

SUPPLEMENT ARTICLE



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Immunoadsorption and plasmapheresis at the ICU – A description of the frequencies and indications in a single center experience and a case report

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Abstract

Immunologically mediated diseases can lead to severe courses that have to be treated in an intensive care unit. The use of extracorporeal organ support systems (ventilation, ECMO) is common. A therapeutic principle for these diseases is the removal of disease-causing antibodies. This can be done nonspecifically by plasmapheresis or specifically by immune adsorption. While most intensive care units have the facilities for plasmapheresis (membrane plasma filtration), immunoadsorption is much less common. Over a period of 10 years, the numbers of immunoadsorption and plasmapheresis treatments performed in a single center intensive care unit are shown according to their indication (IA: 18 Pts, 58 treatments. PA: 54 Pts, 148 treatments). A case study of a patient with granulomatosis with polyangiitis shows the successful treatment with immunoadsorption. The advantages of immunoadsorption in patients with complex coagulation disorders and a critical clinical picture in terms of SIRS and ARDS are shown.

KEYWORDS

granulomatosis with polyangiitis, immuno adsorption, intensive care

1 | INTRODUCTION

A large number of immunologically mediated diseases lead to severe courses that have to be treated in an intensive care unit (ICU) due to complications.

The immunological diseases come from very different disciplines. Most of them are diseases from neurology (Guillain-Barre syndrome, myasthenia gravis, autoimmune encephalitis [1]), internal medicine (ANCA vasculitides, lupus [2], forms of glomerulonephritis), dermatology (bullous pemphigoid), and transplant medicine (acute rejections) [3].

In most cases, it is vasculitides that were diagnosed late and thus show particularly severe courses or rejection reactions of transplanted organs that lead to intensive medical care. The organ systems affected can vary, usually several organ systems are affected. Frequent serious side effects that require intensive medical care occur in the lungs.

In addition to intensive medical monitoring and basic therapy, the use of extracorporeal organ support systems (ventilation, extracorporeal membrane oxygenation - ECMO, CVVH) is often necessary. The combination of several organ support systems is very complex and

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complicated by the management of anticoagulation for the individual procedures and the creation of appropriate vascular access [4]. Ventilation, ECMO, and renal replacement procedures are modern procedures that are established in ICUs worldwide and are performed by intensive care physicians, mostly anesthetists.

The therapy of immunologically triggered diseases is based on the suppression of the immune response in order to reduce the formation of antibodies or activity of immune cells. Drug therapy suppresses the formation of new antibodies, but does not affect antibodies that have already been formed. These can still maintain the disease process according to their half-life.

Another fundamental therapy principle for immunological diseases is the direct removal of disease-causing antibodies or immune complexes [5, 6]. With the removal of the pathological antibodies, the disease process is immediately slowed down, and the onset of action is significantly faster than with drug therapy [7]. This is a great advantage over drug therapy. The removal of the antibodies or immune complexes circulating in the blood can be done nonspecifically with the help of plasmapheresis (PE) or specifically with the help of immune adsorption. However, in order to interrupt or reduce further antibody production, an accompanying drug therapy is always necessary.

In PE, all components contained in the blood plasma are removed. The removed plasma is replaced by an albumin-containing electrolyte solution or by donor plasma. The pathological and pathogenetically relevant substances are removed effectively. However, all other plasma components (drugs, coagulation factors, and hormones) are also removed. In particular, short-term effects on coagulation are difficult to predict in the short term. Substitution with solutions containing albumin can have a negative effect on coagulation, and substitution with donor plasma can significantly improve coagulation, which is not always desirable. However, in the case of bleeding or other coagulopathies, the use of fresh frozen plasma can bring significant benefits and reduce the tendency to bleed. The treated plasma volume is usually limited to the patient's single plasma volume; in special cases (liver replacement), the treatment volume can be expanded up to twice the plasma volume.

Immunoabsorption (IA) is used to remove pathological plasma components very selectively. Usually, plasma infusion with specific adsorbers is used for this purpose. By using specific adsorbers, it is possible to remove only the pathological plasma components. These can be antibodies (e.g., in ANCA vasculitis, lupus, and acute transplant injections) or other plasma components (immune complexes, lipoproteins, etc.). All other plasma components, especially drugs, coagulation factors, and

