

ADVANCED ORGAN SUPPORT: Positive results from the register, indication and further development of the ADVOS procedure

Chair: Prof. Dr. Valentin Fuhrmann, Münster and Prof. Dr. Wolfgang Huber, Munich

ADVITOS INDUSTRY SYMPOSIUM DIVI 2019

19th Congress of the German Interdisciplinary Association for Intensive Care and Emergency Medicine 04. – 06.12.2019

In this symposium the results from the ADVOS registry with over 470 treatments for combined support for multi-organ failure of liver, lung and kidney as well as the correction of the acid-base balance will be presented. In addition, the indications for combined multi-organ support in liver failure will be shown. Further developments of the ADVOS method will be presented.



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ADVOS procedure in Germany: results from the ADVOS registry with more than 470 treatments

Prof. Dr. Valentin Fuhrmann, Münster

- 118 patients (470 treatments) with an average of three failing organs (mean SOFA Score: 14) and an expected mortality rate of 80% were included in the analysis.
- All participating hospitals showed a trend toward lower mortality compared with the SOFA Score prediction. 28-day mortality decreased to 60%, 90-day mortality decreased to 65%.
- Survivors had a lower SOFA Score. With a higher SOFA Score the mortality increased as expected. With earlier use of the ADVOS procedure, this mortality could be even lower.

The 2-year analysis of the ADVOS registry showed a trend toward lower mortality in all participating hospitals compared with the SOFA Score prediction. The ADVOS procedure eliminated water-soluble and protein-bound substances, corrected acid-base balance, and proved safe in clinical practice, reported Prof. Dr. Valentin Fuhrmann, Medical Clinic B for Gastroenterology and Hepatology, Münster University Hospital.

Treatment results for patients with multiple organ failure (MOF) have improved in the last decades, but if four organs fail at the same time, mortality is still 60-80% today. Meanwhile, the importance of liver failure has increased significantly: 10-15 years ago, only 5% suffered liver failure, today this figure is around 20%. A recent meta-analysis of the available 25 randomized controlled trials (predominantly albumin dialysis) in Intensive Care Medicine showed a survival benefit from extracorporeal liver support.¹ The number of treatments required for survival in acute-on-chronic liver failure is 16, for acute liver failure it is 22.

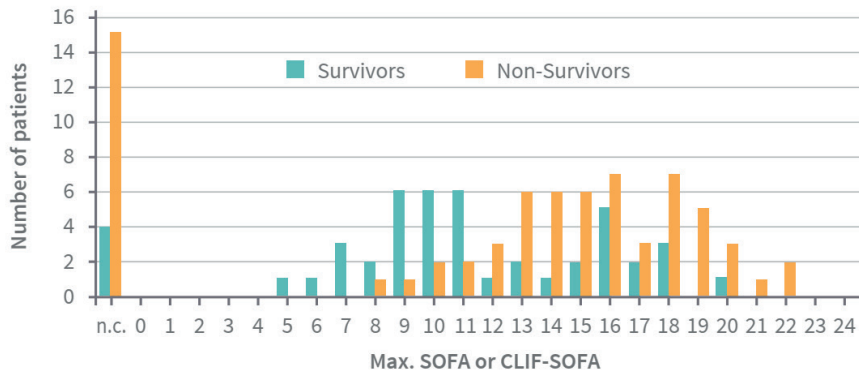


Figure 1: Mortality and SOFA Score in surviving and non-surviving patients from the ADVOS patient registry.

ADVOS procedure and ADVOS register

The ADVOS method is an approved dialysis procedure that eliminates water-soluble and protein-bound substances, regulates the acid-base balance and modifies the temperature.

In the acidotic subcircuit (addition of hydrochloric acid), cations are dissolved from the albumin bond, and in the alkaline subcycle (addition of sodium hydroxide solution), anions such as bilirubin are eliminated from the protein bond. These substances are subsequently filtered as in water-soluble normal dialysis. Since the targeted addition of acid and base allows the dialysate pH to be changed, it is also possible to intervene very effectively in the acid-base balance. Depending on the desired pH (7.2-9), the ADVOS multi adds a little more acid or base.

