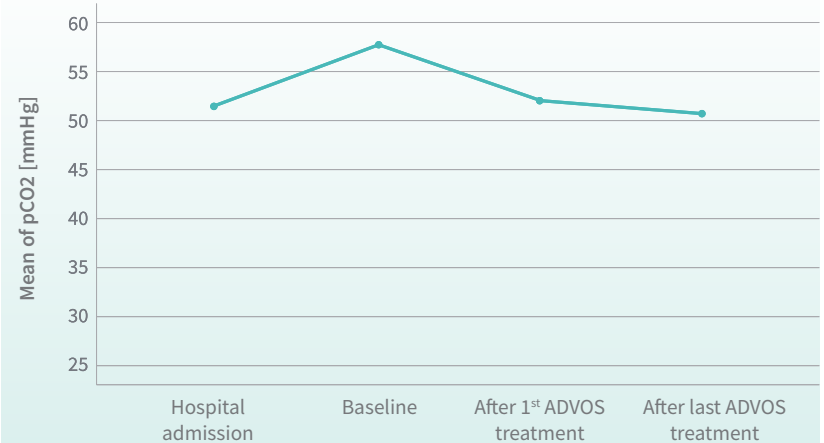
pH



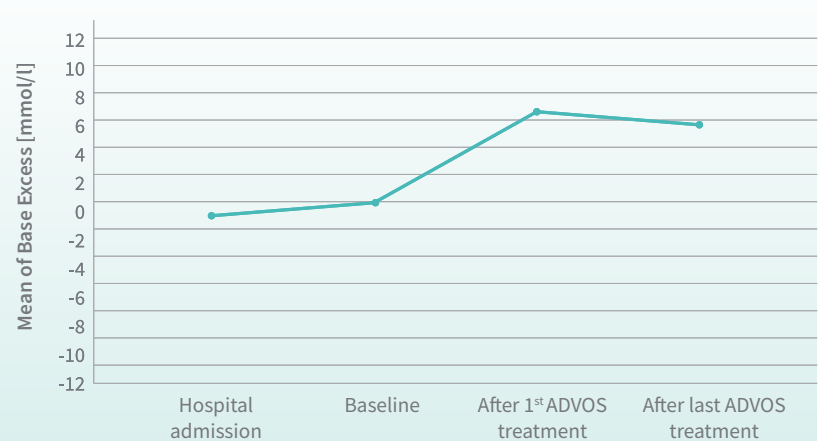
HCO_3^-



pCO_2



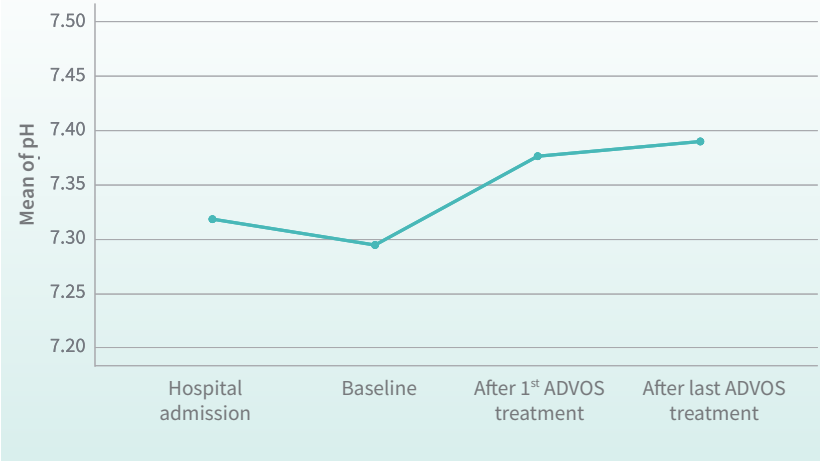
Base Excess



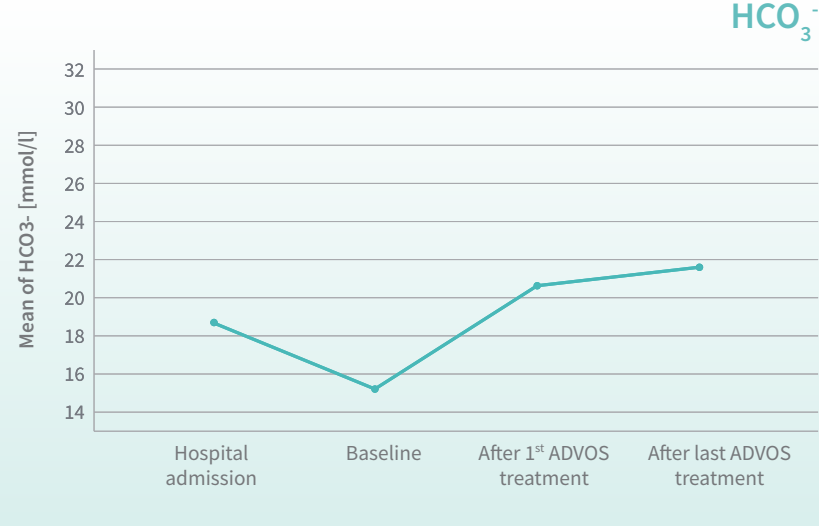
Blood pH Management and Lung Support

Rapid improvement of pH and bicarbonate during **metabolic acidosis**[3]