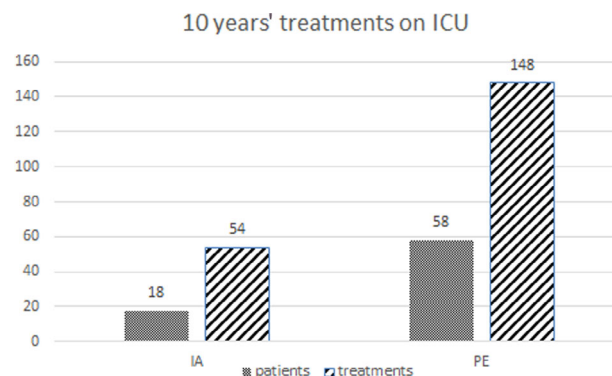


FIGURE 1 10 years' experience on ICU. IA, immunoabsorption; PA, plasmaexchange

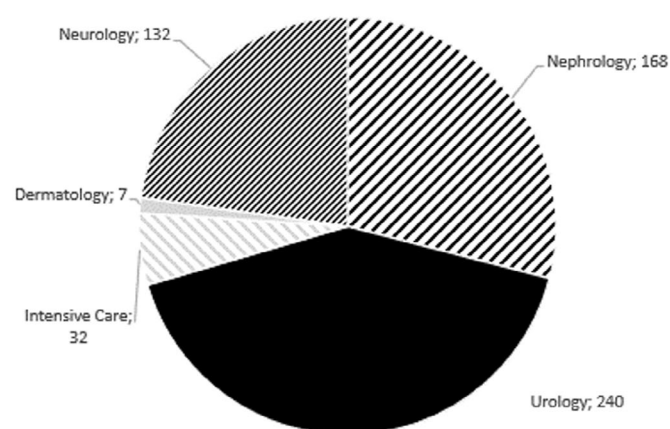
hormones or inflammatory mediators, remain in the plasma. IA procedures are more complex than simple PE. In addition to the specific adsorbers, special device platforms are often required to carry out the therapy. These are often manufacturer-specific, so that not all adsorbers can be used on all device platforms. The performance of IAs also requires an increased need for well-trained personnel.

While most ICUs have the facilities for PE (membrane plasma filtration procedures based on continuous hemodialysis machines are predominantly used here), IA for the specific removal of antibodies or immune complexes is much less common. IA treatment in the ICU is mostly reserved for larger centers that have their own dialysis and apheresis units. An actual search (07/2021) in PubMed for (IA) AND (intensive care) currently shows only 55 entries, many of which are case reports. For (PE) AND (intensive care) PubMed reported 1191 entries, for (plasmaexchange) AND (intensive care) PubMed reported 12 entries. A search for (IA) AND (intensive care) AND (vasculitis) shows only one entry [8].

Over a period of 10 years, the numbers of IAs performed in the internal and surgical ICUs in a university hospital are shown according to indication area and compared with PE treatments. The dialysis and apheresis procedures, as well as liver replacement procedures, are carried out in our hospital by the nephrology section and the affiliated dialysis unit. Apheresis treatments (PE and IA) are carried out in the ICUs by trained staff. In total, about 12 000 extracorporeal procedures are carried out by the section per year, of which about 200 plasmaphereses and 80 IAs per year. Apheresis can be performed in the ICU at any time (see Figure 1).

Compared to the total number of PE and IA treatments performed, the number of treatments in ICUs is rather low. IA or PE therapy is often started in the ICUs

Total number of treatments IA



Total number of treatments PE

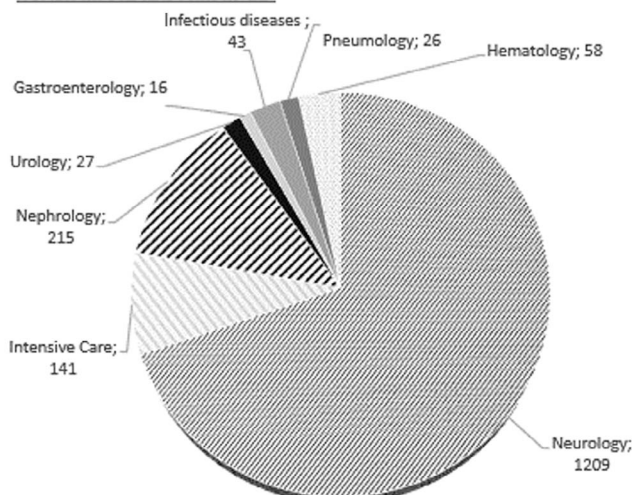


FIGURE 2 Comparison of treatment numbers at all by indication area

and then continued after transfer to the normal wards (see Figure 2).

Statistical analysis of the cases is difficult because the underlying diseases and clinical pictures of the treated patients differed greatly and there were no control groups (PE or conventional drug therapy). The two groups IA and PE were too different in terms of indication. The presentation is retrospective, there was no randomization. All treatments were carried out without complications; in particular no bleeding complications occurred. The treatments were assessed as effective on the basis of the clinical course.