The ADVOS procedure is used in 20 hospitals (university hospitals and non-university institutions) in Germany. The aim of the ADVOS registry is to evaluate the performance safety under real-life conditions. In the first phase from 1/2017 to 2/2019, four German hospitals (University Medical Center Hamburg-Eppendorf, Klinikum Weiden, Essen University Hospital, Johannes Gutenberg University Mainz) analyzed 118 patients with an average of three failing organs, a mean SOFA Score of 14 and an expected mortality rate of 80%.

Safe and effective application

A total of 470 treatments with an average duration of 16 hours were evaluated. The patients were treated an average of three times. Blood flow was low at 120 ml/min, concentrate flow was 160 ml/min, and the median pH of the dialysate was 7.9. By applying the treatment, protein-soluble (bilirubin) and water-soluble (creatinine) substances were significantly reduced. A slight decrease in electrolyte values, which were always within the acceptable range, was recorded. No serious disturbances occurred. Acidosis was also normalized by the ADVOS treatment.

Indications for combined multi-organ support for liver failure

Prof. Dr. Wolfgang Huber, Munich

- An indication for the use of the ADVOS procedure as multi-organ support, Prof. Huber sees in cases of dialysis requirement, hepatic encephalopathy grade 3 or 4, increased SOFA Score, pH <7.32 or lactate above 2.3 mmol/l.
- Considering the SOFA Score for ADVOS indication in patients with secondary acute liver failure and primary nonhepatic multi-organ failure is useful.
- For SOFA Scores of 1-6, mortality is low, whereas for scores of 17 and higher, mortality is very high. In between, there is a window of opportunity in which the ADVOS procedure can be used most effectively.

If the three main detoxification organs (i.e. liver, lungs, and kidneys) fail, the prognosis for MOF patients is poor. However, organ support with the ADVOS procedure can positively influence the treatment outcome, explained Prof. Dr. Wolfgang Huber,

The slight decrease in thrombocytes is comparable to conventional dialysis procedures. During the 470 treatments, 79 adverse events were documented. Only 13 (3%) of these were attributable to the ADVOS procedure and related to clotting, which were resolved without further sequels.

Better prognosis with the ADVOS procedure

According to the SOFA Score, the expected mortality was 80%. In all four centers, mortality decreased with ADVOS treatment. The 28-day mortality decreased to 60%, and the 90-day mortality decreased to 65%. The severity correlates with the number of decompensated organs and therefore also the mortality rate: Survivors had a slightly lower SOFA Score, but even with a score of 16, there was still a chance of surviving (Figure 1). Patients who died were significantly sicker. **The initiation of an extracorporeal procedure should therefore not be delayed for too long.** At higher SOFA Score, mortality increased as expected. With an even earlier use of the ADVOS procedure this mortality could be even lower.

Munich, Medical Clinic and Polyclinic II, Klinikum rechts der Isar, Technical University of Munich. The German DIVI registry showed a clear correlation between the number of organ dysfunctions and survival based on 23,795 patients². Without

organ failure, mortality was less than 5%, with organ failure of two organs 30% died, with the failure of four organs the mortality was 70-80%. The strongest influence was exerted by the liver failure.³ While most organ failures increase mortality by a factor of 1.5, it increases to 2.2 times at a bilirubin of 3. If the bilirubin is above 10, the mortality quadruples.

Multi-organ support with the ADVOS procedure

To support the liver and also to eliminate protein-bound substances, albumin must be added to the dialysate. However, a mortality benefit could only be shown in subgroups of the RELIEF and HELIOS studies (e.g., MELD >30 in HELIOS, ACLF ≥2 in RELIEF).^{4,5} In contrast, with plasmapheresis, mortality in 182 patients with acute liver failure was statistically significantly reduced by 11%.⁶ The ADVOS procedure can support the liver and kidneys and correct the acid-base balance. For the past 2-3 years, the ADVOS procedure can also eliminate CO₂. A dialysate with a reduced bicarbonate concentration is used for this purpose. CO₂ is transported in the blood as H⁺ ions (hydrogen) and HCO₃⁻ (bicarbonate). In respiratory acidosis, H⁺ ions and HCO₃⁻ can be removed from the blood and the pH is raised. In

metabolic acidosis H⁺ ions are directly removed from the blood and HCO₃⁻ is produced.