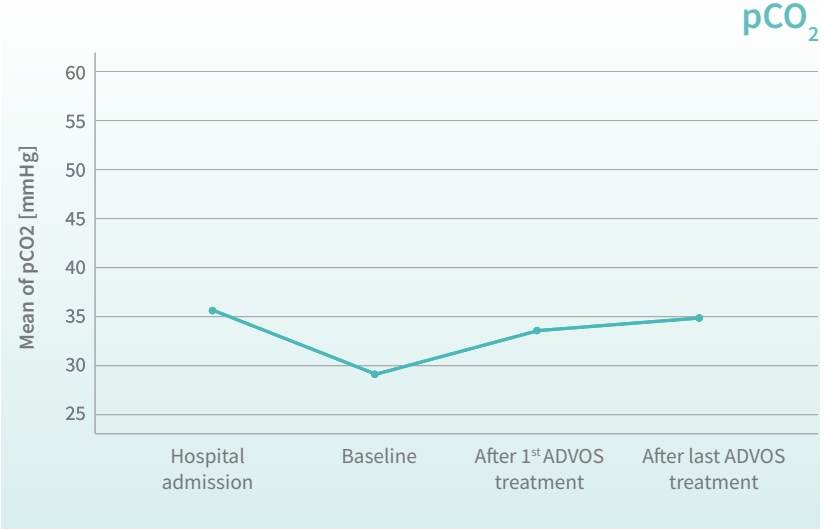
pH



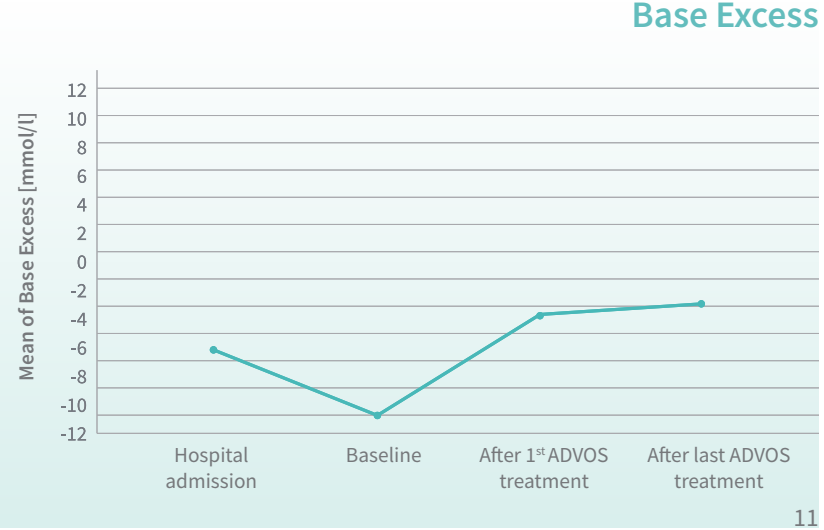
HCO_3^-



pCO_2



Base Excess

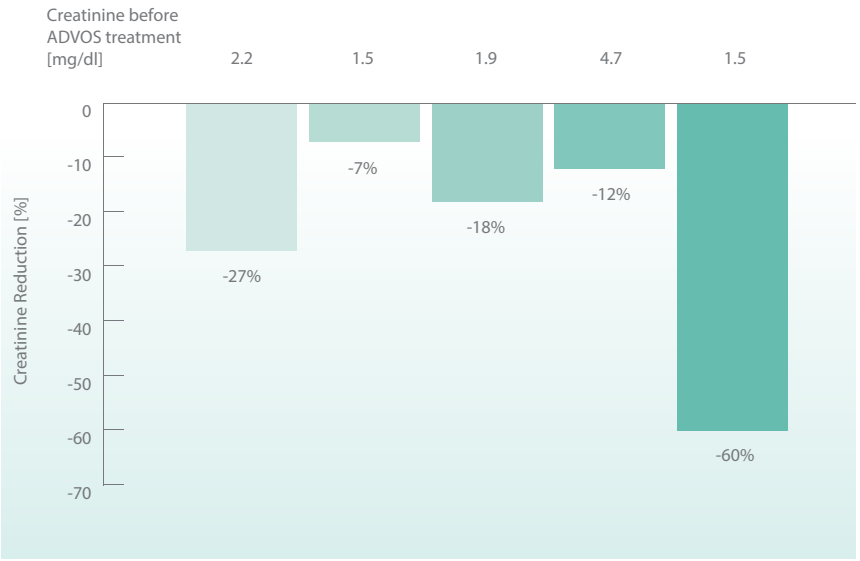


Clinical Results

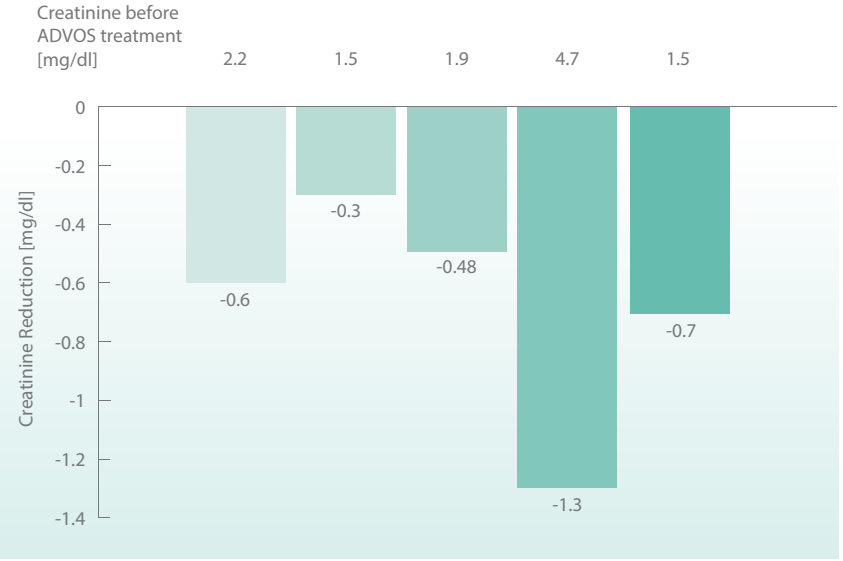
Kidney Support

Creatinine reduction in patients with acute kidney injury