Top 3 indications for IA: antibody mediated rejection after transplantation, vasculitis, and encephalitis.

Top 3 indications for PE: liver support, sepsis/disseminated intravascular coagulation (DIC), and hematological disorders.

2 | CASE STUDY

A 44-year-old previously healthy obese patient (1.8 m tall, 120 kg) is referred from a smaller hospital with an acute deterioration of condition and increasing shortness of breath. The patient's first complaint was joint pain, which had been present for about 2 months. Shortness of breath and a deterioration of her general condition had occurred 5 days before her presentation at the hospital. The patient continues to deteriorate rapidly with increased shortness of breath, new pulmonary hemorrhages, and circulatory insufficiency. The patient had to be intubated and ventilated due to the increase in pulmonary hemorrhages and suspected intracerebral hemorrhage. For circulatory support, high-dose catecholamine

therapy was necessary. Severe erosive gastritis led to gastric bleeding. Increasing oxygenation disturbance necessitated the use of ECMO therapy. DIC complicated the treatment of the bleeding and the management of the necessary anticoagulation for ECMO therapy.

Based on the clinical picture (acute disease with pulmonary hemorrhage, typical bilateral infiltrates in the chest x-rays) and the laboratory findings (high CrP values with initially no evidence of infection, high ANTI-PR3, and C-ANCA antibody titers), the diagnosis of granulomatosis with polyangiitis (Wegener's disease) was made [9, 10]. Drug immunosuppressive therapy was started immediately with methylprednisolone (1 g/day for 3 days, then 100 mg prednisolone/day). Cyclophosphamide therapy with 1150 mg as i.v. bolus therapy was also started. Due to the severity of the disease, the indication for extracorporeal removal of the disease-causing autoantibodies (anti-PR3, C-ANCA) was given. PE therapy is considered the standard therapy for this in other cases. However, influencing coagulation should be avoided under all circumstances. Decreasing the coagulation ability could have led to an increase in pulmonary hemorrhage, intracerebral hemorrhage, and gastrointestinal hemorrhage. Too much improvement in the clotting situation could have led to problems with ECMO therapy. The patient was difficult to oxygenate under ECMO. The heparinization and coagulation situation should not be changed.

Therefore, IA was performed using a Life18 therapy device (Miltenyi Biotec, Germany) and Therasorb IgPro adsorbers (Miltenyi Biotec, Germany). With a calculated plasma volume of 4.5 L, a treatment volume of 9 L per treatment was determined. Anticoagulation was performed as regional citrate anticoagulation. No additional heparin was administered. The standard anticoagulation