Safety

The ADVOS procedure is a highly effective system with two dialyzers and an extracorporeal volume of 500 ml. Possible circulatory effects are hardly clinically relevant and well manageable. In 50 treatments of 16 critically ill patients (SOFA Score: 12), there were no relevant changes in heart rate, mean blood pressure, stroke volume and cardiac output.

Acute-on-chronic liver failure (ACLF)

The CLIF-SOFA Score modifies the SOFA Score for liver patients. In this case, the creatinine limits (>2mg/dl) are shifted, terlipressin is considered as a vasoactive substance and the Glasgow Coma Scale replaced by hepatic encephalopathy (grades 3-4) to define failure of the corresponding organ. In addition, cutoff values for bilirubin (>12 mg/dl), PaO₂/FIO₂ (<200), and coagulation (INR >2.5; platelets ≤ 20,000) are established. According to a scheme, ACLF patients are then assigned an organ failure score that correlates closely with mortality (Figure 2).⁷

This classification is of limited use for prescribing the ADVOS therapy in ACLF. Even with a mortality rate of 0 and very severe hepatic failure,

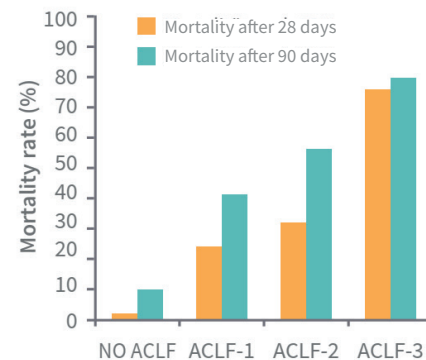


Figure 2: Mortality depending on ACLF Score⁷

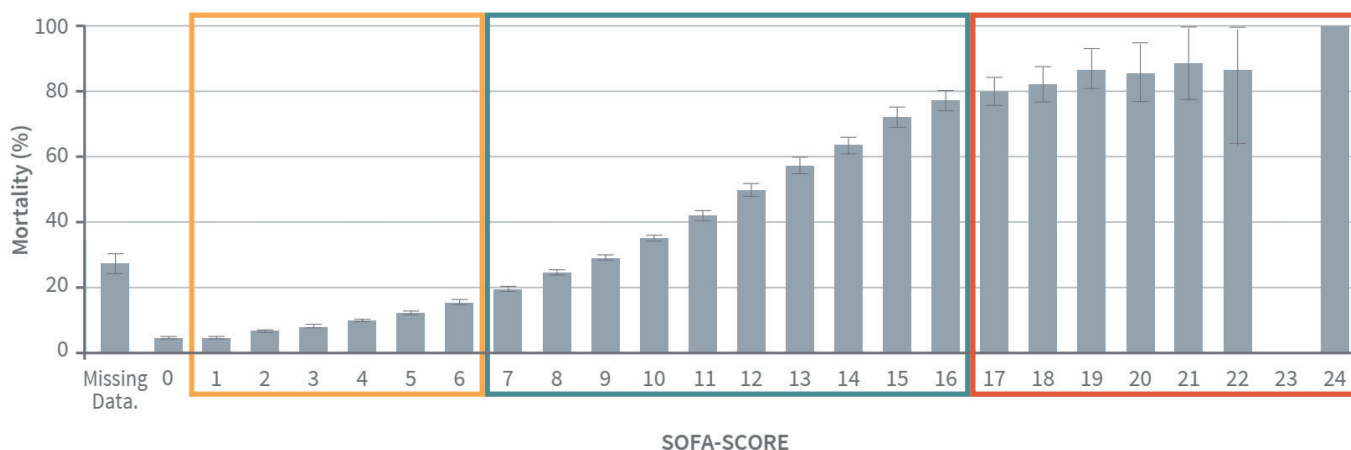
ADVOS may be indicated.