Relative Reduction in Creatinine



Absolute Reduction in Creatinine

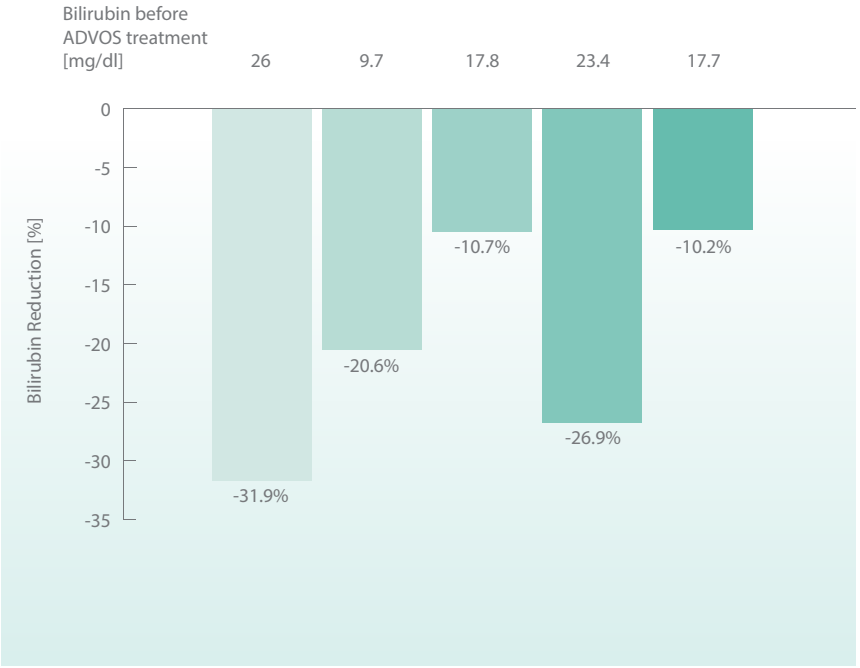


- Huber et al. 2017 - 14 patients[4]
- Fuhrmann et al. 2020 - 34 patients[5]
- Falkensteiner et al. 2020 - 18 patients[6]
- Kaps et al. 2021 - 26 patients[7]
- Allescher et al. 2021 - 9 patients[8]