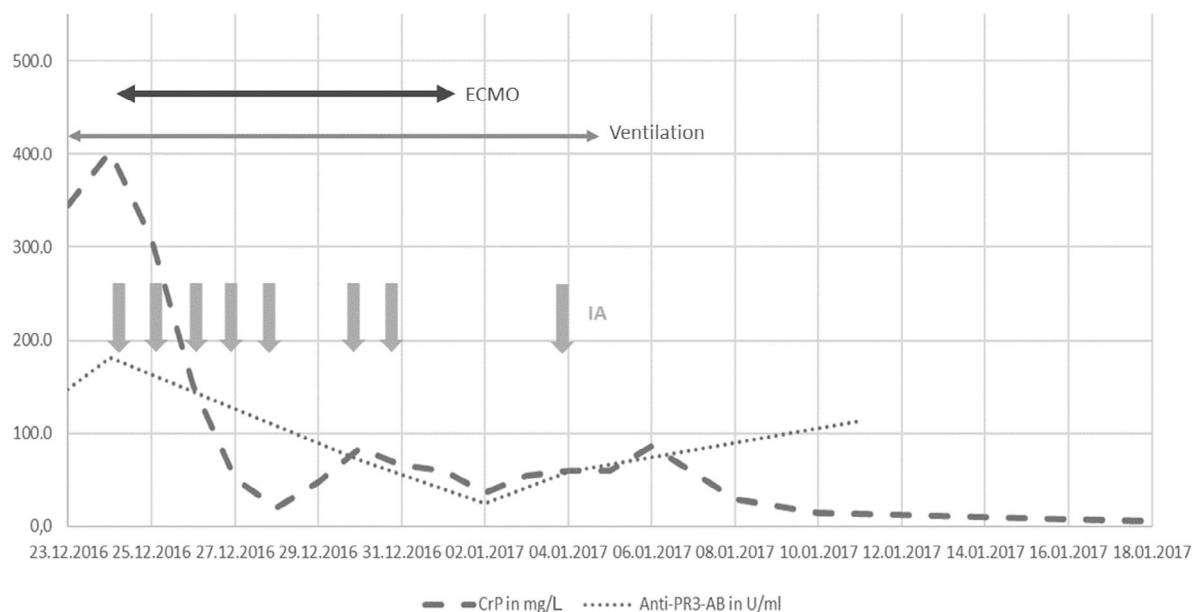


FIGURE 3 Time course of treatment

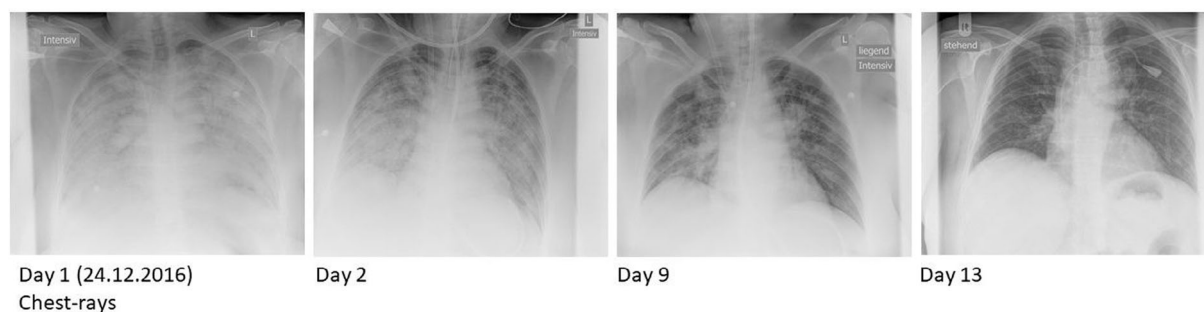


FIGURE 4 Time course of chest rays

for the procedure is mixed heparin and citrate anticoagulation. The heparin dose should not be changed because of bleeding issues and ongoing ECMO therapy. The additional citrate anticoagulation as regional anticoagulation safely prevented clotting of the adsorbers. The patient was already receiving heparin for the treatment of DIC and ECMO. The first five treatments were performed daily and another three treatments were performed at longer intervals (see Figure 3).

The treatments were uncomplicated. There was no impairment of coagulation and ECMO could be continued without complications. The clinical picture and the x-rays of the chest (see Figure 4) improved rapidly during the therapy. The pulmonary and gastrointestinal hemorrhages were stopped, the small intracerebral hemorrhage did not require intervention, and the DIC improved.

The patient was easily weaned off ECMO and ventilation. After another 2 days, the patient was transferred to a normal ward and then discharged to further uncomplicated outpatient care. Outpatient prednisolone therapy

was reduced to 10 mg/day, cyclophosphamide therapy was continued every 3 weeks for 5 months, and then the maintenance therapy with azathioprine was started. In the further course, the patient was relapse-free for 2 years.

3 | SUMMARY AND CONCLUSIONS

In the case presented, IA as a selective procedure to remove autoantibodies proved to be a safe and very effective procedure for the treatment of a patient suffering from granulomatosis with polyangiitis. The combination of IA with ventilation and ECMO therapy was possible without complications. This is also due to the high selectivity and the associated low influence on coagulation.

IA as an extracorporeal procedure for intensive care cases has been described less frequently so far. This is possibly due to the availability of the procedure in ICUs,

which unfortunately limits its application. The high selectivity certainly also offers advantages in the treatment of other diseases. With the rapidly advancing discovery of new antibody-mediated diseases (especially autoimmune-mediated encephalitides [11,12]), it is to be expected that further indications for IA in the ICU will be added. The conduct of randomized larger clinical trials is complicated by the overall rarity of the diseases. Studies comparing the effectiveness of IA and PE in autoimmune diseases would be desirable. The cooperation between intensive care physicians and nephrologists experienced in apheresis is gaining in importance.

ACKNOWLEDGMENTS

The authors received no financial support for the presented research, authorship and publication of this article. For the retrospective analysis of the presented data and anonymous presentation of the data no clinical trial registration, ethics approval or patient consent statement was applicable. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

S. Koball received speaker fees from Miltenyi Biotech, all other authors have nothing to declare.

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How to cite this article: Koball S, Rogge J, Frimmel S, Hinz M, Mitzner S. Immunoabsorption and plasmapheresis at the ICU – A description of the frequencies and indications in a single center experience and a case report. *Ther Apher Dial.* 2022;26(S1):97–101. <https://doi.org/10.1111/1744-9987.13865>