The same applies to serious encephalopathy or severe renal failure, since all patients have concomitant liver cirrhosis.

Liver failure = multi-organ failure

Acute liver failure is usually simultaneously multi-organ failure. Already a creatinine >3 mg/dl, a bilirubin >18 mg/dl, a metabolic acidosis with lactate increase and pH<7.3, or a hepatic encephalopathy of grade 2 or higher significantly impair the prognosis. Prof. Dr. Huber sees an indication for the use of the ADVOS method as multi-organ support in cases of dialysis requirement, hepatic encephalopathy grade 3 or 4, increased SOFA Score, pH <7.32 or lactate above 2.3 mmol/l. In this case, one of these parameters is sufficient.

Figure 3: Mortality as a function of SOFA Score, SIRS criteria, and qSOFA Score on admission to the ICU in patients with suspected infection (N = 184 875).⁸



Beginning of therapy

A major challenge is to decide the right time to start the ADVOS therapy. There is probably a “window of opportunity” of approximately one week to influence the fate of the patient after the triggering insult. This first week is crucial to prevent the development of SIRS, prevent sepsis and multiple organ failure.

Prof. Dr. Huber recommends using the SOFA Score as a guide for ADVOS indication in patients with secondary acute liver failure and primary non-hepatic multi-organ failure.⁸ Mortality is low for scores of 1-6, but is extremely high for scores of 17 and higher (Figure 3). In between is a window of opportunity, in which mortality increases by 5% per score-point. In this range the ADVOS method can be used most effectively, emphasized Prof. Dr. Huber.

Literature

- 1 Alshamsi F et al. Intensive Care Med 2019 Oct 7. doi: 10.1007/s00134-019-05783-y
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Further development of the ADVOS system

PD Dr. Bernhard Kreymann, Munich

- Further developments of the ADVOS multi enable an even faster correction of the acid-base balance. To accelerate detoxification, the binding capacity of albumin is also increased from the current 50% to 70-80%.
- Integration of oxygenation into the ADVOS system: With low blood flows the patient is to be supplied with 30% of the oxygen required.

Future developments of the ADVOS multi will enable an even faster correction of the acid-base balance. Studies are currently underway to demonstrate the safety of the ADVOS procedure even with more alkalized dialysate, reported **PD Dr. Bernhard Kreymann, CEO of ADVITOS GmbH, Munich.**

Further developments include new pumps, the modification of air sensors and additions to the hydraulic system. These more stable materials ensure that the ADVOS multi runs without problems.

The future ADVOS multi generation will have completely renewed electronics, get new brackets for the dialyzers and balance with an accuracy of 0.1%. In addition,

the binding of albumin will be increased from the current 50 to 70-80% in order to accelerate detoxification.

Acid-base regulation with the ADVOS method

The ADVOS method enables a transfer of hemoglobin-bound H⁺ ions into the dialysate. There they are bound to albumin and transported away. Depending on pH, blood flow and CO₂ supply, the ADVOS procedure is very effective. However, the pH currently can only be set to maximum 9. This is currently being optimized so that future pH settings of 9.5 will be possible. For effective CO₂ removal, bicarbonate elimination is required, as H⁺ ion removal increases bicarbonate production. The new ADVOS multi

prototype therefore has two basic partial circuits and one can set bicarbonate concentrations from 0-20. This will significantly optimize CO₂ removal.

Oxygenation

The next project is the integration of oxygenation into the ADVOS system. With relatively low blood flows, 30% of the required oxygen is to be supplied to the patient. The future ADVOS oxygenator will replicate the functions of fish gills.

The need for ADVOS oxygenation results from the negative consequences of mechanical ventilation, emphasized PD Dr. Kreymann. Many patients develop post-traumatic stress months after their intensive care stay, which has a catastrophic impact on their quality of life. The patient may have survived, but suffers from depression and other psychological disorders.



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