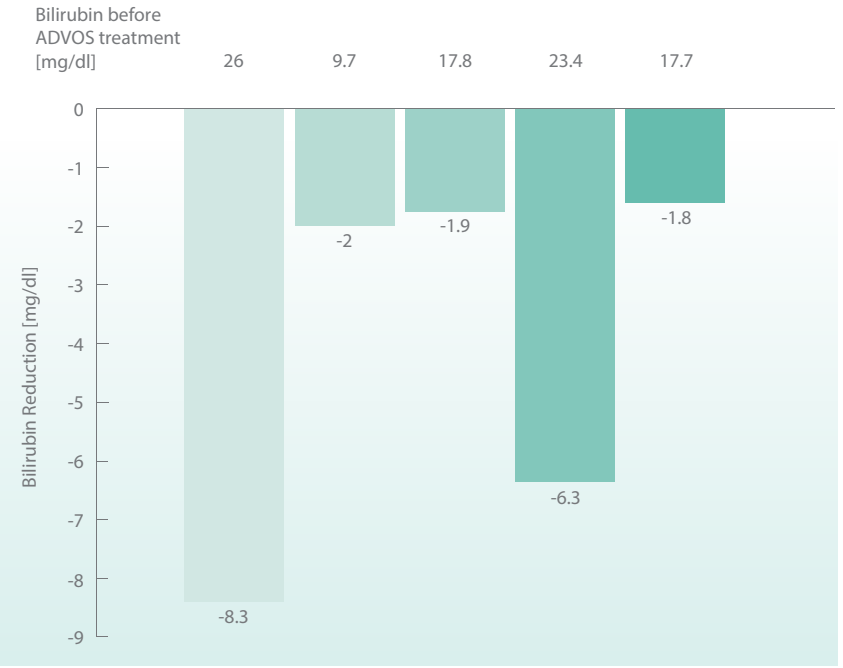
Liver Support

Concentration-dependent bilirubin removal in patients with liver failure

Relative Reduction in Bilirubin



Absolute Reduction in Bilirubin



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- Kaps et al. 2021 - 26 patients[7]
- Scharf et al. 2021 - 6 patients[9]

Clinical Results

Dose Dependent Reduction of Driving Pressure, Norepinephrine (NE) and Bilirubin[10]

Driving pressure before ADVOS treatment (mbar)	Relative driving pressure variation for each ADVOS treatment (%)	Number of ADVOS treatments	Treatments with reduction of driving pressure (%)
<15	0.0 (-1.4; 8.33)	29	27.6%
15-20	-6.3 (-17.1; 0.0)	35	57.1%
≥20	-17.7 (-31.8; -6.8)	8	75.0%

NE dose before ADVOS treatment (µg/kg/min)	Relative NE dose variation for each ADVOS treatment (%)	NE dose reduction during ADVOS treatment (%)	No NE requirement following ADVOS treatment (%)
≥ 0.001 - 0.100	-95 (-100; -41)	100	43%
≥ 0.100 - 0.500	-25 (-48; 0.0)	68	3%
≥ 0.500	-20 (-53; 0.0)	73	6%

Bilirubin before ADVOS treatment (mg/dl)	Relative bilirubin elimination for each ADVOS treatment (%)	Treatments with level reduction (%)
<6	0.0 (-20.0; 28.8)	38%
6-12	-10.8 (-19.7; -4.7)	86%
>12	-23.0 (-30.5; -17.4)	97%

Safety – Registry on Extracorporeal Multiple Organ Support with the Advanced Organ Support (ADVOS) System[11]

Adverse events documented during 429 ADVOS treatments

	Total	Device-related
Catheter problems	4	0
Bleeding	14	0
Allergic reaction	0	0
Clotting	29	13
Electrolyte imbalance	23	0
Infection	9	0

ADVOS multi and User Benefits

- Citrate and heparin anticoagulation possible
- Blood flow rates up to 500 ml/min zur to maximise toxin removal efficacy – especially for CO_2 and H^+

- User-friendly, intuitive information panel with dialysis-like menu guidance

Flexible fluid management system that eliminates the need to connect to a reverse osmosis system at the point of treatment

- Container with 85 l filling capacity eliminates the need for frequent bag changes – container can be changed during treatment after up to 8 hours, depending on settings
- External pump units for filling and emptying the container – eliminates the need to fill and empty the permeate and filtrate bags manually

- Little user interaction is necessary during ongoing therapy
- Quick set-up and easy operation supported by video-based instructions
- Intermittent or continuous treatment for up to 24h
- Flexible fluid management system, eliminating need for connection to reverse osmosis
- 24/7 hotline for application support

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10 Table adapted from: Fuhrmann et al. 2020. Advanced organ support (ADVOS) in the critically ill: first clinical experience in patients with multiple organ failure. Ann. Intensive Care 10:96

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